Abstract

**Background:** Interest is rising in smokeless tobacco as a safer alternative to smoking, but published reviews on smokeless tobacco and cancer are limited. We review North American and European studies and compare effects of smokeless tobacco and smoking.

**Methods:** We obtained papers from MEDLINE searches, published reviews and secondary references describing epidemiological cohort and case-control studies relating any form of cancer to smokeless tobacco use. For each study, details were abstracted on design, smokeless tobacco exposure, cancers studied, analysis methods and adjustment for smoking and other factors. For each cancer, relative risks or odds ratios with 95% confidence intervals were tabulated. Overall, and also for USA and Scandinavia separately, meta-analyses were conducted using all available estimates, smoking-adjusted estimates, or estimates for never smokers. For seven cancers, smoking-attributable deaths in US men in 2005 were compared with deaths attributable to introducing smokeless tobacco into a population of never-smoking men.

**Results:** Eighty-nine studies were identified; 62 US and 18 Scandinavian. Forty-six (52%) controlled for smoking. Random-effects meta-analysis estimates for most sites showed little association. Smoking-adjusted estimates were only significant for oropharyngeal cancer (1.36, CI 1.04–1.77, n = 19) and prostate cancer (1.29, 1.07–1.55, n = 4). The oropharyngeal association disappeared for estimates published since 1990 (1.00, 0.83–1.20, n = 14), for Scandinavia (0.97, 0.68–1.37, n = 7), and for alcohol-adjusted estimates (1.07, 0.84–1.37, n = 10). Any effect of current US products or Scandinavian snuff seems very limited. The prostate cancer data are inadequate for a clear conclusion.

Some meta-analyses suggest a possible effect for oesophagus, pancreas, larynx and kidney cancer, but other cancers show no effect of smokeless tobacco. Any possible effects are not evident in Scandinavia. Of 142,205 smoking-related male US cancer deaths in 2005, 104,737 are smoking-attributable. Smokeless tobacco-attributable deaths would be 1,102 (1.1%) if as many used smokeless tobacco as had smoked, and 2,081 (2.0%) if everyone used smokeless tobacco.

**Conclusion:** An increased risk of oropharyngeal cancer is evident most clearly for past smokeless tobacco use in the USA, but not for Scandinavian snuff. Effects of smokeless tobacco use on other cancers are not clearly demonstrated. Risk from modern products is much less than for smoking.
Background
Over the last 10 years, interest in smokeless tobacco (ST) as a possible safer alternative to smoking has risen. Although a number of recent reviews have considered the evidence relating ST to cancer, some have not included meta-analyses [1-3], and others have only provided quantitative summaries for specific sites: oropharyngeal cancer [4], pancreatic cancer [5], or oropharyngeal, oesophageal, pancreatic and lung cancer [6]. No formal comparisons have been conducted with the well-known effects of smoking [7,8].

The review described in this paper is restricted to studies in Western populations. In practice this predominantly means studies in the USA and Sweden, the only North American and European countries where the two major types of ST – chewing tobacco and snuff – are commonly used [2]. Although ST is also widely used in developing countries, particularly parts of Central and South-East Asia, the tobacco is often used in combination with other products, such as betel nut quid, slaked lime, areca nut and even snail shells [1,2,9]. This review also does not consider the limited data on nicotine chewing gum.

Our first objective is to carry out a comprehensive review of the available epidemiological evidence in Western countries relating ST to cancer, including meta-analyses for as many cancer types as the data justify. In meeting this objective, we take proper account of the potential confounding role of smoking by distinguishing effect estimates which are unadjusted for smoking and those which take smoking into account (either by adjustment in analyses based on the whole population of smokers and non-smokers combined or by restricting analysis to lifelong never smokers). Our second objective is to provide a quantitative indication of the relative effects of ST and cigarette smoking.

Methods
Study identification and selection
All reports had to satisfy the following inclusion criteria: published in a peer reviewed journal or the results publicly available, epidemiological study in humans, of cohort or case-control design, study location specified, any form of cancer as the outcome, and chewing tobacco, oral snuff or unspecified ST as the exposure. They also had to fall outside the exclusion criteria: conducted in an Asian or African population, no control group, or inappropriate design (case report, qualitative study or review/meta-analysis). Relevant papers were sought from a MEDLINE search conducted in May 2008 of "cancer" AND ("smokeless tobacco" OR "chewing tobacco" OR "snuff" OR "snus"), supplemented by citations in recent reviews [1-6,10] and in the papers obtained.

Data extraction
Reports were grouped by study, and for each study details were abstracted (see Tables 1 and 2 [11-114]) relating to the design, period, location, controls used and size, the exposure (method of assessment, type of ST, exposure doses and durations considered), the outcome (cancer sites studied) and issues relating to analysis (type of effect measure, analysis methods, extent of adjustment for smoking and other factors, and availability of dose-response data). The extent of adjustment for smoking for a study was categorised into five groups: A. no information – effect estimates are provided but no details are given of any adjustments made; B. no adjustment – effect estimates are available for the whole population, but smoking is not taken into account; C. never smokers – the only effect estimates available are for never smokers; D. some adjustment – effect estimates adjusted for smoking are available, but the adjustment is relatively simple, using two or three level broad groupings (for example, ever/never smoked, current/non-current smoker, current/former/never smoker), and takes no account of daily amount smoked or duration of smoking; and E. more adjustment – effect estimates are available that take into account daily amount smoked, duration of smoking and/or their product (pack-years). Studies were categorised under D or E if smoking-adjusted effect estimates are available, regardless of whether some results for never smokers are also presented. The method used to adjust for smoking is not always clear. Studies where the authors merely report that they ‘adjusted for cigarette smoking’ are included in category D.

Based on the availability of relevant data, 13 cancer groupings (oropharyngeal, oesophageus, stomach, pancreas, other digestive, larynx and nasal, lung, prostate, bladder, kidney, haematopoietic and lymphoid, other and all), were selected, with results for each grouping tabulated in a standard way, with details given of the source, exposure to ST, smoking group, sex, number of cases and adjustment factors for each effect estimate or indication of association (see tables dealing with individual effects estimates, below). For each study the intent is to extract the relative risk (RR) or odds ratio (OR) adjusted for the most factors, relevant to current, former or ever exposure to chewing tobacco, snuff or overall/undefined ST. Where relevant results for a study are reported in more than one paper, those based on the greatest number of cases are used.

Results are included, where available, for the whole population and for never smokers, and for sexes separately. RR or OR estimates based on zero exposed cases (or controls) are not included as providing too little information and because a valid confidence interval (CI) cannot be calculated. Suitable estimates of effect (RR or OR) and precision (CI) provided by the authors are used if possible, estimates otherwise being calculated from available data
Table 1: Cohort studies of smokeless tobacco and cancer

| Study                      | Country              | Follow-up period   | Baseline population                  | Exposure | Reference | Cancers studied (cases) |
|----------------------------|----------------------|--------------------|--------------------------------------|----------|-----------|------------------------|
| Lutheran Brotherhood cohort | USA                  | 1966 to 1986       | 17,633 white men aged 35+ years      | ST       | Hsing et al. 1990 [11]  | Prostate (149)          |
|                            |                      |                    |                                      |          | Knepler et al. 1991 [12] | Stomach (75)            |
|                            |                      |                    |                                      |          | Zheng et al. 1993 [13]  | Pancreas (57)           |
|                            |                      |                    |                                      |          | Hsing et al. 1991 [15]  | Prostate (4,607)        |
|                            |                      |                    |                                      |          | Heineman et al. 1992 [16]| Multiple myeloma (582)   |
|                            |                      |                    |                                      |          | Zahn et al. 1992 [17]   | Soft tissue sarcoma (119), pharynx (55), buccal cavity (74) |
|                            |                      |                    |                                      |          |                       |                        |
| US Veterans cohort         | USA                  | 1954/57 to 1980    | 248,046 US veterans aged 31–84 years, over 99.5% men | ST       | Hsing et al. 1990 [11]  | Prostate (4,607)        |
|                            |                      |                    |                                      |          |                       |                        |
| Iowa cohort                | USA                  | 1986/89 to 1995    | 1,572 men aged 40+ years, controls in a case-control study | ST       | Heineman et al. 1995 [18]| Colon (3,812), rectum (1,100) |
|                            |                      |                    |                                      |          | Putnam et al. 2000 [20] | Prostate (101)          |
| NHANES I follow-up cohort  | USA                  | 1971/75 to 2002    | 14,407 adults aged 25–74 years       | ST       | Accort et al. 2002 [21] | All, lung               |
|                            |                      |                    |                                      |          |                       |                        |
| CPS-I                     | USA                  | 1959 to 1972       | 77,407 never smoking men aged 30+ years from 25 states | ST       | Henley et al. 2005 [23] | All, lung, breast, digestive, oral, prostate |
|                            |                      |                    |                                      |          |                       |                        |
| CPS-II                    | USA                  | 1982 to 2000       | 114,809 never smoking men aged 30+ years nationwide | ST       | Henley et al. 2005 [23] | All (6,140), oral (46), digestive (1,999), lung (400), genitourinary (1,709), haematopoietic (923) |
|                            |                      |                    |                                      |          |                       |                        |
| Norwegian cohorts         | Norway               | 1982 to 1996       | 467,788 men aged 30+ years nationwide | ST       | Chao et al. 2002 [24]  | Stomach (996)           |
|                            |                      |                    |                                      |          |                       |                        |
| Swedish construction workers | Sweden              | 1974 to 1985       | 135,036 men                          | Snuff    | Bolinder et al. 1994 [28]| All (1,269), lung (204) |
|                            |                      |                    |                                      |          |                       |                        |
| Uppsala County cohort     | Sweden               | 1973/74 to 2002    | 9,976 men                            | Snuff    | Roosaa et al. 2008 [35] | All (1,572), smoking-related (493), oral (34) |

\*Only exposures for which results are available are shown. 

\*Main references. Other references supplying limited data are indicated in footnotes. 

\*Numbers of cases are totals for the sexes specified. Numbers of cases exposed to ST are shown in the tables presenting results by site. Cases are deaths, unless indicated. Oral is used as an abbreviation for oropharynx. 

\*Some limited additional results for the Lutheran Brotherhood cohort, based on follow-up to 1981, were reported earlier for cancers of the prostate, pancreas and oesophagus in IARC Monograph 37 in 1985 [14]. 

\*Some limited additional results for the US Veterans cohort, based on follow-up from 1954 to 1969 were presented earlier for a range of cancers in an abstract by Winn et al. in 1982 [19]. 

\*Cancers listed are incident cases. 

\*NHANES I = First National Health and Nutrition Examination Survey. 

\*Data on ST use were only collected in 3,847 subjects at baseline in 1971–1975, but were collected for all subjects in follow-up surveys in 1982–1984. 6,805 subjects were considered in the mortality analyses [21] and 7,779 in the incidence analyses [22]. 

\*Numbers of cases not given. 

\*CPS-I = Cancer Prevention Study I. 

\*CPS-II = Cancer Prevention Study II. Some additional results for lung cancer, based on mortality to 2002, comparing 111,952 men who quit cigarette smoking with 4,443 who switched to ST, were presented by Henley et al. in 2007 [25]. 

\*Results for chewing and snuff are also given for all cancers and lung cancers. 

\*Some limited additional results, based on follow-up to 1978, were reported by Heuch et al. in 1983 [27] for pancreatic cancer incidence and in IARC Monograph 37 in 1985 [14] for cancers of the buccal cavity/pharynx, oesophagus, pancreas and prostate. 

\*Cancers listed include incidental cases. 

\*Includes cutaneous malignant melanoma, melanoma in situ and intraocular malignant melanoma. 

\*Numbers are incident cases. An analysis of overall cancer based on 1,574 deaths was also conducted. 

ST = smokeless tobacco.
Table 2: Case-control studies of smokeless tobacco and cancer

| Study                                | Country       | Study period*     | Controls* | Sexb | Exposures studiedc | Cancers studied (cases)d |
|--------------------------------------|---------------|-------------------|-----------|------|-------------------|--------------------------|
| Broders 1920 [37]                    | USA           | NA                | Hospital  | M+F  | Chew, snuff, ST   | Oral (537)               |
| Doll and Hill 1952 [38]              | UK            | 1948–1952         | Hospital  | M    | Chew, snuff       | Lung (1,209)             |
| Moore et al. 1953 [39]               | USA           | 1951–1952         | Hospital  | M    | ST                | Oral (112), face (93)    |
| Wynder et al. 1957 [40]              | Sweden        | 1952–1955         | Hospital  | M    | Chew              | Oral (166), oesophagus (39), larynx (60) |
| Wynder and Bross 1957 [41]           | USA           | NA                | Hospital  | M    | Chew              | Oral (543)               |
| Peacock et al. 1960 [42]             | USA           | 1952–1958         | Hospital  | M+F  | ST                | Oral (45)                |
| Lockwood 1961 [43]                   | Denmark       | 1942–1956         | Population | M+F  | ST                | Bladder (282)            |
| Wynder and Bross 1961 [44]           | USA           | 1956–1959         | Hospital  | M    | Chew              | Oesophagus (150)         |
| Vogler et al. 1962 [36]              | USA           | 1956–1957         | Hospital  | M+F  | Chew, snuff       | Oral (228)               |
| Vincent and Marchetta 1963 [45]      | USA           | NA                | Hospital  | M    | Snuff             | Oral (66), larynx (23)   |
| Wynder et al. 1963 [46]              | USA           | 1957–1960         | Hospital  | M    | Chew, snuff, ST   | Bladder (300)            |
| Bennington and Laubscher 1968 [47]   | USA           | 1951–1956         | Hospital  | M    | Chew              | Kidney (88)              |
| Dunham et al. 1968 [48]              | USA           | 1958–1964         | Hospital  | M+F  | ST                | Bladder (493)            |
| Martinez 1969 [49]                   | Puerto Rico   | 1966              | Hospital  | M+F  | Chew              | Oral (221), oesophagus (179) |
| Keller 1970 [50]                     | USA           | 1958–1962         | Hospital  | M    | ST                | Oral (314)               |
| Cole et al. 1971 [51]                | USA           | 1967–1968         | Hospital  | M+F  | Chew, snuff       | Bladder (470)            |
| Bjelke et al. 1974 [52]              | Norway        | NA                | NA        | NA   | Chew              | Colorectal (373), oesophagus (52), stomach (83) |
| Armstrong et al. 1976 [53]           | UK            | 1972–1974         | Hospital  | M    | ST                | Kidney (96)              |
| Browne et al. 1977 [54]              | UK            | 1957–1971         | Population | M+F  | Chew              | Oral (75)                |
| Williams and Horm 1977 [55]          | USA           | 1969–1971         | Hospital  | M+F  | ST                | Many types (7,518)*      |
| Wynder and Stallman 1977 [56]        | USA           | 1969–1975         | Hospital  | M    | Chew, snuff, ST   | Oral (593), bladder (589), larynx (387), lung (1,051), oesophagus (183) |
| Engzell et al. 1978 [57]             | Sweden        | 1961–1971         | Population | M    | Snuff             | Nose (36)                |
| Howe et al. 1980 [58]                | Canada        | 1974–1976         | Population | M    | Chew              | Bladder (480)            |
| Westbrook et al. 1980 [59]           | USA           | 1955–1975         | Hospital  | F    | Snuff             | Oral (55)                |
| Pottern et al. 1981 [60]             | USA           | 1975–1977         | Decedent  | M    | Chew, snuff       | Oesophagus (120)         |
| Winn et al. 1981 [61]                | USA           | 1975–1978         | Hospital  | F    | Snuff             | Oral (255)               |
| Mønnsen and Aagaard 1983 [62]        | Denmark       | 1977–1980         | Population | M    | Chew              | Bladder (165)            |
| Wynder et al. 1983 [63]              | USA           | 1977–1980         | Hospital  | M    | Chew, snuff, ST   | Oral (414)               |
| Brinton et al. 1984 [64]             | USA           | 1970–1980         | Hospital  | M+F  | Chew, snuff, ST   | Nose (160)               |
| McLaughlin et al. 1984 [65]          | USA           | 1974–1979         | Population | M    | Chew, snuff, ST   | Kidney (313)             |
| Hartge et al. 1985 [66]              | USA           | 1977–1978         | Population | M    | Chew, snuff, ST   | Bladder (2,240)          |
| Weinberg et al. 1985 [67]            | USA           | 1978–1980         | Decedent  | M    | Chew              | Stomach (178)            |
| Goodman et al. 1986 [68]             | USA           | 1977–1983         | Population | M+F  | Chew              | Kidney (267)             |
| Kabat et al. 1986 [69]               | USA           | 1976–1983         | Hospital  | F    | Snuff             | Bladder (152)            |
| Stockwell and Lyman 1986 [70]        | USA           | 1982              | Population | M+F  | ST                | Oral (1,462), nose (92), larynx (161) |
| Young et al. 1986 [71]               | USA           | 4 yr period       | Hospital  | M+F  | ST                | Oral (317), larynx (179) |
| Lindquist et al. 1987 [72]           | Sweden        | 1980–1983         | Population | M    | Snuff             | Leukaemia (76)           |
| Asal et al. 1988 [73]                | USA           | 1981–1984         | Hospital  | M    | Snuff             | Kidney (209)             |
| Blot et al. 1988 [74]                | USA           | 1984–1985         | Population | M    | ST                | Oral (1,114)             |
| Falk et al. 1988 [75]                | USA           | 1979–1983         | Hospital  | M+F  | Chew, snuff      | Pancreas (363)           |
| Morris Brown et al. 1988 [76]        | USA           | 1982–1984         | Population | M    | ST                | Oesophagus (207)         |
| Slattery et al. 1988 [77]            | USA           | 1977–1983         | Population | M    | Chew, snuff, ST  | Bladder (332)            |
| Spitz et al. 1988 [78]               | USA           | 1985–1987         | Hospital  | M+F  | Chew, snuff, ST  | Oral (185)               |
| Burch et al. 1989 [79]               | Canada        | 1979–1982         | Population | M    | Chew, snuff       | Bladder (627)            |
| Franco et al. 1989 [80]              | Brazil        | 1986–1988         | Hospital  | M+F  | ST                | Oral (232)               |
| Zahm et al. 1989 [81]                | USA           | 1976–1982         | Population | M    | ST                | Soft tissue sarcoma (133) |
| Farrow et al. 1990 [82]              | USA           | 1982–1986         | Population | M    | Chew              | Pancreas (148)           |
| Blomqvist et al. 1991 [83]           | Sweden        | NA                | Hospital  | M+F  | Snuff             | Oral (61)                |
| Ghadirian et al. 1991 [84]           | Canada        | 1984–1988         | Population | M+F  | Chew              | Pancreas (179)           |
| Madsen et al. 1992 [85]              | USA           | 1985–1989         | Population | M    | ST                | Oral (131)               |
| Marshall et al. 1992 [86]            | USA           | 1975–1983         | Population | M+F  | Chew              | Oral (290)               |
| Morris Brown et al. 1992 [87]        | USA           | 1981–1984         | Population | M    | ST                | Leukaemia (578)          |
| Morris Brown et al. 1992 [88]        | USA           | 1981–1984         | Population | M    | ST                | Non-Hodgkin’s lymphoma (622) |
Table 2: Case-control studies of smokeless tobacco and cancer (Continued)

| Source                        | USA  | 1986 | Population | M+F | Snuff, ST | All cancer (459,792), oral (6,976), all digestive (109,514) |
|-------------------------------|------|------|------------|-----|-----------|-------------------------------------------------------------|
| Mashberg et al. 1993 [90]     | USA  | 1972–1989 | Hospital M | Chew, snuff, ST | Oral (359) |
| Perry et al. 1993†           | USA  | About 1992 | Hospital M+F | ST | Oral (108) |
| Sprott et al. 1993 [92]       | USA  | 1987–1991 | Hospital M+F | Chew | Oral (359) |
| Chow et al. 1994 [93]         | USA  | 1985–1997 | Population M | Chew | Stomach (338) |
| Hansson et al. 1994 [94]      | Sweden | 1989–1992 | Population M+F | Chew, snuff | Non-Hodgkin's lymphoma (105) |
| Hardell et al. 1994 [95]      | Sweden | 1974–1988 | Population M | Snuff | Oral (1,560) |
| Hayes et al. 1994 [96]        | USA  | 1986–1989 | Population M | Chew, snuff, ST | Prostate (981) |
| Kapetan et al. 1994 [97]      | USA  | 1977–1990 | Hospital M+F | Chew, snuff | Oral (1,560) |
| Bundgaarda et al. 1995 [98]   | Denmark | 1986–1990 | Population M+F | Chew | Oral (161) |
| McLaughlin et al. 1995 [99]   | 5 countries† | 1989–1991 | Population M+F | ST | Kidney (1,732) |
| Muscat et al. 1995 [100]      | USA  | 1977–1993 | Hospital M | Chew | Kidney (543) |
| Muscat et al. 1997 [101]      | USA  | 1985–1993 | Hospital M | Chew, snuff | Pancreas (290) |
| Lewin et al. 1998 [102]       | Sweden | 1980–1989 | Population M | Snuff | Oral (266), larynx (157), oesophagus (122) |
|                           |      |      |            |     |           |                                                              |

*NA = not available.
*M = male, F = female, M+F = both sexes. Studies of both sexes with results reported only for males are shown as M.
†Only exposures for which results are available are shown.
‡Oral (oropharyngeal) is defined as in Weitkunat et al. 2007 [4] to include any of the following sites: buccal mucosa, floor of mouth, gingival, gum/palate, lip, oral cavity/mouth, pharynx/alveolus, tongue, tonsils, salivary glands and oral unspecified. This reference also shows the actual sites presented in an essentially identical format, with a standard set of information included for each effect estimate included. Points to note about the entries in the various columns are discussed below.
§Results were presented for the following known tobacco-related sites: oral (298 cases), oesophagus (72), larynx (119), lung (931) and bladder (306), with comparisons made with all other 'non-related' sites. Results were also presented for various non-related sites: stomach (266), small intestine (19), colon (722), rectum (339), liver (45), gall bladder/bile duct (81), pancreas (224) breast (1,177), cervix (266), uterus (38), ovary (180), vulva (31), prostate (331), male genitalia (53), kidney (126), connective tissue (84), melanoma (99), nervous system (136), thyroid gland (94), lymphosarcoma (121), Hodgkin's disease (84), other lymphomas (33), multiple myeloma (86), leukaemia (172) and other or unknown primaries (385), with comparisons made with all other non-related sites combined.
‖Includes larynx cancer.
*Attributable oral cancer risk due to smokeless tobacco use based on a case-control study at Sinai Hospital in Detroit’; Perry et al., unpublished. Cited by Gross et al. 1995 [91].
Australia, Denmark, Germany, Sweden and USA.
ST = smokeless tobacco.

Data presentation

Study-specific results for the different types of cancer are presented in an essentially identical format, with a standard set of information included for each effect estimate included. Points to note about the entries in the various columns are discussed below.

Source

For the case-control studies, the source reference is shown. For the cohort studies, the source reference is also shown, but the study is also identified by name.
**ST use – type**
The exposure is identified as chewing tobacco (‘chew’), ‘snuff’ or smokeless tobacco (‘ST’). ST implies the results relate to smokeless tobacco unspecified by the author, or to use of either chewing tobacco or snuff or both.

**ST use – exposure**
Results are presented for current, former or ever use, or simply for ‘use’ where the timing of exposure was unspecified by the author. For current, former or ever use, the comparison is with never use; for use, it is with non-use.

**Smoking**
Results are presented only for any smoking (that is, based on the combined population of ever and never smokers) and for never smokers.

**Sex**
Results are shown, where available, for the sexes separately, though in some studies results are given only for the sexes combined.

**RR/OR id**
Within each table, each effect estimate (RR or OR) is given a unique identification number, so that those which are included in specific meta-analyses can readily be seen.

**Cases**
The number of ST-exposed cases is shown. Total numbers of cases are given elsewhere. Estimates are not presented unless there is at least one exposed case.

**Estimate (95% CI)**
This is the RR for cohort studies or the OR for case-control studies, together with its 95% CI. For many studies, the estimates are not given directly in the source paper, but were calculated from data provided. This involved one or more of the following: estimating numbers of exposed and unexposed cases and controls from proportions exposed given numerically or graphically and, where appropriate, combining numbers over level of exposure or cancer subtype; calculating estimates from a 2 × 2 table, or multiple independent 2 × 2 tables using standard methods [115], and calculating estimates from non-independent RR/ORs by level of exposure or by cancer type using the method of Hamling et al. 2007 [118]. Fuller details of the method of calculation used for each estimate are available on request. In a limited number of studies, as indicated in the tables, estimates were available separately for chewing tobacco and for snuff, but data were lacking for joint use. Here estimates for combined ST use were calculated assuming that no one used both chewing tobacco and snuff. Where there is a choice of relevant estimates from a study, preference is given to the estimate adjusted for the most potential confounding factors, and, for cohort studies, the estimate from the publication with a longer follow-up period.

**Adjustment factors**
The adjustment factors used for each estimate are shown. For matched case-control studies, the matching factors are not included unless the estimate specifically took this into account (for example, by conditional logistic regression). The factors used have been simplified into a relatively short consistent list, rather than repeating verbatim the wide variety of variable descriptions given by the original authors. Thus ‘res’ (area of residence) includes any variable based on the location of the subject and, for example, includes centre in multicentre case-control studies. ‘Diet’ includes any aspect of diet, and ‘alc’ (alcohol) any aspect of alcohol use. Estimates relevant to never smokers are not listed as being adjusted for smoking (‘smok’).

**Layout**
For the five columns, ST use – type, ST use – exposure, smoking, sex and adjustment factors, any blank entry for a particular effect estimate is assumed to be the same as in the first previous non-blank entry in that column. This avoids needless repetition and makes the tables easier to read.

**Meta-analysis**
Estimates with no CI are not included in the meta-analyses. The standard error of the logarithm of estimates of effect size was calculated from its reported or estimated CI, assuming that the effect size was log-normally distributed. The logarithms of the effect sizes and their corresponding standard errors form the data points for fixed-effect and random-effects meta-analysis [116].

For most cancer groupings, results of nine random-effect meta-analyses are presented, subject to availability of data (see tables summarising meta-analysis results, below). In the first set of three, any, there is no restriction of estimates on type of exposure or region. In the second set, any ST use (USA), estimates are restricted to those from studies conducted in the USA (or on occasion in Puerto Rico), while in the third set, snuff (Scandinavia), estimates are restricted to those for snuff and for studies conducted in Scandinavia. Each of the three sets of meta-analyses is divided into overall data, smoking-adjusted and never smokers. In the overall data analyses, estimates are not restricted on smoking status or on adjustment for
smoking. The smoking-adjusted analyses only include estimates that are for the whole population and adjusted for smoking or are for never smokers. The never smokers analyses are restricted to estimates for never smokers. For oropharyngeal cancer, where more estimates are available, some additional meta-analysis results are shown, based on estimates that are smoking and alcohol adjusted, and on estimates published since 1990.

To avoid double-counting multiple non-independent estimates from the same study, estimates from each study are selected for inclusion in the meta-analyses using order of preference lists for ST exposure (ever use/unspecified use/current use/former use), then smoking status (any – based on the combined population of smokers and non-smokers/never smokers), and then ST type (ST/snuff/chew), with each list being in order of most to least preferred. At each step we retain those estimates highest up the list, discarding any estimate lower in the preference order. If the procedure ends up with separate estimates for males and for females, both are included in the analysis. In one study [36], the results available are for males for chewing and for females for snuff (see Table 3). Although the procedure, strictly applied, selects only the snuff estimate, it was decided to include both in the relevant meta-analyses.

The presentation of the meta-analyses shows the number of estimates combined; the identification numbers of these estimates (so that they can be related to the preceding table of individual effect estimates); the combined random-effects estimate, with its 95% CI [116], the chi-squared and P value of homogeneity [119] and the I² statistic [120]. The meta-analyses conducted also include a test for publication bias [121] where five or more estimates are combined. Findings significant at $P < 0.1$ are indicated.

Forest plots are also included for most of the cancers. These are generally based on the smoking-adjusted analyses, with the estimates split by region and shown with cohort data first, then case-control, presented in order of publication year.

Sensitivity analysis

For each estimate included, the value of $Q^2$ is calculated by $w (x - \bar{x})^2$, where $w$ is the inverse-variance weight, $x$ is the logarithm of the effect size and $\bar{x}$ its mean. $Q^2$ is the contribution of the estimate to the heterogeneity chi-squared statistic [116]. Where there is significant ($P < 0.05$) heterogeneity of estimates, sensitivity to potentially outlying estimates is tested by removing that with the largest $Q^2$ value and rerunning the analyses. This process is continued until there is no longer significant heterogeneity.

Sensitivity to the criterion for including estimates based on ST exposure is also tested by rerunning the meta-analyses with the preference list for ST exposure changed from ever use/unspecified use/current use/former use to current use/ever use/unspecified use/former use.

Meta-regression analysis

For oropharyngeal cancer, fixed-effects regression analysis is used to investigate how the estimates selected for the first set of meta-analyses vary by region (USA; Scandinavia; other), period × study type (cohort; case-control published before 1990; case-control published after 1990), sex (male; female; combined), ST exposure (ever or unspecified use; current use), smoking (any, adjusted for smoking; any, unadjusted for smoking; never) and alcohol adjustment (yes; no). For those other cancers where more than five estimates are available and where there was evidence of significant ($P < 0.05$) heterogeneity, the meta-regression analyses use a more limited variable list: region, sex, and smoking as above, and also study type (cohort; case-control).

Regression analyses are only conducted based on the overall data and smoking-adjusted data. The analyses successively introduce the most significant factor into the model, stopping when no further factor significant at $P < 0.05$ can be added. Significance is estimated by treating the ratio of the deviance per degree of freedom (d.f.) explained by the factor to the residual deviance per d.f. as an F statistic. For oropharyngeal cancer some additional analyses investigate the drop in deviance resulting from introducing each factor individually, and others are conducted having excluded ‘outlying’ observations with a very high $Q^2$ value.

Estimating deaths attributable to smoking

RRs for current and former cigarette smokers (compared with never cigarette smokers) for men aged 35+ for seven major cancers caused by smoking (lip/oral cavity/pharynx, oesophagus, pancreas, larynx, lung, bladder, kidney/other urinary organs) were obtained from the American Cancer Society Cancer Prevention Study II (CPS-II) [122]. Numbers of deaths for these seven cancers occurring in US men aged 35+ in 2005 were obtained from WHO [123]. Estimates of the proportion of current and former cigarette smokers in US men aged 35+ in 2005 were obtained from the National Health Interview Survey [124].

Defining $D_i$ as the number of deaths for cancer i ($i = 1, \ldots, 7$), $R_{c i}$ and $R_{f i}$ as the RRs for current and former cigarette smokers for cancer i, and $p_c$ and $p_f$ as the proportions of current and former cigarette smokers in the population, the estimated number of deaths, $D_i^*$, that would have occurred
Table 3: Oropharyngeal cancer; individual effect (relative risk/odds ratio) estimates

| Sourcea | Typeb | Exposurec | Smoking | Sex | Id. Casesd | Estimate (95%CI) | Adjustment factors e |
|----------|--------|-----------|---------|-----|------------|------------------|----------------------|
| **Cohort studies** | | | | | | | |
| US Veterans: Zahm et al. 1992 [17] | ST | Ever | Any | M | 1 | 129 4.11 (2.90 – 5.84) | age, time |
| CPS-I: Henley et al. 2005 [23] | ST | Current | Ever | Never | M | 2 | 4 2.02 (0.53 – 7.74) | age, alc, asp, bmi, diet, exer, occ, race |
| CPS-II: Henley et al. 2005 [23] | ST | Current | Never | M | 3 | 1 0.90 (0.12 – 6.71) | age, alc, asp, bmi, diet, exer, occ, race |
| Norway Cohorts: Boffetta et al. 2005 [26] | Snuff | Current | Any | M | 4 | 6 1.13 (0.45 – 2.83) | age, smok |
| | | Former | | | | 3 1.04 (0.31 – 3.50) |
| Swedish construction workers: Luo et al. 2007 [32] | Snuff | Current | Ever | Any | M | 7 NA | 0.70 (0.50 – 0.90) | age, bmi, smok |
| | | Former | Never | | | 9 1.00 (0.40 – 2.60) |
| | | | | | 10 | 1.00 (0.04 – 1.70) |
| Uppsala County: Roosaa et al. 2008 [35] | Snuff | Ever | Any | M | 11 | 11 3.10 (1.50 – 6.60) | age, alc, res, smok, time |
| | | Never | | | | 5 2.30 (0.70 – 8.30) |
| **Case-control studies** | | | | | | | |
| Broders 1920 [37] | Chew | Use | Any | M+F | 13 | 128 2.05 (1.48 – 2.83) | smok |
| | Snuff | | | | | 14 2.05 (1.48 – 2.83) |
| | ST | | | | | 15 1.76 (0.12 – 26.52) |
| Moore et al. 1953 [39] | ST | Use | Any | M | 16 | 65 3.00 (1.37 – 6.54) |
| Wynder et al. 1957 [40] | ST | Use | Any | M | 17 | NA | no association h |
| Wynder and Bross 1957 [41] | ST | Use | Any | M | 18 | 19 2.00 (1.16 – 3.47) | smok |
| Peacock et al. 1960 [42] | ST | Use | Any | M | 19 | 14 3.06 (1.08 – 8.63) | age, ins |
| | | F | | | | | |
| Vogler et al. 1962 [36] | ST | Use | Any | M | 20 | 21 3.76 (4.31 – 12.63) |
| | Snuff | | | | | 22 1.76 (0.01 – 32.69) |
| Vincent and Marchetta 1963 [45] | Snuff | Use | Any | M | 23 | 12 4.22 (1.41 – 12.63) |
| Martinez et al. 1969 [49] | Chew | Use | Any | M | 24 | 4 2.29 (0.62 – 8.48) |
| | | F | | | | 25 | 1.04 (0.04 – 2.79) |
| Keller 1970 [50] | ST | Use | Any | M | 26 | 11 3.63 (1.02 – 12.95) | smok |
| | | Never | | | | 27 | 4.00 (0.62 – 14.99) |
| Browne et al. 1977 [54] | Chew | Use | Any | M+F | 28 | 7 0.67 (0.27 – 1.66) |
| Williams and Horn 1977 [55] | ST | Use | Any | M | 29 | 16 0.91 (0.53 – 1.56) |
| | | Never | | | | 30 | 2.00 (0.37 – 6.42) |
| Wynder and Stellman 1977 [56] | Chew | Ever | Any | M | 31 | 10 0.62 (0.32 – 1.21) |
| | Snuff | | | | | 32 | 6.15 (0.85 – 15.55) |
| Stockwell and Lyman 1980 [59] | Snuff | Ever | Any | M | 33 | 24 54.00 (60.97 – 4782.82) |
| Winn et al. 1981 [61] | Snuff | Ever | Any | F | 34 | 107 2.67 (1.83 – 3.90) | race, smok |
| Wynder et al. 1983 [63] | Chew | Ever | Any | M | 35 | 37 1.00 (0.62 – 1.61) |
| | Snuff | | | | | 36 | 12 0.41 (0.01 – 2.79) |
| Stockwell and Lyman 1986 [70] | ST | Ever | Any | M+F | 38 | 11 2.02 (1.01 – 4.02) |
| Young et al. 1986 [71] | ST | Ever | Any | M | 39 | 10 0.62 (0.32 – 1.21) |
| Blot et al. 1988 [74] | ST | Ever | Any | M | 40 | 16 0.85 (0.57 – 1.26) |
| Stockwell and Lyman 1986 [70] | ST | Ever | Any | M+F | 41 | 11 3.44 (1.09 – 10.91) |
| | | Never | | | | 42 | 6.20 (1.90 – 19.80) | age, race, res, resp |
| Spitz et al. 1988 [78] | Chew | Ever | Any | M+F | 43 | 23 1.00 (0.54 – 1.85) |
| | Snuff | | | | | 44 | 9 3.40 (1.00 – 10.90) |
| | ST | | | | | 45 | 25 1.05 (0.57 – 1.91) |
| Franco et al. 1989 [80] | ST | Use | Any | M+F | 46 | 9 1.40 (0.59 – 3.33) |
| Blommqvist et al. 1991 [83] | Snuff | Ever | Never | M+F | 47 | 2 0.67 (0.08 – 5.75) |
| Maden et al. 1992 [85] | ST | Ever | Any | M | 48 | 4 4.50 (1.50 – 14.30) |
| Marshall et al. 1992 [86] | Chew | Use | Any | M | 49 | 10 NA | no significant association |
| Sterling et al. 1992 [89] | ST | Ever | Any | M+F | 50 | 19 2.68 (1.04 – 6.83) | age, alc, occ, race, sex, smok |
| | Snuff | Ever | Any | M+F | 51 | 12 0.42 (0.04 – 2.68) |
| | | NA | | | | 52 | 2.42 (1.28 – 4.59) | age, race, sex |
| Mashberg et al. 1993 [90] | Chew | Ever | Any | M | 53 | 12 0.80 (0.40 – 1.90) |
| | Snuff | | | | | 54 | 0.80 (0.40 – 1.90) |
| | ST | | | | | 55 | 0.96 (0.70 – 1.33) |
The number of deaths avoided from these seven cancers, had the whole population the risk of never smokers (that is, the deaths attributable to smoking) is then estimated by:

\[ E = \sum_{i=1}^{7} (D_i - D_i^*) \]

Estimating deaths attributable to ST in a population of never smokers

Let us further define \( R_{si} \) as the estimated relative risk from ST for cancer \( i \) based on the meta-analyses using smoking-adjusted effect estimates. Where \( R_{si} \) is estimated to be less than 1, it is taken to be 1 for the purposes of calculating deaths attributable to ST.

For a population of never smokers, the number of deaths from cancer \( i \) that would have occurred had the same proportion of men used ST as had ever smoked is then estimated by:

\[ D_i^{**} = D_i^* + (p_e + p_f)R_{si} \]

The increase in overall deaths from these seven cancers is then given by:

\[ I_1 = \sum_{i=1}^{7} (D_i^{**} - D_i^*) \]

\( I_1 \) can then be compared with \( E \) as an indicator of the relative effects of ST and smoking.

Also for a population of never smokers, the number of deaths from cancer \( i \) that would have occurred had all the men used ST, is estimated by:

\[ D_i^{***} = D_i^*R_{si} \]
The increase, compared with $E$, is then calculated by:

$$I_2 = \sum_{i=1}^{7} (D_i - D_i^*)$$

Results

The MEDLINE search identified 690 publications. Two hundred and thirty-eight were rejected as describing studies conducted in Asia or Africa or relating to products typically used there, 96 as not describing epidemiological studies, 112 as not relating to cancer and 163 as being reviews, letters or comments not providing primary data. This left 61 apparently relevant publications. Taking into account also citations in recent reviews [1-6,10], and eliminating publications that referred to studies more recently or completely covered in other publications, a total of 104 publications were considered. Twenty-five related to nine cohort studies, and 79 to 80 case-control studies. Fuller details of the search are given in Figure 1, whilst the studies and publications considered are presented in the following two sections.

Cohort studies

Results relating ST use to mortality or incidence have been reported for nine cohort studies, with results provided by multiple publications for some studies. Six studies have been conducted in the USA and are based on the Lutheran Brotherhood cohort [11-14], the US Veterans cohort [15-19], the Iowa cohort [20], the First National Health and Nutrition Examination Survey (NHANES I) Follow-up cohort [21,22], and the American Cancer Society Cancer Prevention Study I (CPS-I) [23] and Study II (CPS-II) [23-25]. One study was based on two Norway cohorts [14,26,27] while the remaining two were conducted in Sweden; one based on construction workers [28-34], and the other on a cohort in Uppsala County [35]. Fuller details of these studies are given in Table 1. A number of these studies (US Veterans, CPS-I, CPS-II, Swedish Construction Workers) are extremely large, involving at least 100,000 subjects, though the number of ST users is less than this,

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**Figure 1**

Flow chart for search strategy for review of literature on smokeless tobacco and cancer. The flow chart shows the number of publications identified by the MEDLINE search, and the number excluded by reason. The number of additional publications identified from reviews and secondary references is also indicated, as is the total number of publications considered in the review and meta-analysis, subdivided by study type.
particularly in the CPS-I and CPS-II studies where the analyses of Henley et al. [23] restricted attention to never smokers of cigarettes. The US studies generally present results for combined ST use, the main exception being the analyses of CPS-II [23] where some separate analyses are presented for snuff and chewing tobacco. The results from the Swedish studies relate to snuff use, as do the main results from the Norwegian study [26].

Case-control studies
Results relating ST use to cancer have been reported for 80 case-control studies, with Table 2 providing details for each study, in chronological order of publication, of the location, period and controls, as well as the exposures, cancer types and sexes studied. Eighteen were published between 1920 and 1975 [36-52], 30 between 1976 and 1990 [53-82] and 32 between 1991 and 2007 [83-114]. In general there was one publication per study, but Bjelke [52] reported results from two studies, while the reference to Gross et al. [91] is to a review, which cites results from unpublished studies by Perry et al. Of the 80 studies, 56 were conducted in the USA, 11 in Sweden, three in each of Canada, Denmark and the UK, and one in each of Brazil, Norway and Puerto Rico, with one study conducted in five countries. Most of the studies involve only one or a small number of cancer types, but one study [55] involves a very wide range. The majority of the studies involve less than 1,000 cancer cases but 10 are larger than this [38,55,56,66,70,74,89,97,99,106]. The numbers of cancers in ST-exposed subjects are typically much lower than this, as will become evident when the results for the individual sites are presented. Of the different cancer sites, oral cancer is by far the most often studied. Of the 80 studies, 56 provide results only for chewing tobacco, five only for snuff, and 18 only for ST, with the remaining 22 results for more than one type. Seven of the 11 studies in Sweden restricted attention to snuff, with three also considering chewing and one only considering chewing.

Adjustment for smoking
ST use is not a major subject for many of the publications from which results have been extracted. While reference is made to ST in the title of one or more papers relating to six of the nine cohort studies (NHANES I, CPS-I, CPS-II, Norway Cohorts, Swedish Construction Workers and Uppsala County), the same is true for only 15 of the 80 case-control studies. For many of the other studies [39,42,59,61,66,70,89,91,102,104,108,109,111,113,114], the reports only provide limited information about ST use in the text, simply giving percentages of users in the cases and controls or even saying there was an association or no association, but without giving supportive data. Many papers consider ST independently of smoking, with no attempt to adjust ST effect estimates for smoking, even though for many of the cancers considered smoking is known to be a cause, and often a major cause.

To summarise the extent to which the available effect estimates were adjusted for smoking, the studies were divided into five groups (A = no information, B = no adjustment, C = never smokers, D = some adjustment, E = more adjustment) as described more fully in the methods. Of the nine cohort studies, the numbers in the five categories were, respectively, 0, 1, 3, 3 and 2. The Iowa study [20] failed to take smoking into account at all, while the CPS-I and CPS-II studies [23] and the main results from NHANES I [22] were restricted to never smokers. In the remaining five cohort studies, the extent of smoking adjustment varied from publication to publication, but amount smoked or duration of smoking were never taken into account in the US Veterans, Norway cohorts and Uppsala County studies so they are classified as group D. In the Lutheran Brotherhood study, amount smoked was taken into account in the analyses of pancreatic cancer [13] and stomach cancer [12], and in the Swedish Construction Workers study, amount smoked was adjusted for in the analyses of stomach and oesophageal cancer [34], and cutaneous squamous cell carcinoma [29], and they are therefore classified as group E.

Of the 80 case-control studies considered, details of the adjustment factors used are not provided in either of the studies reported by Bjelke [52] or in two other studies [93,109] (category A). For a further 38 studies [36,38-40,42,44-46,49,51,53,54,56,57,59,60,63,64,67,70-73,75,76,78,80-82,84-86,92,95,96,98,100,103,110] the results available for ST are for the whole population, with no adjustment for smoking (category B). In 14 studies [43,47,48,66,69,74,76,83,87,88,99,101,111,112] the only relevant smoking-adjusted results reported are for never smokers (category C). In the remaining 24 studies, some smoking-adjusted results are available for the whole population. Fourteen of these [37,41,50,58,61,62,65,94,97,102,104,107,108,114] can be classified into category D. In only 10 reports [55,68,77,79,89-91,105,106,113] is some account taken of daily dose and/or duration of smoking (category E).

Oropharyngeal cancer
Table 3 presents individual effect estimates from six cohort and 34 case-control studies, with 36 of the 40 studies providing estimates with CI that could be used in meta-analyses, the other four [40,71,86,92] finding no significant relationship. Thirty-eight of the 41 estimates included in the first meta-analysis (see Table 4) are those given in our earlier review of ST and oral cancer [4], three recently published studies [32,35,113] being introduced.

http://www.biomedcentral.com/1741-7015/7/36
into the current analysis. The overall data show an association with any ST use (1.79, 1.36–2.36) that, though highly significant, is based on an extremely heterogeneous set of estimates (P < 0.001). Limiting consideration to smoking-adjusted data, the estimate reduces substantially, to 1.36 (1.04–1.77, n = 19), though it is still significant, and marked heterogeneity remains (P < 0.001). Further limiting attention to estimates adjusted for both smoking and alcohol, the two major risk factors for oropharyngeal cancer [7,8], eliminates both heterogeneity and excess risk (1.07, 0.84–1.37, n = 10). A significant relationship is seen in never smokers (1.72, 1.01–2.94, n = 9), though the estimates are heterogeneous (P = 0.044), and generally based on a very small number of oropharyngeal cancer cases that used ST.

Table 4: Oropharyngeal cancer; meta-analysis results

| Type of ST (region) | Adjustments/restrictionsa | Number of estimates (RR/OR ids)c | Random-effects RR/OR (95% CI) | Heterogeneity |
|--------------------|---------------------------|----------------------------------|-----------------------------|---------------|
|                    |                           |                                  |                             |               |
| Any                | Overall data              | n = 41 (1, 2, 3, 6, 7, 11, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 30, 33, 34, 35, 38, 39, 41, 42, 46, 47, 48, 49, 51, 55, 56, 58, 60, 63, 65, 73, 74, 77) | 1.79 (1.36–2.36) | 335.6 88.1 < 0.001 |
|                    | Smoking-adjusted          | n = 19 (2, 3, 6, 7, 11, 13, 18, 26, 35, 43, 48, 51, 55, 56, 58, 63, 69, 74, 77) | 1.36 (1.04–1.77) | 69.5 74.1 < 0.001 |
|                    | Smoking and alcohol adjusted | n = 10 (2, 3, 11, 51, 55, 56, 63, 69, 74, 77) | 1.07 (0.84–1.37) | 12.5 28.0 0.186 |
|                    | Never smokers             | n = 9 (2, 3, 10, 12, 27, 43, 48, 59, 72) | 1.72 (1.01–2.94) | 15.9 49.7 0.044 |
|                    | – alcohol adjusted        | n = 3 (2, 3, 12) | 1.87 (0.82–4.27) | 0.6 0.0 0.731 |
| Any (USA)d         | Overall data              | n = 31 (1, 2, 3, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 29, 30, 33, 34, 35, 38, 41, 42, 46, 49, 51, 55, 56, 58, 65, 74) | 2.16 (1.55–3.02) | 275.8 89.1 < 0.001 |
|                    | Smoking-adjusted          | n = 12 (2, 3, 13, 18, 26, 35, 43, 51, 55, 56, 58, 74) | 1.65 (1.22–2.25) | 33.6 67.3 < 0.001 |
|                    | Smoking and alcohol adjusted | n = 6 (2, 3, 51, 55, 56, 74) | 1.04 (0.80–1.35) | 1.8 0.0 0.875 |
|                    | Never smokers             | n = 5 (2, 3, 27, 43, 59) | 3.33 (1.76–6.32) | 3.5 0.0 0.476 |
|                    | – alcohol adjusted        | n = 2 (2, 3) | 1.58 (0.52–4.81) | 0.4 0.0 0.512 |
| Snuff (Scandinavia)| Overall data              | n = 7 (6, 7, 11, 48, 63, 69, 77) | 0.97 (0.68–1.37) | 14.5 58.8 0.024 |
|                    | Smoking-adjusted          | n = 7 (6, 7, 11, 48, 63, 69, 77) | 0.97 (0.68–1.37) | 14.5 58.8 0.024 |
|                    | Smoking and alcohol adjusted | n = 4 (11, 63, 69, 77) | 1.01 (0.64–1.90) | 10.7 71.9 0.014 |
|                    | Never smokers             | n = 4 (10, 12, 48, 72) | 1.01 (0.71–1.45) | 2.2 0.0 0.524 |
|                    | – alcohol adjusted        | n = 1 (12) | 2.30 (0.67–7.92) | – – – |
| Published since 1990| Overall data              | n = 18 (1, 2, 3, 6, 7, 11, 48, 49, 51, 55, 56, 58, 60, 63, 65, 73, 74, 77) | 1.28 (0.94–1.76) | 81.7 79.2 < 0.001 |
|                    | Smoking-adjusted          | n = 14 (2, 3, 6, 7, 11, 48, 51, 55, 56, 58, 63, 69, 74, 77) | 1.00 (0.83–1.20) | 18.5 29.8 0.139 |
|                    | Smoking and alcohol adjusted | n = 10 (2, 3, 11, 51, 55, 56, 63, 69, 74, 77) | 1.07 (0.84–1.37) | 12.5 28.0 0.186 |
|                    | Never smokers             | n = 7 (2, 3, 10, 12, 48, 59, 72) | 1.24 (0.80–1.90) | 7.5 20.1 0.277 |
|                    | – alcohol adjusted        | n = 3 (2, 3, 12) | 1.87 (0.82–4.27) | 0.6 0.0 0.731 |

aFor each study/sex, the RR/OR for ST from Table 3 was included if available, otherwise that for chewing tobacco or snuff was used.
bSmoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
cThe actual estimates included are identified by their RR/OR identification numbers as given in Table 3.
dIncludes estimates 24 and 25 from a study in Puerto Rico [49].
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.
When the analyses are restricted to US studies, the pattern is similar to that for the overall data, with the effect estimates reduced when attention is limited to those that are smoking-adjusted, and close to 1.0 when estimates that are adjusted both for smoking and alcohol are considered. The effect estimate for never smokers is significantly increased (3.33, 1.76–6.32), based on five small studies, in total involving 19 ST-exposed oropharyngeal cancer cases.

No real evidence of a relationship with snuff use is seen in studies conducted in Scandinavia, where seven estimates, all adjusted for smoking, and four additionally adjusted for alcohol, give a combined estimate of 0.97 (0.68–1.37). However some heterogeneity should be noted, a high RR of 3.1 (1.5–6.6) in the Uppsala County study [35] conflicting with six other estimates ranging from 0.67 to 1.10.

Many of the higher estimates seen in Table 4 come from older studies which often did not adjust for smoking. If attention is limited to studies published since 1990, which generally did adjust, no association is seen. Indeed, the combined estimate from the 14 smoking-adjusted studies published since 1990 is 1.00 (0.83–1.20), and shows no significant heterogeneity.

While the choice of 1990 as the cut-point was not defined a priori, the change in estimates about that time is very clear. As shown in Figure 2, smoking-adjusted estimates for case-control studies published between 1920 and 1988 are consistently high (overall 2.38, 95% CI 1.87–3.04), while estimates for case-control studies published between 1991 and 2005 show no association at all (0.98, 0.83–1.16). There is no evidence of heterogeneity within either period (P = 0.34 for pre-1990 and P = 0.93 for post-1990) and a highly significant (P < 0.001) difference between estimates in the two periods. Smoking-adjusted estimates for the cohort studies which, though published between 2005 and 2008, generally cover a long follow-up period extending from before 1990, give an intermediate result (1.32, 0.65–2.68).

The findings are very similar to those in an earlier review [4]. That review provides additional meta-analyses of the slightly smaller data set, further investigating variation by type of ST, sex, study design, study location and study period. It also provides full details of the various types of cancer that have been considered in the source papers.

The evidence presented suggests that snuff as used in Scandinavia has no effect on oropharyngeal cancer risk. Products used in the past in the USA may have increased the risk but any effect that exists now seems likely to be quite small.

**Oesophageal cancer**

Table 5 summarises the data from four cohort and 10 case-control studies. For five of these studies effect estimates with CI are not available, one of these [52] reporting a ‘synergistic effect of tobacco chewing and alcohol’, another [19] presenting a RR of 2.28, but not whether it was significant, and the others [14,40,60] showing no significant relationship. Of the remaining nine studies, six provide smoking-adjusted estimates, three of which are also adjusted for alcohol. Though estimates are generally somewhat above 1.0 in these nine studies, they are rarely significant, exceptions being the estimate of 1.92 (1.00–3.68) for snuff in never smokers in the Swedish Construction Workers study [34] and that for chewing of 2.39 (1.23–4.64) in the Wynder and Bross case-control study [44].

The meta-analyses (see Table 6 and Figure 3) show some indication of an association, though this is not always statistically significant. Based on all available smoking-adjusted data, the combined estimate for any ST use is 1.13 (0.95–1.36, n = 7), somewhat lower than when there is no restriction to smoking-adjusted data (1.25, 1.03–1.51, n = 10). The corresponding analyses show no real indication of an effect for snuff in Scandinavia, but are more suggestive for the USA. Even here, the smoking-adjusted estimate is not significant (1.89, 0.84–4.25), though this is based on only three small studies, involving a total of 11 cases using ST. The estimates based on all the available smoking-adjusted data include an any smoking RR of 1.00 (0.79–1.27) from the study with the largest weight, the Swedish Construction Workers study [34], this RR being derived by combining the findings for adenocarcinoma and squamous cell carcinoma. The meta-analyses for never smokers give a higher combined estimate of 1.91 (1.15–3.17, n = 4) for any ST use, mainly because they use a higher (combined adenoid/squamous) estimate of 1.92 (1.00–3.68) for the Swedish Construction Workers study [34].

Overall, the data must be regarded as providing suggestive evidence of a possible weak relationship between ST use and oesophageal cancer.

**Stomach cancer**

Table 7 presents results from 12 studies, eight of which provide a total of 17 estimates which could be used in meta-analyses. Although the Swedish construction workers study [34] shows a significant increase in risk of stomach cancer associated with snuff use for never smokers (RR 1.33, 95% CI 1.03–1.72), no other significant associations are reported, and the meta-analyses conducted (see Table 8 and Figure 4) are all non-significant. Based on smoking-adjusted estimates from eight studies, the combined RR estimate is 1.03 (95% CI 0.88–1.20). Four studies did not provide...
Figure 2
Smokeless tobacco and oropharyngeal cancer by study type and period of publication (smoking-adjusted data).
The 19 individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates separated by study type, and for case-control studies by period of publication, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication. In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 3 for further details relating to the estimates, and Table 4 for fuller details of the meta-analyses.
detailed data. No association with stomach cancer was reported by Weinberg et al. [67] or for the US data considered by Bjelke [52]. However, Bjelke did report an “Association ... with tobacco chewing” for the Norwegian data, and a standardised mortality ratio of 1.51 was given for the US Veterans’ Study [19], but not whether this was statistically significant.

The combined evidence does not indicate an effect of ST use on the risk of stomach cancer.

### Pancreatic cancer

Table 9 presents results from four cohort and seven case-control studies. For four of the studies effect estimates that can be included in meta-analyses are not available; two [75,84] of these studies merely reported finding no association, one [19] reported an elevated RR of 1.65 with no CI, and another [82] a reduced RR of 0.80, also with no CI. Of the other seven studies, significant increases have been reported in two. The Norway cohorts study [26] reports an increase in ever users of snuff in a
Table 6: Oesophageal cancer; meta-analysis results

| Type of ST (region)^a | Adjustments/restrictions^b | Number of estimates (RR/OR ids)^c | Random-effects RR/OR (95% CI) | Heterogeneity |
|-----------------------|-----------------------------|-----------------------------------|-------------------------------|---------------|
| Any Overall data      |                             | 10 (5, 6, 9, 10, 11, 13, 16, 19, 22, 23) | 1.25 (1.03–1.51) | 10.3 13.0 0.324 |
| Smoking-adjusted      |                             | 7 (5, 6, 10, 11, 19, 22, 23)      | 1.13 (0.95–1.36) | 4.4 0.0 0.623 |
| Never smokers         |                             | 4 (7, 10, 11, 19)                 | 1.91 (1.15–3.17) | 1.0 0.0 0.810 |
| Any (USA)^d           |                             | 6 (9, 10, 11, 13, 16, 19)         | 1.56 (1.11–2.19) | 5.2 4.6 0.387 |
| Smoking-adjusted      |                             | 3 (10, 11, 19)                    | 1.89 (0.84–4.25) | 1.0 0.0 0.617 |
| Never smokers         |                             | 3 (10, 11, 19)                    | 1.89 (0.84–4.25) | 1.0 0.0 0.617 |
| Snuff (Scandinavia)   |                             | 4 (5, 6, 22, 23)                  | 1.10 (0.92–1.33) | 1.8 0.0 0.61 |
| Smoking-adjusted      |                             | 4 (5, 6, 22, 23)                  | 1.10 (0.92–1.33) | 1.8 0.0 0.61 |
| Never smokers         |                             | 1 (7)                             | 1.92 (1.00–3.68) | 1.0 1.0 1.0 |

^a For each study/sex, the RR/OR for ST from Table 5 was included if available, otherwise that for chewing tobacco or snuff was used.
^b Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
^c The actual estimates included are identified by their RR/OR identification numbers as given in Table 5.
^d Includes estimates 10 and 11 from a study in Puerto Rico [49]
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Figure 3
Smokeless tobacco and oesophageal cancer by region (smoking-adjusted data). The seven individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 5 for further details relating to the estimates, and Table 6 for fuller details of the meta-analyses.
smoking-adjusted analysis based on the whole population (1.67, 95% CI 1.12–2.50) but not in an analysis based on never smokers (0.85, 0.24–3.07). Conversely, the Swedish construction workers study shows no increase in a smoking-adjusted analysis based on the whole population (0.9, 0.7–1.2), but an increase in never smokers (2.0, 1.2–3.3). None of the three meta-analyses presented in Table 10 (see also Figure 5) for any ST use show any significant increase, though they all show evidence of heterogeneity. Smoking-adjusted overall population effect estimates are available for all seven studies considered, the combined estimate being 1.07 (0.71–1.60). For never smokers, the estimate is 1.23 (0.66–2.31, n = 5). No significant associations are seen in the separate meta-analyses for the USA and Scandinavia.

At most, the overall data weakly suggest a possible effect of ST on pancreatic cancer risk. A fuller discussion of these data is available elsewhere [5].

Other cancers of the digestive system

Table 11 summarises evidence relating to cancers of the digestive system other than those considered already in Tables 5, 7 and 9. Nine studies are considered, four

Table 7: Stomach cancer; individual effect (relative risk/odds ratio) estimates

| Source                        | ST use | Type | Exposure | Smoking | Sex | Id. | Cases | Estimate (95%CI) | Adjustment factors |
|-------------------------------|--------|------|----------|---------|-----|-----|-------|-----------------|--------------------|
| Lutheran Brotherhood: Kneller et al. 1991 [12] | ST     | Ever | Any      | M       | I   | 18  | 1.60 (0.58–4.50) | age, byr, smok    |
| US Veterans: Winn et al. 1982 [19] | ST     | Ever | Never    | M       | 2   | 3   | 3.80 (1.00–14.32) | age, byr           |
| CPS-II: Chao et al. 2002 [24] | ST     | Current | Never | M†      | 3   | NA  | 1.51 (NA)       | age               |
| Norway cohorts: Boffetta et al. 2005 [26] | Snuff  | Current | Any    | M       | 4   | 8   | 1.58 (0.76–3.28) | age, asp, diet, edu, fhis, race, vit |
| Swedish construction workers: Zendehdel et al. 2008 [34] | Snuff  | Ever | Any    | M       | 10  | 311 | 1.08 (0.96–1.22) | age, bmi, smok |
| Case-control studies          |        |      |         |         |     |     |       |                 |                    |
| Bjelke 1974 (USA) [52]        | Chew   | Use  | Any     | NA      | 12  | NA | no association | NA                |
| Bjelke 1974 (Norway) [52]     | Chew   | Use  | Any     | NA      | 13  | NA | association    | NA                |
| Williams and Horm 1977 [55]   | ST     | Ever | Any     | M       | 14  | 12 | 1.31 (0.71–2.43)† | age, race, smok   |
| Weinberg et al. 1985 [67]     | Chew   | Ever | Any     | M       | 16  | NA | no association | none              |
| Hansson et al. 1994 [94]      | Snuff  | Use  | Any     | M+F     | 17  | NA | 0.70 (0.47–1.06) | age, ses, sex, smok |
| Ye et al. 1999 [107]          | Chew   | Ever | Any     | M+F     | 18  | 8  | 1.30 (0.54–3.12)† | none              |
| Lagergren et al. 2000 [108]   | Snuff  | Ever | Any     | M+F     | 21  | 53 | 1.20 (0.80–1.80) | age, alc, bmi, diet, edu, exer, rflx, sex, smok |

*Fuller details of the studies are given in Tables 1 and 2.
*ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
*Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
*NA = not available.
*‘Id.’ is the RR/OR identification number used in Table 8, and ‘Cases’ is the number of cases in ST users as defined. NA = not available.
*Abbreviations used: alc = alcohol, asp = aspirin, bmi = body mass index, byr = birth year, edu = education, exer = exercise, fhis = family history of stomach cancer, incm = incidence or mortality, res = area of residence, rflx = reflux symptoms, ses = socioeconomic status, smok = smoking, vit = vitamins, NA = not available.
*The population included < 0.5% females.
*Estimated from data provided in the source.
*RRs for cardia (1.0, 95% CI 0.8–1.4) and noncardia stomach cancer (1.1, 1.0–1.3) combined.
*RRs for cardia (0.9, 95% CI 0.4–2.0) and noncardia stomach cancer (1.4, 1.1–1.9) combined.
*CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.
Table 8: Stomach cancer; meta-analysis results

| Type of ST (region) | Adjustments/restrictions | Number of estimates (RR/OR ids) | Random-effects RR/OR (95% CI) | Heterogeneity |
|---------------------|---------------------------|---------------------------------|------------------------------|---------------|
|                     |                           |                                 |                              |               |
| Any                 | Overall data              | 9 (1, 6, 9, 10, 14, 15, 17, 19, 21) | 1.03 (0.90–1.19) | 10.5 24.0 0.230 |
|                     | Smoking-adjusted          | 8 (1, 6, 9, 10, 14, 17, 19, 21) | 1.03 (0.88–1.20) | 10.3 31.9 0.173 |
|                     | Never smokers             | 4 (2, 6, 11, 20)                | 1.27 (0.75–2.13) | 7.0 57.2 0.072  |
| Any (USA)           | Overall data              | 4 (1, 6, 14, 15)               | 1.41 (0.95–2.10) | 0.1 0.0 0.988 |
|                     | Smoking-adjusted          | 3 (1, 6, 14)                   | 1.41 (0.93–2.12) | 0.1 0.0 0.942 |
|                     | Never smokers             | 2 (2, 6)                       | 1.96 (0.82–4.70) | 1.6 38.2 0.203 |
| Snuff (Scandinavia) | Overall data              | 5 (9, 10, 17, 19, 21)          | 0.98 (0.82–1.17) | 8.1 50.4 0.089 |
|                     | Smoking-adjusted          | 5 (9, 10, 17, 19, 21)          | 0.98 (0.82–1.17) | 8.1 50.4 0.089 |
|                     | Never smokers             | 2 (11, 20)                     | 0.90 (0.35–2.30) | 4.2 76.4 0.040 |

For each study/sex, the RR/OR for ST from Table 7 was included if available, otherwise that for chewing tobacco or snuff was used.

Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.

The actual estimates included are identified by their RR/OR identification numbers as given in Table 7.

CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Figure 4
Smokeless tobacco and stomach cancer by region (smoking-adjusted data). The eight individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 7 for further details relating to the estimates, and Table 8 for fuller details of the meta-analyses.
cohort and five case-control, with one or two studies providing data for colon cancer, rectal cancer, colorectal cancer, small intestine cancer, liver cancer, gall bladder and bile duct cancer. These data, which are insufficient for meta-analysis, include two statistically significant effect estimates: an RR of 1.9 (1.2–3.1) for rectal cancer and ST use from the US Veterans study [18] and a remarkably high OR from the case-control study of Chow et al. [93] of 18.0 (1.4–227.7) for bile duct cancer and chewing tobacco, based on only three exposed cases.

There are rather more data for the combined category of all cancers of the digestive system. Of the four studies providing data, all conducted in the USA, NHANES I

| Source                                      | Type | Exposure | Smoking | Sex | Cases | RR/OR          | Adjustment factors |
|---------------------------------------------|------|----------|---------|-----|-------|----------------|--------------------|
| Lutheran Brotherhood: Zheng et al. 1993     | ST   | Ever     | Any     | M   | 16    | 1.70 (0.90–3.10) | age, alc, smok    |
| US Veterans: Winn et al. 1982 [19]          | ST   | Ever     | Never   | M   | 2     | 1.65 (NA)      | age               |
| Norway cohorts: Boffetta et al. 2005 [26]   | Snuff| Current  | Any     | M   | 27    | 1.60 (1.00–2.55) | age, smok         |
|                                             |      | Former   |         |     | 18    | 1.80 (1.04–3.09) |                   |
|                                             |      | Ever     |         |     | 45    | 1.67 (1.12–2.50) |                   |
|                                             |      | Ever     | Never   | M   | 3     | 0.85 (0.24–3.07) | age               |
| Swedish construction workers: Luo et al.    | Snuff| Current  |         |     | 18    | 2.10 (1.20–3.60) | age, bmi          |
| 2007 [32]                                   |      | Former   |         |     | 2     | 1.40 (0.40–5.90) |                   |
|                                             |      | Ever     |         |     | 20    | 2.00 (1.20–3.30) |                   |
| Williams and Horm 1977 [55]                 | ST   | Ever     | Any     | M   | 11    | 0.29 (0.09–0.92) | age, race, smok   |
| Falk et al. 1988 [75]                       | Chew | Use      | Any     | M+F | 12    | NA no association | none              |
| Farrow and Davis 1990 [82]                  | Chew | Ever     | Any     | M   | 14    | 0.80 (NA)      | edu, race         |
| Ghadarian et al. 1991 [84]                  | Chew | Use      | Any     | M+F | 15    | NA no association | none              |
| Muscat et al. 1997 [101]                    | Chew | Ever     | Never   | M   | 16    | 2.82 (0.85–9.39) | none              |
| Alguacil and Silverman 2004 [111]           | ST   | Ever     | Never   | M+F | 18    | 1.10 (0.40–3.10) | age, race, res, sex, smok |
| Hassan et al. 2007 [114]                    | Chew | Ever     | Any     | M+F | 19    | 0.70 (0.40–1.10) | age, alc, diab, edu, mar, race, res, sex, smok |
|                                             |      | Never    |         |     | 20    | 0.60 (0.30–1.40) | age, alc, diab, edu, mar, race, res, sex, smok |
|                                             |      | Snuff    | Ever    | Any | 21    | 0.60 (0.30–1.10) | age, alc, diab, edu, mar, race, res, sex, smok |
|                                             |      | Never    |         |     | 22    | 0.50 (0.10–1.50) | age, alc, diab, edu, mar, race, res, sex, smok |
|                                             |      | ST       | Ever    | Any | 23    | 0.65 (0.43–0.97) | age, alc, diab, edu, mar, race, res, sex, smok |
|                                             |      | Never    |         |     | 24    | 0.57 (0.29–1.11) | age, alc, diab, edu, mar, race, res, sex, smok |

aFuller details of the studies are given in Tables 1 and 2.
bST implies smokeless tobacco unspecified, or combined snuff use or chewing.
cEver, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
d‘Id.’ is the RR/OR identification number used in Table 10, and ‘Cases’ is the number of cases in ST users as defined. NA = not available.
eNA = not available.
fAbbreviations used: alc = alcohol consumption, bmi = body mass index, diab = diabetes, edu = education, mar = marital status, res = area of residence, smok = smoking.
gThe population included < 0.5% females.
hRR/OR and/or 95% CI estimated from data provided in the source.
iIncludes long-term (10+ years) quitters.
jPersonal communication from Dr Muscat. The estimate given in the source of 3.60 (1.00–12.80) is for noncurrent smokers.
kEstimates are for never cigarette smokers with adjustment for other tobacco use.
IRR/OR and/or 95% CI estimated from data provided in the source assuming that no one both chewed and used snuff.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.
Table 10: Pancreatic cancer; meta-analysis results

| Type of ST (region) | Adjustments/restrictions | Number of estimates (RR/OR ids) | Random-effects RR/OR (95% CI) | Heterogeneity |
|---------------------|--------------------------|---------------------------------|--------------------------------|---------------|
|                     |                          |                                 | $\chi^2$ | $I^2$ | $P(\chi^2)$ |
| Any (overall data)  |                          | 7 (1, 5, 7, 11, 17, 18, 23)    | $1.00$ (0.68–1.47) | 18.5 | 67.5 | 0.005 |
| Smoking-adjusted    |                          | 7 (1, 5, 7, 11, 17, 18, 23)    | $1.07$ (0.71–1.60) | 21.2 | 71.7 | 0.002 |
| Never smokers       |                          | 5 (6, 10, 16, 18, 24)          | $1.23$ (0.66–2.31) | 10.7 | 62.7 | 0.030 |
| Any (USA)           |                          | 5 (1, 11, 17, 18, 23)          | $0.86$ (0.47–1.57) | 10.2 | 61.0 | 0.037 |
| Smoking-adjusted    |                          | 5 (1, 11, 16, 18, 23)          | $0.99$ (0.51–1.91) | 13.8 | 71.0 | 0.008 |
| Never smokers       |                          | 3 (16, 18, 24)                 | $1.09$ (0.44–2.67) | 5.4  | 63.0 | 0.067 |
| Snuff (Scandinavia) |                          | 2 (5, 7)                       | $1.20$ (0.66–2.20) | 6.3  | 84.1 | 0.012 |
| Smoking-adjusted    |                          | 2 (5, 7)                       | $1.20$ (0.66–2.20) | 6.3  | 84.1 | 0.012 |
| Never smokers       |                          | 2 (6, 10)                      | $1.61$ (0.77–3.34) | 1.5  | 33.2 | 0.221 |

- For each study/sex, the RR/OR for ST from Table 9 was included if available, otherwise that for chewing tobacco or snuff was used.
- Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
- The actual estimates included are identified by their RR/OR identification numbers as given in Table 9.

CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Figure 5
Smokeless tobacco and pancreatic cancer by region (smoking-adjusted data). The seven individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 9 for further details relating to the estimates, and Table 10 for fuller details of the meta-analyses.
and CPS-II [23] show no relationship, CPS-I [23] a weak, but significant, positive relationship, and the case-control study of Sterling et al. [89] a significant negative relationship. Overall, the combined estimate (see Table 12 and Figure 6), all based on smoking-adjusted data, is 0.86 (0.59–1.25, n = 5), with significant evidence of heterogeneity (P = 0.002). The analysis for never smokers removes the case-control study and eliminates the heterogeneity. However the combined estimate of 1.14 (0.99–1.33, n = 4) remains non-significant.

More data are needed before any conclusion can be drawn for these cancers.

### Table 11: Other cancers of the digestive system; individual effect (relative risk/odds ratio) estimates

| Source | ST use | Type | Exposure | Smoking | Sex | Id. | Cases | Estimate (95%CI) | Adjustment factors |
|--------|--------|------|----------|---------|-----|-----|-------|-----------------|--------------------|
| **Cohort studies** | | | | | | | | |
| US Veterans: Heineman et al. 1995 [18] | ST | Ever | Never | M | 1 | 39 | 1.20 (0.90–1.70) | age, sed, ses, time, yriv |
| - colon cancer | | | | | | | | |
| US Veterans: Winn et al. 1982 [19] | ST | Ever | Never | M | 2 | 17 | 1.90 (1.20–3.10) | age |
| - liver cancer | | | | | | | | |
| NHANES I: Accortt et al. 2005 [22] | ST | Ever | Never | M | 3 | NA | 2.81 (NA) | age |
| - digestive cancer | | | | | | | | |
| CPS-I: Henley et al. 2005 [23] | ST | Current | Never | M | 6 | 153 | 1.26 (1.05–1.52) | age, alc, asp, bmi, diet, edu, exer, occ, race |
| - digestive cancer | | | | | | | | |
| CPS-II: Henley et al. 2005 [23] | ST | Current | Never | M | 7 | 48 | 1.04 (0.77–1.38) | age, alc, asp, bmi, diet, edu, exer, occ, race |
| - digestive cancer | | | | | | | | |
| Former | | | | | | | | |
| Ever | | | | | | | | |
| **Case-control studies** | | | | | | | | |
| Bjelke 1974 [52] USA | Chew | Use | Any | NA | 10 | NA | No association | NA |
| - colorectal cancer | | | | | | | | |
| Bjelke 1974 [52] Norway | Chew | Use | Any | NA | 11 | NA | No association | NA |
| - colorectal cancer | | | | | | | | |
| Williams and Horm 1977 [55] | ST | Ever | Any | M | 12 | 2 | 3.11 (0.65–14.8) | age, race, smok |
| - small intestine cancer | | | | | | | | |
| ST | Ever | Any | M | 13 | 30 | 1.36 (0.90–2.07) | age, race, smok |
| - colorectal cancer | | | | | | | | |
| ST | Ever | Any | M | 14 | 7 | 1.28 (0.58–2.87) | age, race, smok |
| - rectal cancer | | | | | | | | |
| ST | Ever | Any | M | 15 | 13 | 0.75 (0.42–1.35) | age, race, smok |
| - liver cancer | | | | | | | | |
| ST | Ever | Any | M | 16 | 2 | 0.87 (0.21–3.62) | none |
| - gall bladder cancer | | | | | | | | |
| Sterling et al. 1992 [89] | ST | Ever | Any | M | 17 | 1 | 0.58 (0.08–4.39) | none |
| - digestive cancer | | | | | | | | |
| ST | Ever | Any | M | 18 | 1 | 0.41 (0.05–3.04) | none |
| Chow et al. 1994 [93] | Chew | Use | Any | M | 19 | 555 | 0.40 (0.24–0.69) | age, alc, occ, race, sex, smok |
| - bile duct cancer | | | | | | | | |
| **Notes:** | | | | | | | | |
| aFuller details of the studies are given in Tables 1 and 2. | | | | | | | |
| bST implies smokeless tobacco unspecified, or combined snuff use or chewing. | | | | | | | |
| cEver, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use. | | | | | | | |
| dNA = not available. | | | | | | | |
| e‘Id.’ is the RR/OR identification number used in Table 12, and ‘Cases’ is the number of cases in ST users as defined. NA = not available. | | | | | | | |
| fAbbreviations used: alc = alcohol, asp = aspirin, bmi = body mass index, edu = education, exer = exercise, occ = occupation, pov = poverty, sed = sedentary lifestyle, ses = socioeconomic status, smok = smoking, yriv = year of interview, NA = not available. | | | | | | | |
| gThe population included < 0.5% females. | | | | | | | |
| hRR/OR and/or 95% CI estimated from data provided in the source. | | | | | | | |
| iResults are for cancer of ampulla of Vater; extrahepatic bile duct cancers were also studied, but results were not given for chewing. CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk. | | | | | | |
The data shown in Table 13 are quite limited. The evidence for nasal cancer is based on only three studies, none reporting a significant association with ST use. Seven studies investigated the relationship of ST to larynx cancer, two providing no effect estimates and merely reporting a lack of association. Control for confounding variables is very limited, with only two studies providing estimates adjusted for smoking, only one adjusting for alcohol and no study presenting any results for never smokers. The only study to adjust for smoking and alcohol [102], which shows no relationship of snuff to risk of larynx cancer, is the only study conducted in Scandinavia. Two US studies [55,56] report a significant relationship, however, and, as shown in Table 14 (see also Figure 7), an association is seen in the overall data (1.43, 1.08–1.89, n = 5).

Given the independent role of smoking and alcohol in larynx cancer [7,8], and the lack of association in the one study that has adjusted for both these factors [102], any independent association of ST use with larynx cancer risk has not been established. More data are needed before any conclusion can be drawn on the role of ST in larynx and nasal cancers.

### Table 12: Overall digestive cancer; meta-analysis results

| Type of ST (region)a | Adjustments/restrictionsb | Number of estimates (RR/OR ids)c | Random-effects RR/OR (95% CI) | Heterogeneity |
|----------------------|---------------------------|---------------------------------|-----------------------------|---------------|
| Any (USA)d         | Overall data              | 5 (4, 5, 6, 9, 19)              | 0.86 (0.59–1.25)            | 17.3 76.9 0.002 |
|                     | Smoking-adjusted          | 5 (4, 5, 6, 9, 19)              | 0.86 (0.59–1.25)            | 17.3 76.9 0.002 |
|                     | Never smokers             | 4 (4, 5, 6, 9)                 | 1.14 (0.99–1.33)            | 3.1 2.1 0.382 |

a For each study/sex, the RR/OR for ST from Table 11 was included if available, otherwise that for chewing tobacco or snuff was used.

b Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.

c The actual estimates included are identified by their RR/OR identification numbers as given in Table 11.

d All the available data for overall digestive cancer are from US studies.

CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

### Figure 6

Smokeless tobacco and overall digestive cancer (USA smoking-adjusted data). The five individual relative risk (RR) and 95% confidence interval (CI) estimates, all smoking-adjusted and for the USA, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown is the combined estimate, derived by random-effects meta-analysis. This is represented by a diamond of standard height, with the width indicating the 95% CI. See Table 11 for further details relating to the estimates, and Table 12 for fuller details of the meta-analysis.
Lung cancer

Table 15 summarises data from six cohort and three case-control studies. The case-control studies provide only estimates for smokers and non-smokers combined, and only one of these is adjusted for smoking. The cohort studies all provide estimates for never smokers, with two also giving smoking-adjusted results for the overall population. The meta-analyses (see Table 16 and Figure 8) show no evidence that ST use increases risk of lung cancer, with the combined estimate for smoking-adjusted data 0.99 (95% CI 0.71–1.37). However, there is considerable heterogeneity (P < 0.001), the major contributors to this being the high RR of 6.80 (1.60–28.5) in never smokers in NHANES I [22], the significant increase of 1.77 (1.14–2.74) from CPS-II [23], and the low RR of 0.70 (0.60–0.70) for the Swedish construction workers study [32]. While the combined estimate for never smokers for any ST use is greater than 1.0 (1.34, 0.80–2.23, n = 5), it is not statistically significant.

While the data have unexplained heterogeneity, they do not provide any clear indication of a relationship of lung cancer to ST use.

Not included in Table 15 are results from an analysis conducted by Henley et al. in 2007 [25] based on follow-up of the CPS-II cohort from 1982 to 2002. They report an increased risk of lung cancer (1.46, 1.24–1.73) in men who switched from cigarette smoking to ST compared with those who quit entirely, after adjusting for age, other demographic variables, as well as variables associated with smoking history. This analysis may be biased by reliance on tobacco use data recorded in 1982, and by residual confounding, with the paper reporting...
Table 14: Larynx and nasal cancer; meta-analysis results

| Type of ST (region)\(^d\) | Adjustments/restrictions\(^b\) | Number of estimates (RR/OR ids)\(^c\) | Random-effects RR/OR (95% CI) | Heterogeneity |
|---------------------------|---------------------------------|--------------------------------------|-----------------------------|---------------|
| Larynx cancer\(^d\)      |                                 |                                      |                             |               |
| Any Overall data         | 5 (2, 3, 6, 12, 16)             | 1.43 (1.08–1.89)                     | 4.8                         | 17.4          | 0.304          |
| Smoking-adjusted         | 2 (3, 16)                       | 1.34 (0.61–2.95)                     | 4.0                         | 75.3          | 0.044          |
| Any (USA) Overall data   | 4 (2, 3, 6, 12)                 | 1.56 (1.21–2.00)                     | 1.7                         | 0             | 0.646          |
| Smoking-adjusted         | 1 (3)                           | 2.01 (1.15–3.51)                     | –                           | –             | –              |
| Snuff (Scandinavia)      | Overall data                    | 1 (16)                               | 0.90 (0.50–1.50)            | –             | –              |
| Smoking-adjusted         | 1 (16)                          | 0.90 (0.50–1.50)                     | –                           | –             | –              |
| Nasal cancer\(^e\)       | Overall data                    | 2 (10, 11)                           | 1.14 (0.73–1.77)            | 0.9           | 0             | 0.339          |

\(^a\)For each study/sex, the RR/OR for ST from Table 13 was included if available, otherwise that for chewing tobacco or snuff was used.
\(^b\)Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
\(^c\)The actual estimates included are identified by their RR/OR identification numbers as given in Table 13.
\(^d\)For larynx cancer there are no data for never smokers.
\(^e\)For nasal cancer the only data are from US studies and not smoking-adjusted.

CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Figure 7
Smokeless tobacco and larynx cancer by region (overall data). The five individual relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 13 for further details relating to the estimates, and Table 14 for fuller details of the meta-analyses. Only estimates 3 and 16 are smoking adjusted.
marked differences between switchers and quitters in a range of characteristics, with adjustment substantially reducing the RR estimate from the age-adjusted estimate of 1.92 (1.63–3.26).

Prostate cancer

Table 17 presents data from five cohort and two case-control studies, all conducted in the USA. No significant association between ST and prostate cancer is evident in five studies, but significant increases are seen in the Lutheran Brotherhood Study [11] and, for current snuff users only, in the case-control study by Hayes et al. [96]. Based on the five studies which provide usable data, the overall estimate (see Table 18 and Figure 9) is 1.20 (95% CI 1.03–1.40).

Table 15: Lung cancer; individual effect (relative risk/odds ratio) estimates

| Source | Type | Exposure | Smoking | Sex | Id. | Cases | Estimate (95%CI) | Adjustment factors |
|--------|------|----------|---------|-----|-----|-------|-----------------|-------------------|
| US Veterans: Winn et al. 1982 [19] | ST | Ever | Never | M | 1 | NA | 0.60 (NA) | age |
| NHANES I: Accortt et al. 2005 [22] | ST | Ever | Never | F | 2 | 4 | 6.80 (1.60–28.5) | age, pov, race |
| CPS-I: Henley et al. 2005 [23] | ST | Current | Never | M | 3 | 18 | 1.08 (0.64–1.83) | age, alc, asp, bmi, diet, edu, exer, occ, race |
| CPS-II: Henley et al. 2005 [23] | ST | Current | Never | M | 4 | 18 | 2.00 (1.23–3.24) | age, alc, asp, bmi, diet, edu, exer, occ, race |
| Norwegian cohorts: Boffetta et al. 2005 [26] | ST | Ever | Never | M | 5 | 4 | 1.17 (0.43–3.14) | age, pov |
| | ST | Former | Never | M | 6 | 22 | 1.77 (1.14–2.74) | age, pov, race |
| | Snuff only | Current | Never | M | 7 | 12 | 1.97 (1.10–3.54) | age, pov, race |
| | Current | Any | M | 8 | 2 | 2.08 (0.51–8.46) | age, pov |
| Swedish construction workers: Luo et al. 2007 [32] | Snuff | Ever | Any | M | 9 | 44 | 0.80 (0.58–1.11) | age, pov |
| | | Current | Never | M | 10 | 28 | 0.80 (0.54–1.19) | age, pov |
| | | Former | Never | M | 11 | 72 | 0.80 (0.61–1.05) | age, pov |
| | | Ever | Never | M | 12 | 3 | 0.96 (0.26–3.56) | age, pov |
| Case-control studies | Chew | Ever | Any | M | 13 | NA | 0.70 (0.60–0.70) | age, pov |
| Doll and Hill 1952 [38] | Snuff | Ever | Any | M | 14 | 15 | 0.80 (0.40–1.30) | age, pov |
| | | Former | Never | M | 15 | 3 | 0.90 (0.30–3.00) | age, pov |
| | | Ever | Never | M | 16 | 18 | 0.80 (0.50–1.30) | age, pov |
| Williams and Horm 1977 [55] | ST | Ever | Any | M | 17 | 40 | 0.61 (0.41–0.92) | none |
| | | Former | Never | M | 18 | 33 | 0.76 (0.48–1.21) | none |
| | ST | Ever | Any | M | 19 | 73 | 0.66 (0.41–0.90) | age, race, pov |
| | F | | | | 20 | 36 | 0.69 (0.47–1.00) | age, pov |
| Wynder and Stellman 1977 [56] | Chew | Ever | F | | 21 | 1 | 0.38 (0.05–2.80) | none |
| | Snuff | Ever | M | 22 | 117 | 1.26 (0.99–1.59) | none |
| | ST | None | | | 23 | 35 | 1.25 (0.83–1.89) | none |

*aFuller details of the studies are given in Tables 1 and 2.

*bST implies smokeless tobacco unspecified, or combined snuff use or chewing.

*cEver, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.

*dId. is the RR/OR identification number used in Table 16, and 'Cases' is the number of cases in ST users as defined. NA = not available.

*eNA = not available.

*fAbbreviations used: alc = alcohol consumption, asp = aspirin, bmi = body mass index, edu = education, exer = exercise, occ = occupation, pov = poverty, smok = smoking.

*gThe population included < 0.5% females.

*hRR/OR and/or 95% CI estimated from data provided in the source.

CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.
Table 16: Lung cancer; meta-analysis results

| Type of ST (region) | Adjustments/restrictions | Number of estimates (RR/OR ids) | Random-effects RR/OR (95% CI) | Heterogeneity |
|--------------------|--------------------------|---------------------------------|-------------------------------|---------------|
| Any                | Overall data             | 9 (2, 3, 6, 11, 13, 19, 20, 21, 24) | 0.96 (0.73–1.27)               | 53.2 85.0 < 0.001 |
|                    | Smoking-adjusted         | 6 (2, 3, 6, 11, 13, 20)         | 0.99 (0.71–1.37)              | 28.7 82.6 < 0.001 |
|                    | Never smokers            | 5 (2, 3, 6, 12, 16)             | 1.34 (0.80–2.23)              | 11.5 65.3 0.021 |
| Any (USA)          | Overall data             | 6 (2, 3, 6, 20, 21, 24)         | 1.22 (0.82–1.83)              | 18.5 73.0 0.002 |
|                    | Smoking-adjusted         | 4 (2, 3, 6, 20)                 | 1.38 (0.72–2.64)              | 16.5 81.9 0.001 |
|                    | Never smokers            | 3 (2, 3, 6)                     | 1.79 (0.91–3.51)              | 6.2 67.8 0.045 |
| Snuff (Scandinavia)| Overall data             | 2 (11, 13)                      | 0.71 (0.66–0.76)              | 0.9 0.0 0.354  |
|                    | Smoking-adjusted         | 2 (11, 13)                      | 0.71 (0.66–0.76)              | 0.9 0.0 0.354  |
|                    | Never smokers            | 2 (12, 16)                      | 0.82 (0.52–1.28)              | 0.1 0.0 0.798  |

*aFor each study/sex, the RR/OR for ST from Table 15 was included if available, otherwise that for chewing tobacco or snuff was used.

*bSmoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.

*cThe actual estimates included are identified by their RR/OR identification numbers as given in Table 15.

*dTest for publication bias 0.05 ≤ P < 0.1.

CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Figure 8
Smokeless tobacco and lung cancer by region (smoking-adjusted data). The six individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 15 for further details relating to the estimates, and Table 16 for fuller details of the meta-analyses.
Table 17: Prostate cancer; individual effect (relative risk/odds ratio) estimates

| Source                     | ST use | RR/OR          |
|----------------------------|--------|----------------|
|                            | Type   | Exposition     | Id. | Estimate (95%CI) | Adjustment factors |
|                            |        |                | Cases |               |                  |
|                            |        | Smoking        |       |               |                  |
| Cohort studies             |        |                |       |               |                  |
| Lutheran Brotherhood: Hsing et al 1990 [11] | ST     | Ever           | 1    | 38             | 1.51 (1.03–2.19) | age, smok          |
|                            |        | Never          | 2    | 10             | 4.50 (2.10–9.70) | age              |
| US Veterans: Hsing et al 1991 [15] | ST     | Ever           | 3    | 48             | 1.17 (0.88–1.56) | age              |
|                            |        | Never          | 4    | NA             | no association   |                  |
| Iowa cohort: Putnam et al 2000 [20] | ST     | Ever           | 5    | 19             | 1.20 (0.50–3.40) | age, pov, race    |
|                            |        | Any            | 6    | NA             | no association   | age, res, smok   |
| NHANES I: Accortt et al 2005 [22] | ST     | Use            | 7    | NA             | no association   |                  |
| Norway cohorts: IARC Monograph 37 1985 [14] | ST     | Use            | 8    | 14             | 0.56 (0.30–1.06) | none             |
|                            |        | Ever           | 9    | 56             | 1.08 (0.75–1.55) |                  |
|                            |        | Never          | 10   | 70             | 0.91 (0.67–1.25) |                  |
|                            |        | Any            | 11   | 10             | 6.74 (1.47–30.84) |                  |
|                            |        | Former         | 12   | 10             | 0.79 (0.36–1.74) |                  |
|                            |        | Ever           | 13   | 20             | 1.42 (0.75–2.67) |                  |
|                            |        | Smokeless       | 14   | 24             | 0.92 (0.54–1.58) |                  |
|                            |        | Tobacco         | 15   | 66             | 1.03 (0.74–1.43) |                  |
|                            |        | Any            | 16   | 90             | 1.00 (0.75–1.33) |                  |
| Case-control studies       |        |                |       |               |                  |
| Williams and Horm 1977 [55] | ST     | Ever           | 17   | 65             | 1.32 (0.94–1.84) | age, race, smok  |
| Hayes et al 1994 [96]      | Chew   | Current        | 18   | 14             | 0.56 (0.30–1.06) | none             |
|                            |        | Any            | 19   | 56             | 1.08 (0.75–1.55) |                  |
|                            |        | Former         | 20   | 48             | 1.17 (0.88–1.56) | age              |
|                            |        | Ever           | 21   | 10             | 4.50 (2.10–9.70) | age              |

*Fuller details of the studies are given in Tables 1 and 2.
*ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
*Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
*Id.’ is the RR/OR identification number used in Table 18, and ‘Cases’ is the number of cases in ST users as defined. NA = not available.
*Abbreviations used: pov = poverty, res = area of residence, smok = smoking.
*RR/OR and/or 95% CI estimated from data provided in the source.
*RR/OR and/or 95% CI estimated from data provided in the source assuming that no one both chewed and used snuff.
*CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Table 18: Prostate cancer; meta-analysis results

| Type of ST (region) | Adjustments/restrictions | Number of estimates (RR/OR ids) | Random-effects RR/OR (95% CI) | Heterogeneity |
|---------------------|--------------------------|---------------------------------|--------------------------------|---------------|
| Overall             |                          | 5 (1, 3, 5, 7, 16)              | 1.20 (1.03–1.40)               | 3.3 0.0 0.506 |
| Smoking-adjusted    |                          | 4 (1, 3, 5, 7)                  | 1.29 (1.07–1.55)               | 1.2 0.0 0.764 |
| Never smokers       |                          | 3 (2, 3, 5)                     | 1.81 (0.76–4.30)               | 10.5 81.0 0.005 |

*For each study/sex, the RR/OR for ST from Table 17 was included if available, otherwise that for chewing tobacco or snuff was used.
*Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
*The actual estimates included are identified by their RR/OR identification numbers as given in Table 17.
*All the available data for prostate cancer are from US studies.
*CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Bladder cancer

Table 19 summarises data from the Norway cohorts study [26] and from 12 case-control studies. None of the case-control studies were conducted after 1990, and with the exception of two studies in Denmark [43,62], all were carried out in the USA or Canada. The great majority of the estimates are non-significant, and based on 10 smoking-adjusted estimates the overall estimate (see Table 20 and Figure 10) is 0.95 (95% CI 0.71–1.29). However, there is significant heterogeneity due mainly to estimates 8, 12 and 22, which show a positive association, the last two of which are significant, and estimate 31 which shows a significant negative association.

Considered together, the data provide no real evidence of an association between ST and bladder cancer.

Kidney cancer

Table 21 summarises evidence from one cohort and nine case-control studies, none conducted in Sweden. The estimates are generally based on small numbers of cases
using ST, and are variable, with four studies [47,68,73,100] providing a statistically significant OR estimate exceeding 3.0, and other studies (and other estimates from the four studies) showing notably smaller estimates, that are not significant. Most of the meta-analysis estimates shown in Table 22 (see also Figure 11) are elevated, with some evidence of heterogeneity, but none are statistically significant. Based on five smoking-adjusted estimates the overall estimate for any ST use is 1.09 (0.69 – 1.71).

While there is a suggestion of a possible relationship, more data are needed before any firm conclusions can be reached.

**Haematopoietic and lymphoid cancer**

Table 23 summarises evidence from three cohort and seven case-control studies for overall haematopoietic cancer and for specific types. The only report of a significant association is the OR of 4.0 (1.3–12.0) for non-Hodgkin’s lymphoma in the case-control study of Bracci and Holly [112]. However, the combined evidence from the five studies (see Table 24 and Figure 12) for non-Hodgkin’s lymphoma shows no significant relationship (1.20, 0.83–1.75), though there is significant heterogeneity (\( P = 0.01 \)), due mainly to the Bracci and Holly estimate. The evidence for other endpoints – multiple myeloma, Hodgkin’s disease, leukaemia, and overall haematopoietic cancer – is more limited, and does not suggest any relationship with ST use.

**Other cancers**

Table 25 summarises evidence from six cohort and four case-control studies relating to cancers of types not considered in Tables 3 to 24. Most of the results relate to specific cancer types, though some relate to broader groupings, such as genitourinary cancer and smoking-related cancer, which include cancer types considered earlier. Due to the variety of types, and the limited numbers of estimates relating to any one type, no meta-analyses were attempted. One of the studies [109] simply reported a lack of association (with glioma), and the remaining studies provided a total of 24 effect estimates with CI. Six of these are statistically significant. Zahm et al. [81] report an age-adjusted OR of 1.80 (95% CI 1.10–2.90) for soft tissue sarcoma based on a case-control study, though fail to confirm this later using data from the US Veterans Study [17]. The Williams and Horm study [55] provides a smoking-adjusted estimate of 4.18 (2.08–8.43) for cancer of the cervix, no other study giving relevant results. Moore et al. [39], in a study conducted in 1953, report a crude estimate of 2.41 (1.09–5.35) for cancer of the face, again an endpoint not considered by others. Roosaar et al. [35] report an increased risk of smoking-related cancer (1.6, 1.1–2.5) for never

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**Id, Sex, Study name**

| Id, Sex, Study name | Relative Risk | 95% CI       | Relative Risk | 95% CI       |
|---------------------|--------------|--------------|--------------|--------------|
| 1 M Lutheran Brotherhood | 1.51 (1.03, 2.19) |              |              |              |
| 3 M US Veterans     | 1.17 (0.88, 1.56) |              |              |              |
| 5 M NHANES I        | 1.20 (0.50, 3.40) |              |              |              |
| 7 M Williams and Horm 1977 | 1.32 (0.94, 1.84) |              |              |              |
| 16 M Hayes et al 1994 | 1.00 (0.75, 1.33) |              |              |              |

**Figure 9**

**Smokeless tobacco and prostate cancer (USA overall data).** The five individual relative risk (RR) and 95% confidence interval (CI) estimates, all for the USA, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 17 for further details relating to the estimates, and Table 18 for fuller details of the meta-analyses.
## Table 19: Bladder cancer; individual effect (relative risk/odds ratio) estimates

| Source                         | ST use          | Exposure | Smoking | Sex | Cases | Estimate (95%CI) | Adjustment factors |
|-------------------------------|-----------------|----------|---------|-----|-------|------------------|--------------------|
| **Cohort studies**            |                 |          |         |     |       |                  |                    |
| Norway cohorts: Boffetta et al. 2005 [26] | Snuff          | Current | Any     | M   | 40    | 0.72 (0.52–1.06) | age, smok          |
|                               |                 | Former   |         |     |       | 0.98 (0.66–1.47) |                    |
|                               |                 | Ever     |         |     |       | 0.83 (0.62–1.11) |                    |
|                               |                 |          |         |     |       |                  |                    |
| Case-control studies          |                 |          |         |     |       |                  |                    |
| Lockwood 1961 [43]            | ST              | Current  | Never   | M   | 4     | 0.35 (0.07–1.77) | none               |
|                               |                 |          |         |     |       |                  |                    |
| Wynder et al. 1963 [46]       | Chew            | Ever     | Any     | M   | 5     | 1.42 (0.82–2.47) | none               |
|                               | Snuff           |          |         |     | 6     | 0.66 (0.23–1.88) |                    |
|                               | ST              |          |         |     | 7     | 1.21 (0.74–1.98) |                    |
| Dunham et al. 1968 [48]       | ST              | Ever     | Never   | M   | 8     | 2.57 (0.52–12.54) | race               |
|                               |                 |          |         |     | 9     | 0.58 (0.14–2.45) |                    |
| Cole et al. 1971 [51]         | Chew            | Ever     | Any     | M   | 10    | no association  | age                |
|                               | Snuff           |          |         |     | 11    | no association  |                    |
| Williams and Horm 1977 [55]   | ST              | Ever     | Any     | M   | 12    | 1.67 (1.09–2.55) | age, race, smok    |
|                               |                 |          |         |     | 13    | 1.82 (0.11–6.02) | none               |
| Wynder and Stellman 1977 [56] | Chew            | Ever     | Any     | M   | 14    | 0.87 (0.63–1.21) | none               |
|                               | Snuff           |          |         |     | 15    | 0.69 (0.36–1.31) |                    |
|                               | ST              |          |         |     | 16    | 0.82 (0.61–1.10) |                    |
| Howe et al. 1980 [58]         |               | Chew     | Ever    | Any | 17    | NA     | age, smok         |
|                               |                 |          |         |     |       |                  |                    |
| Mommsen and Aagaard 1983 [62] | Chew            | Ever     | Any     | M   | 18    | 1.70 (1.00–2.90) | age, res           |
|                               |                 |          |         |     |       |                  |                    |
| Hartge et al. 1985 [66]       | Chew            | Ever     | Never   | M   | 19    | 1.02 (0.67–1.54) | age, race, res, smok |
|                               | Snuff           |          |         |     | 20    | 0.77 (0.38–1.56) |                    |
|                               | ST              |          |         |     | 21    | 1.14 (0.80–1.61) |                    |
| Kabat et al. 1986 [69]        | Snuff           | Ever     | Never   | F   | 22    | 10.40 (1.07–101.46) | none               |
|                               |                 |          |         |     |       |                  |                    |
| Slattery et al. 1988 [77]     | Chew            | Ever     | Any     | M   | 23    | 0.76 (0.42–1.39) | smok               |
|                               |                 |          |         |     | 24    | 0.36 (0.05–2.82) | none               |
|                               | Snuff           | Ever     | Any     | M   | 25    | 0.92 (0.47–1.82) | smok               |
|                               |                 |          |         |     | 26    | 2.74 (0.45–16.69) |                    |
|                               | ST              | Ever     | Any     | M   | 27    | 0.82 (0.52–1.39) | smok               |
|                               |                 |          |         |     | 28    | 0.86 (0.24–3.07) |                    |
| Burch et al. 1989 [79]        | Chew            | Ever     | Any     | M   | 29    | 0.60 (0.34–1.06) | age, res, smok     |
|                               | Snuff           |          |         |     | 30    | 0.47 (0.21–1.07) |                    |
|                               | ST              |          |         |     | 31    | 0.54 (0.34–0.87) |                    |

* Fuller details of the studies are given in Tables 1 and 2.  
* ST implies smokeless tobacco unspecified, or combined snuff use or chewing.  
* ‘Ever’, ‘former’, and current ST use were compared with never ST use. Use indicates timing not given and comparison is with non use.  
* ‘Id.’ is the RR/OR identification number used in Table 20, and ‘Cases’ is the number of cases in ST users as defined. NA = not available.  
  Abbreviations used: res = area of residence, smok = smoking.  
  RR/OR and/or 95% CI estimated from data provided in the source.  
  RR/OR and/or 95% CI estimated from data provided in the source assuming that no one both chewed and used snuff.  
  Age-adjusted expected number of cases who chewed tobacco was given as 42.3 versus 46 observed.  
  Age-adjusted expected number of cases who used snuff was given as 2.9 versus 3 observed.  
  Estimates were for never cigarette smokers adjusted for other tobacco use.  
  Adjusted for age started to smoke; results adjusted for smoking group, pack years or years stopped are similar.  
  The source paper gave 2.78 (0.38–20.20) which is incorrect based on the numbers in the 2 × 2 table.  
  CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.
### Table 20: Bladder cancer; meta-analysis results

| Type of ST (region) | Adjustments/restrictions | Number of estimates (RR/OR ids) | Random-effects RR/OR (95% CI) | Heterogeneity |
|---------------------|---------------------------|---------------------------------|-------------------------------|---------------|
| Any Overall data    | Smoking-adjusted          | 10 (3, 4, 8, 9, 12, 17, 21, 22, 27, 31) | 0.95 (0.71–1.29) | 22.3 59.6 0.008 |
| Never smokers       |                           | 6 (4, 8, 9, 21, 22, 28)           | 1.10 (0.60–2.02) | 7.7 35.1 0.173 |
| Any (USA) Overall data | Smoking-adjusted        | 9 (7, 8, 9, 12, 13, 16, 21, 22, 27) | 1.11 (0.85–1.45) | 14.8 45.9 0.064 |
| Never smokers       |                           | 5 (8, 9, 21, 22, 28)             | 1.25 (0.69–2.26) | 5.6 29.2 0.227 |
| Snuff (Scandinavia) | Smoking-adjusted         | 1 (3)                           | 0.83 (0.62–1.11) | – – – |

*For each study/sex, the RR/OR for ST from Table 19 was included if available, otherwise that for chewing tobacco or snuff was used.

*Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.

*The actual estimates included are identified by their RR/OR identification numbers as given in Table 19.

*There are no data for never smokers for snuff in Scandinavia.

CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

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**Figure 10**

**Smokeless tobacco and bladder cancer by region (smoking-adjusted data).** The 10 individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 19 for further details relating to the estimates, and Table 20 for fuller details of the meta-analyses.
### Table 21: Kidney cancer; individual effect (relative risk/odds ratio) estimates

| Source a | Type b | Exposure c | Smoking | Sex | Cases d | Estimate (95%CI) | Adjustment factors e |
|----------|--------|------------|---------|-----|---------|------------------|---------------------|
| **Cohort studies** | | | | | | | |
| Norway cohorts: Boffetta et al. 2005 [26] | Snuff | Current | Any | M | 1 | 9 | 0.47 (0.23–0.94) | age, smok |
| | | Former | | | 2 | 13 | 1.17 (0.63–2.16) | |
| | | Ever | | | 3 | 22 | 0.72 (0.44–1.18) | |
| **Case-control studies** | | | | | | | |
| Bennington and Laubscher 1968 [47] | Chew | Use | Any | M | 4 | 5 | 2.22 (0.39–3.85) | none |
| | | Never | | | 5 | 5 | 4.80 (1.18–19.59) | age |
| Armstrong et al. 1976 [53] | ST | Current | Any | M | 6 | 6 | 0.98 (0.30–3.15) | none |
| | | Former | | | 7 | 6 | 0.73 (0.24–2.20) | |
| | | Ever | | | 8 | 12 | 0.84 (0.37–1.92) | |
| Williams and Horm 1977 [55] | ST | Ever | Any | M | 9 | 3 | 0.59 (0.10–2.60) | age, smok |
| | | Never | | | 10 | 1 | 1.26 (0.17–9.33) | |
| McLaughlin et al. 1984 [65] | Chew | Use | Any | M | 11 | NA | 0.40 (0.10–2.60) | age, smok |
| | | Snuff | | | 12 | NA | 1.70 (0.50–6.00) | |
| | | ST | | | 13 | NA | 1.00 (0.37–2.68) | |
| Goodman et al. 1986 [68] | Chew | Ever | Any | M | 14 | 13 | 4.00 (1.13–14.17) | age, hosp, race, tadm |
| Asal et al. 1988 [73] | Snuff | Use | Any | M | 15 | NA | 3.60 (1.10–8.70) | age, hosp, race, tadm |
| McLaughlin et al. 1995 [99] | ST | Use | Never | M+F | 17 | 11 | 1.30 (0.60–3.10) | age, bmi, res, sex |
| Muscat et al. 1995 [100] | Chew | Ever | Any | M | 18 | 14 | 3.20 (1.10–8.70) | age, edu |
| Yuan et al. 1998 [106] | ST | Ever | Any | M+F | 19 | 32 | 1.02 (0.56–1.85) | age, edu, smok |

*Fuller details of the studies are given in Tables 1 and 2.

*ST implies smokeless tobacco unspecified, or combined snuff use or chewing.

*Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.

*Id.’ is the RR/OR identification number used in Table 22, and ‘Cases’ is the number of cases in ST users as defined. NA = not available.

*Abbreviations used: bmi = body mass index, edu = education, hosp = hospital, res = residence, smok = smoking, tadm = time of admission.

*RR/OR and/or 95% CI estimated from data provided in the source.

*Estimated assuming ORs for chewing and snuff are independent.

*The authors also report the results of an analysis adjusting for the effects of the matching factors, body mass index, decaffeinated coffee use and continuous pack-years of cigarette smoking. The authors estimated an OR (95% CI) of 0.87 (0.15–5.14) for the effect of chewing among never smokers of cigarettes, and of 26.00 (4.41–153.00) for the joint effect of pack-years cigarette smoking and chewing tobacco use. These results could not readily be incorporated into the meta-analyses as no overall estimate for chewing tobacco use adjusted for cigarette smoking was available.

*Analysis uses hospital controls.

*Analysis uses population controls.

CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

### Table 22: Kidney cancer; meta-analysis results

| Type of ST (region) a | Adjustments/restrictions b | Number of estimates (RR/OR ids) c | Random-effects RR/OR (95% CI) | Heterogeneity |
|-----------------------|-----------------------------|----------------------------------|-------------------------------|---------------|
| Any | Overall data | 11 (3, 4, 8, 9, 10, 13, 14, 15, 17, 18, 19) | 1.23 (0.86–1.76) d | \( \chi^2 \) 15.6 \( \chi^2 \) 39.2 \( P(\chi^2) \) 0.0087 |
| Smoking-adjusted | 5 (3, 5, 13, 17, 19) | 1.09 (0.69–1.71) f | 6.9 \( \chi^2 \) 41.9 \( P(\chi^2) \) 0.142 |
| Never smokers | 2 (5, 17) | 2.19 (0.63–7.70) | 2.5 \( \chi^2 \) 59.6 \( P(\chi^2) \) 0.116 |
| Any (USA) | Overall data | 8 (4, 9, 10, 13, 14, 15, 18, 19) | 1.52 (0.94–2.46) | 11.1 \( \chi^2 \) 37.1 \( P(\chi^2) \) 0.133 |
| Smoking-adjusted | 3 (5, 13, 19) | 1.41 (0.64–3.10) | 4.2 \( \chi^2 \) 51.8 \( P(\chi^2) \) 0.125 |
| Never smokers | 1 (5) | 4.80 (1.18–19.56) | – | – |
| Snuff (Scandinavia) f | Overall data | 1 (3) | 0.72 (0.44–1.18) | – | – |
| Smoking-adjusted | 1 (3) | 0.72 (0.44–1.18) | – | – |

*For each study/sex, the RR/OR for ST from Table 21 was included if available, otherwise that for chewing tobacco or snuff was used.

*Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.

*The actual estimates included are identified by their RR/OR identification numbers as given in Table 21.

*Test for publication bias 0.05 \( \leq P < 0.1 \).

*Test for publication bias 0.01 \( \leq P < 0.05 \).

*There are no available data for never smokers using snuff in Scandinavia.

CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.
smokers, but not in a smoking-adjusted analysis for smoker and non-smokers combined (1.1, 0.8–1.4). Finally, based on the Swedish construction workers study, Odénbro et al. [29,33] report that snuff use is associated with a reduced smoking-adjusted risk of cutaneous squamous cell carcinoma (0.64, 0.44–0.95) and, in never smokers, with a reduced risk of melanoma (0.65, 0.52–0.82). These isolated reports need confirmation in other studies before any effect of ST can reliably be inferred. A study in Cherokee women [125,126] which shows no association of breast cancer with ever ST use, with an odds ratio adjusted for age at diagnosis estimated as 1.24 (0.26–6.02), is not considered in Table 25 as the study is of cross-sectional design. It contributes little to the evidence.

**Overall cancer risk**

As shown in Table 26, ST use has been related to overall cancer risk in five cohort studies and one case-control study. Two of the 12 estimates shown are smoking-adjusted estimates for smokers and non-smokers combined, one (estimate 10) showing no association at all (RR = 1.00) and the other (estimate 12, based on the case-control study [89]) a reduced OR of 0.64 (95% CI 0.53–0.78). The remaining 10 estimates, all from cohort studies, and all adjusted for age and various other potential confounders, are for never smokers. As shown in Table 27 and Figure 13, the combined estimate for all the smoking-adjusted data is not elevated (0.98, 0.84–1.15, n = 7). However, the combined estimate for never smokers, which excludes the low estimate from the case-control study, is a significant 1.10 (1.02–1.19, n = 6). The estimate for never smokers is similar for the US data (1.10, 1.01–1.20, n = 4) and the Scandinavian snuff data (1.10, 0.94–1.29, n = 2). The data are consistent with any excess risk of cancer in ST users being small.

**Publication bias**

There are 49 meta-analyses presented that combine five or more effect estimates. The test of publication bias [121]
shows none to be significant at $P < 0.01$, and two significant at $P < 0.05$, similar to the numbers one would expect by chance. Both the significant cases (see Tables 22 and 24) arise due to a single high effect estimate, with the other estimates included in the analysis relatively close to 1.0.

**Sensitivity analyses**

Table 28 shows the effect on the smoking-adjusted analyses of successively removing those RR/OR estimates with the largest $Q^2$ values. Results are only shown for those cancers where significant ($P < 0.05$) heterogeneity was evident, and removal continues until no significant
Table 24: Non-Hodgkin’s lymphoma; meta-analysis results

| Type of ST (region)  | Adjustments/restrictions | Number of estimates (RR/OR ids) | Random-effects RR/OR (95% CI) | Heterogeneity |
|----------------------|--------------------------|---------------------------------|-------------------------------|---------------|
| **Any**              | Overall data             | 5 (5, 13, 15, 18, 19)          | 1.20 (0.83–1.75)d            |               |
|                      | Smoking-adjusted         | 3 (5, 13, 19)                  | 1.35 (0.62–2.94)             |               |
|                      | Never smokers            | 3 (5, 13, 19)                  | 1.35 (0.62–2.94)             |               |
| **Any (USA)**        | Overall data             | 3 (13, 18, 19)                 | 1.45 (0.81–2.59)             |               |
|                      | Smoking-adjusted         | 2 (13, 19)                     | 2.07 (0.70–6.13)             |               |
|                      | Never smokers            | 2 (13, 19)                     | 2.07 (0.70–6.13)             |               |
| **Snuff (Scandinavia)** | Overall data             | 2 (5, 15)                      | 1.04 (0.54–1.98)             |               |
|                      | Smoking-adjusted         | 1 (5)                          | 0.77 (0.59–1.01)             |               |
|                      | Never smokers            | 1 (5)                          | 0.77 (0.59–1.01)             |               |

*aFor each study/sex, the RR/OR for ST from Table 23 was included if available, otherwise that for chewing tobacco or snuff was used.

*bSmoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.

*cThe actual estimates included are identified by their RR/OR identification numbers as given in Table 23.

*dTest for publication bias 0.01 ≤ P < 0.05.

CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Figure 12
Smokeless tobacco and non-Hodgkin’s lymphoma by region (overall data). The five individual relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 23 for further details relating to the estimates, and Table 24 for fuller details of the meta-analyses. Only estimates 5, 13 and 19 are smoking-adjusted.
### Table 25: Other cancers; individual effect (relative risk/odds ratio) estimates

| Source | ST use | Type | Exposure | Smoking | Sex | Cases | Estimate (95%CI) | Adjustment factors |
|--------|--------|------|----------|---------|-----|-------|------------------|-------------------|
| **Cohort studies** | | | | | | | | |
| US Veterans: Zahm et al. 1992 [17] | ST | Ever | Any | M | 1 | 21 | 0.85 (0.53–1.36) | age, smok, time |
| NHANES I: Accortt et al. 2005 [22] | ST | Ever | Never | F | 2 | 5 | 1.80 (0.50–6.50) | age, pov, race |
| CPS-I: Henley et al. 2005 [23] | ST | Current | Never | M | 3 | 98 | 0.97 (0.77–1.22) | age, alc, asp, bmi, diet, edu, exer, occ, race |
| CPS-II: Henley et al. 2005 [23] | ST | Current | Never | M | 4 | 44 | 1.15 (0.85–1.56) | age, alc, asp, bmi, diet, edu, exer, occ, race |
| Former | 5 | 16 | 0.97 (0.59–1.59) | |
| Ever | 6 | 60 | 1.10 (0.84–1.42) | |
| Swedish construction workers: Odenbro et al. 2005 [29] | Snuff | Ever | Any | M | 7 | 29 | 0.64 (0.44–0.95) | age, smok |
| Swedish construction workers: Odenbro et al. 2007 [33] | Snuff | Ever | Never | M | 8 | 96 | 0.65 (0.52–0.82) | age, bir, bmi |
| Uppsala County: Roosaar et al. 2008 [35] | Snuff | Ever | Any | M | 9 | 71 | 1.10 (0.80–1.40) | age, alc, res, smok, time |
| Never | 10 | 39 | 1.60 (1.10–2.50) | age, alc, res, time |
| **Case-control studies** | | | | | | | | |
| Moore et al. 1953 [39] | ST | Use | Any | M | 11 | 49 | 2.41 (1.09–5.35) | none |
| Williams and Horm 1977 [55] | ST | Ever | Any | F | 12 | 11 | 0.60 (0.31–1.17) | age, smok |
| - cancer of face | ST | Ever | Any | M | 13 | 2 | 0.47 (0.11–1.94) | None |
| - cancer of male genitalia | ST | Ever | Any | F | 14 | 10 | 4.18 (2.08–8.43) | age, smok |
| - cancer of cervix | ST | Ever | Any | F | 15 | 7 | 1.92 (0.86–4.28) | age, smok |
| - cancer of uterus | ST | Ever | Any | F | 16 | 2 | 0.77 (0.19–3.21) | none |
| - cancer of ovary | ST | Ever | Any | F | 17 | 1 | 2.06 (0.28–15.41) | none |
| - cancer of vulva | ST | Ever | Any | M | 18 | 1 | 0.26 (0.04–1.93) | none |
| - connective tissue | ST | Ever | Any | M | 19 | 1 | 0.30 (0.04–2.18) | none |
| - melanoma | ST | Ever | Any | F | 20 | 1 | 0.18 (0.02–1.32) | none |
| - nervous system cancer | ST | Ever | Any | F | 21 | 2 | 3.28 (0.77–13.99) | none |
| - thyroid cancer | ST | Ever | Any | M | 22 | 1 | 0.36 (0.05–2.69) | none |
| F | 23 | 1 | 0.73 (0.10–5.38) | |
| Zahm et al. 1989 [81] | ST | Ever | Any | M | 24 | 28 | 1.80 (1.10–2.90) | Age |
| Zheng et al. 2001 [109] | Chew | Use | Any | M+F | 25 | NA | no association | NA |
| - brain cancer (glioma) | Snuff | Use | Any | M+F | 26 | NA | no association | NA |

aFuller details of the studies are given in Tables 1 and 2.
bST implies smokeless tobacco unspecified, or combined snuff use or chewing.
cEver, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
d‘Id.’ is the RR/OR identification number, and ‘Cases’ is the number of cases in ST users as defined. NA = not available.
eAbbreviations used: alc = alcohol, asp = aspirin, bir = birth cohort, bmi = body mass index, edu = education, exer = exercise, occ = occupation, pov = poverty, res = area of residence, smok = smoking. NA = not available.
fThe population included < 0.5% females.
gRR/OR and/or 95% CI estimated from data provided in the source.
hIncluding melanoma in situ
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.
### Table 26: Overall cancer; individual effect (relative risk/odds ratio) estimates

| Sourcea | Typeb | Exposurec | Smokings | Sex | Cases | Id. | Estimate (95%CI)d | Adjustment factorse |
|---------|-------|-----------|----------|-----|-------|-----|-------------------|--------------------|
| NHANES I: Accort et al. 2005 [22] | ST | Ever | Never | M | 1 | 38 | 0.80 (0.40–1.60) | age, pov, race |
| | | F | 2 | 26 | 1.20 (0.70–2.10) | age, pov, race |
| CPS-I: Henley et al. 2005 [23] | ST | Current | Never | M | 3 | 357 | 1.07 (0.95–1.20) | age, alc, asp, bmi, diet, edu, exer, occ, race |
| | | ST Former | 5 | | 57 | 1.04 (0.80–1.36) | age, pov, race |
| | | ST Ever | 6 | | 219 | 1.15 (1.00–1.32) | age, pov, race |
| | | Chew only | Current | | 7 | 113 | 1.23 (1.02–1.49) | age, pov, race |
| | | Snuff only | Current | | 8 | 14 | 0.93 (0.55–1.57) | age, pov, race |
| | | ST Ever | 4 | | 162 | 1.19 (1.02–1.40) | age, alc, asp, bmi, diet, edu, exer, occ, race |
| Swedish construction workers: Bolinder et al. 1994 [28] | Snuff | Current | Never | M | 9 | 57 | 1.10 (0.90–1.40) | age, res |
| | | Snuff | Ever | Any | M | 10 | 237 | 1.00 (0.87–1.15) | age, alc, res, smok, time |
| | | Snuff | Never | 11 | 138 | 1.10 (0.90–1.40) | age, alc, res, time |
| Uppsala County: Roosaar et al. 2008 [35] | Snuff | Ever Any | M+F | 12 | 2,498 | 0.64 (0.53–0.78) | age, alc, occ, race, sex, smok |

aFuller details of the studies are given in Tables 1 and 2.
bST implies smokeless tobacco unspecified, or combined snuff use or chewing.
cEver, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
d‘Id.’ is the RR/OR identification number used in Table 27, and ‘Cases’ is the number of cases in ST users as defined.
eAbbreviations used: alc = alcohol, asp = aspirin, bmi = body mass index, edu = education, exer = exercise, occ = occupation, pov = poverty, res = area of residence, smok = smoking.
fRR/OR and/or 95% CI estimated from data provided in the source.
gNumber of cases estimated from data provided in the source.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

### Table 27: Overall cancer; meta-analysis results

| Type of ST (region)a | Adjustments/restrictionsb | Number of estimates (RR/OR ids)c | Random-effects RR/OR (95% CI) | Heterogeneity |
|---------------------|---------------------------|---------------------------------|------------------------------|---------------|
| Any Overall data    | 7 (1, 2, 3, 6, 9, 10, 12) | 0.98 (0.84–1.15)                 | 27.1 77.9 < 0.001            |
| Smoking-adjusted    | 7 (1, 2, 3, 6, 9, 10, 12) | 0.98 (0.84–1.15)                 | 27.1 77.9 < 0.001            |
| Never smokers       | 6 (1, 2, 3, 6, 9, 11)     | 1.10 (1.02–1.19)                 | 1.5 0.0 0.911               |
| Any (USA) Overall data | 5 (1, 2, 3, 6, 12)    | 0.95 (0.74–1.22)                 | 26.5 84.9 < 0.001            |
| Smoking-adjusted    | 5 (1, 2, 3, 6, 12)       | 0.95 (0.74–1.22)                 | 26.5 84.9 < 0.001            |
| Never smokers       | 4 (1, 2, 3, 6)           | 1.10 (1.01–1.20)                 | 1.5 0.0 0.679               |
| Snuff (Scandinavia) Overall data | 2 (9, 10)    | 1.03 (0.91–1.16)                 | 0.5 0.0 0.475               |
| Smoking-adjusted    | 2 (9, 10)                | 1.03 (0.91–1.16)                 | 0.5 0.0 0.475               |
| Never smokers       | 2 (9, 11)                | 1.10 (0.94–1.29)                 | 0.0 0.0 1.000               |

aFor each study/sex, the RR/OR for ST from Table 26 was included if available, otherwise that for chewing tobacco or snuff was used.
bSmoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
cThe actual estimates included are identified by their RR/OR identification numbers as given in Table 26.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.
heterogeneity is seen. For pancreatic, lung and bladder cancer and for non-Hodgkin’s lymphoma, only relatively high estimates are removed, and the random-effects estimate decreased, though only for lung cancer was the estimate now significantly below 1.0. For digestive cancer, the effect is to increase the estimate, but the significance is unchanged. For overall cancer, the effect is also to increase the estimate, here to marginal significance, 1.07 (1.00–1.15). For oropharyngeal cancer, the original substantial heterogeneity (P < 0.001) is seen to be due mainly to four estimates, three high and one low. The excess decreases from a significant 1.36 (1.04–1.77) to a non-significant 1.17 (0.95–1.45) after the removal of these estimates.

Similar analyses for the overall data (not shown) were also carried out. They also did not help to demonstrate any clear effect of ST on risk. For oropharyngeal cancer, where heterogeneity is very marked indeed, this is mainly due to estimates with atypically high values (see particularly Table 3 id. numbers 1, 15, 21, 22, 34 and 35).

Table 29 compares the smoking-adjusted meta-analysis estimates reported earlier with those recalculated preferring, where there was a choice, estimates for current ST use to those for ever use or unspecified ST use. The meta-analyses for the 12 cancers considered are based on a total of 83 effect estimates. In only 19 of these (23%) did the change in order of preference affect the estimate chosen. For 10 of these the estimate for current ST use is higher than that for ever use or unspecified ST use, for eight it is lower, and for the other the two estimates are the same. The largest change is for pancreatic cancer in the Swedish construction workers study [32], where the selected RR value increases from 0.90 (0.70–1.20) in the original analysis to 2.10 (1.20–3.60) in the sensitivity analysis. However most of the changes, in either direction, are quite minor.

Figure 13
Smokeless tobacco and overall cancer by region (smoking-adjusted data). The seven individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 26 for further details relating to the estimates, and Table 27 for fuller details of the meta-analyses.
For 8 of the 12 cancers, the change to the meta-analysis estimate from the altered preference is very small, by ± 0.02 at most. For oropharyngeal cancer it increases by 0.06, for larynx cancer by 0.11, for lung cancer by 0.12 and for pancreatic cancer 0.15. None of these changes materially affect the significance or the interpretation. Although there is perhaps a slight indication that associations may be stronger for current use, the tendency of most studies to report results only for ever or unspecified ST use limits the extent to which this can be investigated. Changing preferences did not materially affect the heterogeneity of the estimates. The effect of similarly changing the preference on the other meta-analyses shown earlier (for example, for never smokers or by country) also did not materially affect the results obtained (data not shown).

Meta-regression analyses
For oropharyngeal cancer, based on the 19 smoking-adjusted estimates, where the deviance (heterogeneity \( \chi^2 \)) is 69.5 \((P < 0.001)\), significant reductions in deviance in ‘one factor at a time’ analysis are seen for period by study type \((P < 0.001, \) drop in deviance 46.7 on 2 d.f.), sex \((P = 0.020, \) drop 26.9 on 2 d.f.) and region \((P = 0.014, \) drop 21.3 on 1 d.f.). However, the tendency for estimates to be high in females and the USA was no longer significant after adjustment for period by study type, this relationship reflecting the tendency for estimates to be high in case-control studies published before 1990, low in case-control studies published after 1990, and intermediate in prospective studies (see Figure 2).

Based on the 41 overall estimates (whether smoking-adjusted or not) for oropharyngeal cancer, where the deviance is 335.6 \((P < 0.001)\), the most significant factor is sex \((P = 0.004, \) drop 83.4 on 2 d.f.). Though drops in deviance of 20 or more are also seen for region, period by study type and smoking status, with estimates high for females, USA, old case-control studies and data unadjusted for smoking, no other factor is significant at \(P < 0.05\) after adjustment for sex. The high deviance of 335.6 is clearly due to very high \(Q^2\) values for some estimates, and further analyses were run excluding these estimates (ids 1, 7, 21, 22 and 34 in Table 3). This reduces the deviance considerably, to 84.4, though it is still highly significant \((P < 0.001)\). However, again sex was the most significant factor \((P = 0.02)\), with no further factor significant at \(P < 0.05\) after adjusting for sex.

Meta-regression analyses were not attempted for larynx, nasal or prostate cancer or for overall digestive cancer or...
Table 29: Further sensitivity analyses for smoking-adjusted data. Effect of preferring estimates for current smokeless tobacco use to those for ever or unspecified smokeless tobacco use

| Cancer                  | Analysis* | N (nc) | Random-effects RR/OR (95% CI) | Heterogeneity | \(\chi^2\) | P     |
|-------------------------|-----------|--------|-------------------------------|---------------|-----------|-------|
| Oropharyngeal           | Table 4   | 19     | 1.36 (1.04–1.77)              |               | 69.5      | < 0.001|
|                         | Sensitivity | (5)    | 1.42 (1.10–1.84)              |               | 51.1      | < 0.001|
| Oesophageal             | Table 6   | 7      | 1.13 (0.95–1.36)              |               | 4.4       | 0.623 |
|                         | Sensitivity | (2)    | 1.11 (0.92–1.34)              |               | 4.1       | 0.665 |
| Stomach                 | Table 8   | 8      | 1.03 (0.88–1.20)              |               | 10.3      | 0.173 |
|                         | Sensitivity | (2)    | 1.01 (0.86–1.19)              |               | 10.4      | 0.165 |
| Pancreatic              | Table 10  | 7      | 1.07 (0.71–1.60)              |               | 21.5      | < 0.001|
|                         | Sensitivity | (2)    | 1.22 (0.75–2.01)              |               | 23.1      | < 0.001|
| Overall digestive       | Table 12  | 5      | 0.86 (0.59–1.25)              |               | 17.3      | 0.002 |
|                         | Sensitivity | (1)    | 0.85 (0.57–1.27)              |               | 17.3      | 0.002 |
| Larynx                  | Table 14  | 2      | 1.34 (0.61–2.95)              |               | 4.0       | 0.044 |
|                         | Sensitivity | (1)    | 1.45 (0.73–2.88)              |               | 2.5       | 0.116 |
| Lung                    | Table 16  | 6      | 0.99 (0.71–1.37)              |               | 28.7      | < 0.001|
|                         | Sensitivity | (3)    | 1.11 (0.73–1.69)              |               | 20.6      | < 0.001|
| Prostate                | Table 18  | 4      | 1.29 (1.07–1.55)              |               | 1.2       | 0.764 |
|                         | Sensitivity | (0)    |                                |               |           |       |
| Bladder                 | Table 20  | 10     | 0.95 (0.71–1.29)              |               | 22.3      | 0.008 |
|                         | Sensitivity | (1)    | 0.94 (0.68–1.29)              |               | 23.7      | 0.005 |
| Kidney                  | Table 22  | 5      | 1.09 (0.69–1.71)              |               | 6.9       | 0.142 |
|                         | Sensitivity | (1)    | 1.07 (0.60–1.91)              |               | 9.6       | 0.048 |
| Non-Hodgkin’s lymphoma   | Table 24  | 3      | 1.35 (0.62–2.94)              |               | 9.5       | 0.009 |
|                         | Sensitivity | (0)    |                                |               |           |       |
| Overall                 | Table 27  | 7      | 0.98 (0.84–1.15)              |               | 27.1      | < 0.001|
|                         | Sensitivity | (1)    | 0.99 (0.83–1.17)              |               | 27.9      | < 0.001|

*For each cancer the first line repeats the original results preferring ever or unspecified ST use shown in the Table indicated, while the second line presents the results of the sensitivity analysis preferring current ST use.

N is the number of estimates included in the original and sensitivity analyses; nc is the number of changed estimates. For each cancer, the identification numbers for the estimates (shown in the Table indicated) included in the sensitivity analysis are shown below, with those not used in the original analysis in italic.

Oropharyngeal (Table 3): 2, 3, 4, 8, 11, 13, 18, 26, 35, 43, 48, 51, 55, 56, 58, 61, 70, 74, 75
Oesophageal (Table 5): 3, 6, 10, 11, 19, 20, 23
Stomach (Table 7): 1, 4, 7, 10, 14, 17, 19, 21
Pancreatic (Table 9): 1, 3, 8, 11, 16, 18, 23
Overall digestive (Table 11): 4, 5, 6, 7, 19
Larynx (Table 13): 3, 14
Lung (Table 15): 2, 3, 4, 9, 14, 20
Prostate (Table 17): 1, 3, 5, 7
Bladder (Table 19): 1, 4, 8, 9, 12, 17, 21, 22, 27, 31
Kidney (Table 21): 1, 5, 13, 17, 19
Non-Hodgkin's lymphoma (Table 23): 5, 13, 19
Overall cancer (Table 26): 1, 2, 3, 4, 9, 10, 12
CI = confidence interval; OR = odds ratio; RR = relative risk.

non-Hodgkin’s lymphoma because of insufficient numbers of estimates, or for oesophageal, stomach and kidney cancer because of lack of heterogeneity. For pancreatic and bladder cancer, none of the factors investigated significantly (at \(P < 0.05\)) explained the heterogeneity. For overall cancer, study type was significant (\(P = 0.001\)), but this merely reflected the low estimate for the single case-control study, evident...
also in the sensitivity analysis shown in Table 28. For lung cancer, a tendency was noted for never-smoking estimates to be high, significant for both the smoking-adjusted data ($P = 0.025$) and the overall data ($P = 0.029$). This difference reflected the two high estimates already noted in the sensitivity analysis.

**Summary of meta-analyses for ST use in Western populations**

Table 30 brings together all the meta-analysis results for ST use in Western populations. Based on smoking-adjusted data, significant increases ($P < 0.05$) are seen for oropharyngeal cancer, though not based on studies published since 1990, and for prostate cancer, but not for any other cancer considered. For never smokers, significant increases are seen for oropharyngeal cancer (again not when based on studies published since 1990), for oesophageal cancer and also for overall cancer. Compared with the smoking-adjusted estimates, the estimates for never smokers tend to be more variable, due to smaller numbers of ST-exposed cases studied, though they consistently exceed 1.0.

**Summary of meta-analyses for ST use in the USA**

Table 31 similarly brings together the results for ST use in the USA. With the exception of oesophageal cancer in never smokers, significant increases seen in Table 28 are again significant here, with an increase additionally seen in the smoking-adjusted estimate for larynx cancer (although based on only a single study).

**Summary of meta-analyses for snuff use in Scandinavia**

As shown in Table 32, the meta-analyses of results provide overall effect estimates that, with one exception, are never significantly increased and generally are close to 1.0. The exception is for oesophageal cancer, where the marginally significant increased RR seen in relation to snuff use for never-smokers (1.92, 1.00–3.68) derives solely from the Swedish Construction Workers study [34]. In that study, no increase was seen in smoking-adjusted analyses for the whole population (1.00, 0.79–1.27). Unlike the corresponding results for the USA, where meta-analysis estimates are predominantly greater than 1.0, the estimates for snuff as used in Scandinavia are as often below 1.0 as above 1.0. Generally, the results do not suggest that snuff as used in Scandinavia has any adverse effect on cancer risk.

**Dose response data**

Results relating the various cancers to dose of exposure to ST are only reported in a few studies and are not presented in detail here.

For oropharyngeal cancer, eight studies were identified that related risk to extent and/or duration of exposure. In seven of these studies, which all show no overall relationship of ST with risk in Table 3, no significant dose-response relationships are seen. It was only in one study [61], that did show a clear overall relationship, that a significant ($P < 0.001$) trend in risk with increasing duration of exposure is seen, though only for cancers of the gum and buccal mucosa, and not for other mouth and pharynx cancers.

For other cancer sites relatively few studies report dose-response data. In the CPS-II study [23] no trends with duration or frequency are seen for either total or lung cancer, while in the Swedish Construction Workers study no trend is seen for cutaneous squamous cell carcinoma with years of snuff dipping [29] or for oral cancer or lung cancer with daily amount of snuff consumed [32]. A significant trend ($P < 0.01$) is reported with daily amount of snuff consumed

### Table 30: Summary of meta-analyses for smokeless tobacco use in Western populations

| Cancer                        | Overall data | Smoking-adjusted data | Never smokers |
|-------------------------------|-------------|-----------------------|--------------|
|                               | n RR/OR (95% CI) | n RR/OR (95% CI) | n RR/OR (95% CI) |
| Oropharyngeal (Table 4)      | 41 1.79 (1.36–2.36) | 19 1.36 (1.04–1.77) | 9 1.72 (1.01–2.94) |
| - (published since 1990)      | 18 1.28 (0.94–1.76) | 14 1.00 (0.83–1.20) | 7 1.24 (0.80–1.90) |
| Oesophageal (Table 6)         | 10 1.25 (1.03–1.51) | 7 1.13 (0.95–1.36) | 4 1.91 (1.15–3.17) |
| Stomach (Table 8)             | 9 1.03 (0.90–1.19)  | 8 1.03 (0.88–1.20)  | 4 1.27 (0.75–2.13) |
| Pancreatic (Table 10)         | 7 1.00 (0.68–1.47)  | 7 1.07 (0.71–1.60)  | 5 1.23 (0.66–2.31) |
| Any digestive (Table 12)      | 5 0.86 (0.59–1.25)  | 5 0.86 (0.59–1.25)  | 4 1.14 (0.99–1.33) |
| Larynx (Table 14)             | 5 1.43 (1.08–1.89)  | 2 1.34 (0.61–2.95)  | 0  - |
| Lung (Table 16)               | 9 0.96 (0.73–1.27)  | 6 0.99 (0.71–1.37)  | 5 1.34 (0.80–2.23) |
| Prostate (Table 18)           | 5 1.20 (1.03–1.40)  | 4 1.29 (1.07–1.55)  | 3 1.81 (0.76–4.30) |
| Bladder (Table 20)            | 14 1.00 (0.80–1.25) | 10 0.95 (0.71–1.29) | 6 1.10 (0.60–2.02) |
| Kidney (Table 22)             | 11 1.23 (0.86–1.76) | 5 1.09 (0.69–1.71)  | 2 2.19 (0.63–7.70) |
| Non-Hodgkin’s lymphoma (Table 24) | 5 1.20 (0.83–1.75)  | 3 1.35 (0.62–2.95)  | 3 1.35 (0.62–2.95) |
| Overall cancer (Table 27)     | 7 0.98 (0.84–1.15)  | 7 0.98 (0.84–1.15)  | 6 1.10 (1.02–1.19) |

n = number of estimates included in meta-analyses.
RR/OR = combined random-effects estimate based on RRs or ORs.
CI = confidence interval; OR = odds ratio; RR = relative risk.
for pancreatic cancer [32] in never smokers, but this merely reflects the overall relationship, with RRs similar in light and heavy users (1.9 for 1–9 g/day, and 2.1 for 10+ g/day relative to never users). For some of the case-control studies considered [38,44,53,55,89,96,100,104,108,110,111,114], dose-response results are available, but these generally show no significant trends. The only exceptions are a study of kidney cancer [100] which reports a significant ($P < 0.05$) trend for risk to increase with frequency of use of chewing tobacco, and a study of pancreatic cancer [111] which reports a significant ($P = 0.04$) trend for risk to increase with ounces per week (oz/wk) ST used, though with the odds ratios forming an erratic pattern (1.0 for nonusers of tobacco, 0.3 for $\leq 2.5$ oz/wk ST and 3.5 for $> 2.5$ oz/wk ST). Generally the rather sparse dose-response data add little to the overall evidence.

### Table 31: Summary of meta-analyses for smokeless tobacco use in the USA

| Cancer     | Overall data | Smoking-adjusted data | Never smokers |
|------------|--------------|-----------------------|---------------|
|            | $n$          | RR/OR (95% CI)        | $n$           | RR/OR (95% CI) | $n$ | RR/OR (95% CI) |
| Oropharyngeal (Table 4) | 31 | 2.16 (1.55–3.02) | 12 | 1.65 (1.22–2.25) | 5 | 3.33 (1.76–6.32) |
| Oesophageal (Table 6) | 6 | 1.56 (1.11–2.19) | 3 | 1.89 (0.84–4.25) | 3 | 1.89 (0.84–4.25) |
| Stomach (Table 8) | 4 | 1.41 (0.95–2.10) | 3 | 1.41 (0.93–2.12) | 2 | 1.96 (0.82–4.70) |
| Pancreatic (Table 10) | 5 | 0.86 (0.47–1.57) | 5 | 0.99 (0.51–1.91) | 3 | 1.09 (0.44–2.67) |
| Any digestive (Table 12) | 5 | 0.86 (0.59–1.25) | 5 | 0.86 (0.59–1.25) | 4 | 1.14 (0.99–1.33) |
| Larynx (Table 14) | 4 | 1.56 (1.21–2.00) | 1 | 2.01 (1.15–3.51) | 0 | – |
| Lung (Table 16) | 6 | 1.22 (0.82–1.83) | 4 | 1.38 (0.72–2.64) | 3 | 1.79 (0.91–3.51) |
| Prostate (Table 18) | 5 | 1.23 (1.03–1.40) | 4 | 1.29 (1.07–1.55) | 3 | 1.81 (0.76–4.30) |
| Bladder (Table 20) | 9 | 1.11 (0.85–1.45) | 6 | 1.24 (0.83–1.85) | 5 | 1.25 (0.69–2.26) |
| Kidney (Table 22) | 8 | 1.52 (0.94–2.46) | 3 | 1.41 (0.64–3.10) | 1 | 4.80 (1.18–19.56) |
| Non-Hodgkin’s lymphoma (Table 24) | 3 | 1.45 (0.81–2.59) | 2 | 2.07 (0.70–6.13) | 2 | 2.07 (0.70–6.13) |
| Overall cancer (Table 27) | 5 | 0.95 (0.74–1.22) | 5 | 0.95 (0.74–1.22) | 4 | 1.10 (1.01–1.20) |

$n$ = number of estimates included in meta-analyses.
RR/OR = combined random-effects estimate based on RRs or ORs.
CI = confidence interval; OR = odds ratio; RR = relative risk.

### Table 32: Summary of meta-analyses for snuff as used in Scandinavia

| Cancer (source) | Overall data* | Never smokers |
|-----------------|---------------|---------------|
|                 | $n$ | RR/OR (95% CI) | $n$ | RR/OR (95% CI) |
| Oropharyngeal (Table 4) | 7 | 0.97 (0.68–1.37) | 4 | 1.01 (0.71–1.45) |
| Oesophageal (Table 6) | 4 | 1.10 (0.92–1.33) | 1 | 1.92 (1.00–3.68) |
| Stomach (Table 8) | 5 | 0.98 (0.82–1.17) | 2 | 0.90 (0.35–2.30) |
| Pancreatic (Table 10) | 2 | 1.20 (0.66–2.20) | 2 | 1.61 (0.77–3.34) |
| Larynx (Table 14) | 1 | 0.90 (0.50–1.50) | 0 | – |
| Lung (Table 16) | 2 | 0.71 (0.66–0.76) | 2 | 0.82 (0.52–1.28) |
| Bladder (Table 20) | 1 | 0.83 (0.62–1.11) | 0 | – |
| Kidney (Table 22) | 1 | 0.72 (0.44–1.18) | 0 | – |
| Non-Hodgkin’s lymphoma (Table 24) | 2 | 1.04 (0.54–1.98) | 1 | 0.77 (0.59–1.01) |
| Overall cancer (Table 27) | 2 | 1.03 (0.91–1.16) | 2 | 1.10 (0.94–1.29) |

$n$ = number of estimates.
RR/OR = combined random-effects estimate based on RRs or ORs.
CI = confidence interval; OR = odds ratio; RR = relative risk.

* all individual estimates included in these meta-analyses are smoking-adjusted or for never smokers except for one for non-Hodgkin’s lymphoma.

Comparison of the effects of smoking and of ST use

Table 33 summarises the results of analyses comparing the effects of smoking and of ST use, for seven smoking-related cancers [127]. Overall in US men aged 35+ a total of 142,205 deaths were seen from these cancers in 2005, with lung cancer (63.4%) by far the most common. Based on RRs from CPS-II for current and former smoking [122] and estimates of the frequency of current and former smoking [124] for US men of this age group, the total number of deaths that would have occurred if the men had the mortality rates of never smokers can be estimated as 37,468, a reduction (E) of 104,737 deaths. This reduction is proportionately largest for the cancers most strongly associated with smoking (lung and oropharynx), and least for those most weakly associated (pancreas, kidney and bladder).
The smoking-adjusted relative risks for any ST use taken from Table 30 are then used to estimate the number of deaths that would have occurred if the population were never smokers, with ST use either at the same frequency as for current and former smoking combined, 53%, or at 100%. In the first situation, the number of cancer deaths rises from 37,468 to 38,570, an increase of 1,102; in the second situation, it rises to 39,548, an increase of 2,081. These numbers of cancers associated with ST use form, respectively, 1.1% and 2.0%, of those associated with smoking.

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**Discussion**

**Estimating the effects of ST use**

We have analysed data relating cancer risk to the consumption of chewing tobacco and snuff as used in Western countries. We have identified 12 cancers (or combined categories) where, as shown in Table 30, it is possible to derive a (random-effects) meta-analysis estimate based on at least five individual independent estimates.

It is notable that no strong association at all is evident and that few of the associations are significant at $P < 0.05$. Indeed, based on smoking-adjusted data, which might be argued to provide a good compromise between avoidance of bias and loss of power, only the estimates for oropharyngeal and prostate cancer are significant, with that for oropharyngeal cancer not evident in more recently published studies. However, it should be noted that while many of the estimates in Table 30 for never smokers have wide confidence limits, and only those for oropharyngeal and oesophageal cancer and for overall cancer are significant, all the estimates are in fact greater than 1.00. Although publication bias may be relevant, and more data are clearly needed, the consistency of these findings suggests that ST may increase the risk of cancer, though any effect is likely to be quite weak. The results in Table 32 suggest, however, that whether smoking-adjusted data or data for never smokers are considered, there is little or no evidence of an effect of snuff as used in Scandinavia.

There are a number of difficulties in interpreting the results of these meta-analyses. The studies are of varying design, size and quality. Many of the individual study reports have limitations and present less information.
than is ideal for a meta-analysis. Shortcomings include small numbers of cases, and in particular of cases exposed to ST, lack of histological confirmation, lack of division by cancer site, as well as an unclear description of inclusion and exclusion criteria, details of case and control selection, and methods of exposure assessment. Furthermore, details such as the type of ST used, and duration and frequency of use, are often not considered. The products used vary by country and over time, and increased risks seen in older studies for some cancers may not reflect the risks of more modern products, with reduced nitrosamine levels [128]. For most cancers, the number of effect estimates available is really too limited to allow a very detailed examination of variation in risk by such factors as type of product used, current or former use, country and sex. Though meta-regressions have been attempted for a number of cancers, they have not added materially to the interpretation, partly because of the limited amount of data for some cancers, and partly because of the number of apparently outlying estimates, notably for oropharyngeal cancer.

A major problem is that many of the studies fail to adjust for smoking and other important potential confounding variables. Although recent major reviews [7,8] consider that all the cancers considered in Table 30, with the exception of prostate cancer and non-Hodgkin’s lymphoma, are caused by smoking, it is evident that a number of the studies do not provide estimates that are either for never smokers or for smokers and non-smokers combined with adjustment for smoking. Even where adjustment for smoking is carried out, this is often by a relatively simple approach, with no account taken of number of cigarettes smoked or duration of smoking. Smokers who also use ST may smoke fewer cigarettes a day than smokers who do not. Failure to adjust for smoking is particularly common for studies of oropharyngeal cancer, with many of the older studies not taking smoking into account at all when considering ST. The potential importance of this is illustrated by the overall estimate for oropharyngeal cancer being substantially reduced, from 1.79 to 1.36, when attention is restricted to smoking-adjusted data.

Adjustment for other risk factors is also important, as shown by the case of oropharyngeal cancer where the smoking-adjusted estimate of 1.36 (1.04–1.77, n = 19) can be compared with the estimate adjusted for smoking and alcohol of 1.07 (0.84–1.37, n = 10). Restricting attention to estimates adjusted for both factors also eliminated the highly significant (P < 0.001) heterogeneity seen in the smoking-adjusted data. Alcohol is also an important factor in the aetiology of oesophageal, larynx and liver cancer [8], but the number of ST effect estimates adjusted both for smoking and alcohol for these three cancers is very low indeed, respectively 2, 1 and 0. Other factors considered rarely, or not at all, include, for example, Helicobacter pylori infection for stomach cancer and diet for digestive cancer.

Another difficulty in interpreting the overall results is the variability of the findings. Heterogeneity significant at least at P < 0.05 is evident in the smoking-adjusted estimates for cancers of the oropharynx (though not in the more recent data), pancreas, larynx, lung and bladder, as well as for overall cancer and overall digestive cancer. As noted above, the evidence is too limited for most of the cancers to allow a proper investigation of the sources of this heterogeneity.

Based on the data analysed, there is little or no evidence of publication bias. However, it should be noted that the number of studies reporting results in a form that cannot be included in the meta-analyses is fairly high, representing up to about 30% for some cancers (see Tables 5, 7, 9, 13 and 17).

We are aware that the smoking-adjusted meta-analysis estimates we report for oropharyngeal cancer (1.36, 95% CI 1.04–1.77), oesophageal cancer (1.13, 0.95–1.36), pancreatic cancer (1.07, 0.71–1.60) and lung cancer (0.99, 0.71–1.37) show much less evidence of a relationship with ST than do corresponding estimates recently reported in a review by Boffetta et al. [6] (oropharynx: 1.8, 1.1–2.9; oesophagus: 1.6, 1.1–2.3; pancreas: 1.6, 1.1–2.2; lung 1.2, 0.7–1.9). Reasons for this, based on a detailed analysis of this review, will be presented in a separate publication in BMC Cancer.

Comparison of the effects of smoking and ST use

In 2005 in US men aged 35 or over, there were a total of 142,205 deaths from seven cancers considered to be caused by smoking. Based on relative risks from CPS-II for current and former smoking [122] and estimates of the frequency of current and former smoking [124] for US men of this age group, we estimate that, had the population at risk the mortality rates of never smokers, the numbers would have reduced by 104,737, with the reduction in lung cancer deaths, 79,195, a major contributor. Any increase in risk resulting from the introduction of ST to a population of never smokers would be much less than this. Even assuming that the smoking-adjusted meta-analysis estimates for the seven cancers all reflect a true effect of ST, the increase in deaths among a never-smoker population would be by 1,102 if 53% of the population used ST (the same proportion as had ever smoked) or by 2,081 if 2,081 if the whole population did. These increases represent, respectively, only 1.1% and 2.0% of the 104,737 deaths attributed to cigarette smoking.

There are a number of objections that can be made in respect of this comparison. These include the following:
1. The RRs for current and former smoking are based on CPS-II, conducted in the 1980s, and may not reflect those appropriate for 2005, given inter alia changes in cigarettes that have occurred since then. However, CPS-II is widely used as a source of data for calculating deaths attributed to smoking (for example, [8,129]).

2. The RR estimates used for ST use are not specifically for the USA, or for males. However, 62 of the 89 studies considered in this review were conducted in the USA, and 41 of the 58 estimates used in the smoking-adjusted meta-analyses for the seven cancers are for males (with 12 for sexes combined and five for females).

3. The RR estimates used for ST are for any ST use, and do not separate current and former use, due to most studies not providing such data.

4. The calculations are limited to those seven cancers which the US Surgeon General, in his 1989 report [122] considered to be caused by smoking and for which RRs were provided for CPS-II. A more recent report [8] includes stomach cancer and leukaemia as caused by smoking. For stomach cancer, the meta-analyses in Table 6 showed virtually no association with ST use (1.03, 0.88–1.20, n = 8), while the more limited data for leukaemia also showed no clear evidence of a relationship.

5. It is theoretically possible that ST use might increase the risk of some cancers not increased by smoking. Here one should note the significant association for prostate cancer (1.29, 1.07–1.55).

6. The calculations do not take into account the fact that a proportion of US males aged 35+ already use ST. Given the relatively weak association between cancer and ST use, any attempt to do this would have had relatively little effect.

7. The calculations also do not take pipe and cigar smoking into account.

8. The approach used is somewhat simplistic, and a more realistic (but more complex) calculation might be to compare predicted cancer deaths over a long-term period in a population continuing to smoke as at present, with the predicted number in a population switching from cigarettes to ST.

Despite all these points, it is clear that any effect of ST on risk of cancer, if it exists at all, is quantitatively very much smaller than the known effects of smoking. This is in any case apparent from a simple comparison of the RRs for cigarette smoking and for ST use.

Conclusion
The available data relating to ST use have a number of weaknesses, including inadequate control for smoking in many, and limited data for never smokers. Nevertheless, it is possible to conduct meta-analyses based on smoking-adjusted estimates for a relatively wide range of cancers. These show no indication of an increased risk of cancer for snuff, as used in Scandinavia. The overall data for oropharyngeal cancer shows a significant increase in risk associated with ST use, but this is not evident for estimates adjusted for smoking and alcohol, or for studies published since 1990. Any effect of ST may relate mainly to products used in the past in the USA. A weak but significant association with prostate cancer, based on limited data from US studies, requires more confirmatory evidence. Reports of significant associations with pancreatic and oesophageal cancer in an earlier review [6] are not confirmed, and reasons for this will be discussed in a later publication. Risk from ST products as used in North America and Europe is clearly very much less than that from smoking, and is not evident at all in Scandinavia.

Abbreviations
CI: 95% confidence interval; CPS-I: American Cancer Society Cancer Prevention Study I; CPS-II: American Cancer Society Cancer Prevention Study II; d.f.: degrees of freedom; NHANES I: First National Health and Nutrition Examination Survey; OR: odds ratio; RR: relative risk; ST: smokeless tobacco.

Competing interests
PNL, founder of PN Lee Statistics and Computing Ltd., is an independent consultant in statistics and an advisor in the fields of epidemiology and toxicology to a number of tobacco, pharmaceutical and chemical companies. JH works for PN Lee Statistics and Computing Ltd.

Authors’ contributions
PNL previously contributed to reviews of some of the data considered here [4,5,10]. He planned the study and carried out the literature search. PNL and JH jointly extracted the estimates and conducted the meta-analyses. The text and tables were drafted by PNL and checked by JH. Both authors read and approved the final manuscript.

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95. Hardell L, Eriksson M and Degerman A: Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin’s lymphoma. Cancer Res 1994, 54:2386–2389.

96. Hayes RB, Pottern LM, Swanson GM, Liff JM, Schoenberg DB, Greenberg RS, Schwartz AG, Brown LM, Silverman DT and Haggerty RN: Tobacco use and prostate cancer in Blacks and Whites in the United States. Cancer Causes Control 1994, 5:221–226.

97. Kabat GC, Chang CJ and Wynder EL: The role of tobacco, alcohol use, and body mass index in oral and pharyngeal cancer. Int J Epidemiol 1994, 23:137–144.

98. Bundgaard T, Wildt J, Frydenberg M, Elbrond O and Nielsen JE: Case-control study of squamous cell cancer of the oral cavity in Denmark. Cancer Causes Control 1995, 6:57–67.

99. McLaughlin JK, Lindblad P, Mellemgard A, McCredie M, Mandel JS, Schlehofer B, Pommier W and Adami HO: International Renal Cell Cancer Study. I. Tobacco use. Int J Cancer 1995, 60:194–199.

100. Muscat JE, Hoffmann D and Wynder EL: The epidemiology of renal cell carcinoma. A second look. Cancer 1995, 75:2552–2557.

101. Muscat JE, Stellman SD, Hoffmann D and Wynder EL: Smoking and pancreatic cancer in men and women. Cancer Epidemiol Biomarkers Prev 1997, 6:15–19.

102. Lewin F, Norell SE, Johansson H, Gustavsson P, Wennerberg J, Schroeder JC, Olshan AF, Baric R, Dent GA, Weinberg CR and Yount B: Tobacco use and non-Hodgkin’s lymphoma. Cancer Res 1998, 58:1186–1191.

103. Ye W, Ekstrom AM, Hansson LO, Nyrén O and Schüz J: Tobacco, alcohol and the risk of major salivary gland cancer. Otolaryngol Head Neck Surg 1998, 119:195–198.

104. Schild E-B, Eriksson M, Hardell L and Magnusson A: Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. Int J Cancer 1998, 77:341–346.

105. Schwartz SM, Daling JR, Doody DR, Wipf GC, Carter JJ, Madeleine MM, Mao E-J, Fitzgibbon ES, Huang S, Beckmann AM, McDougal JK and Ga. Cancer D: Tobacco use and cancer risk in relation to sexual history and evidence of human papillomavirus infection. J Natl Cancer Inst 1998, 90:1626–1636.

106. Yuan J-M, Esteban Castelo J, Gago-Dominguez M, Yu MC and Rubi R: Tobacco use in relation to renal cell carcinoma. Cancer Epidemiol Biomarkers Prev 1998, 7:429–433.

107. Ye W, Ekstrom AM, Hansson L-E, Bergstrom R and Nyrén O: Tobacco, alcohol and the risk of gastric cancer by subsite. Cancer Epidemiol Biomarkers Prev 1998, 7:33–39.

108. Lagergren J, Bergström R, Lindgren A and Nyrén O: Alcohol use, and body mass index in oral and pharyngeal cancer. Int J Epidemiol 1994, 23:137–144.

109. Zheng T, Cantor KP, Zhang Y, Chiu BCH and Lynch CF: Tobacco use and non-Hodgkin’s lymphoma. Cancer Res 1998, 58:1186–1191.

110. Schroeder JC, Oldham AF, Baric R, Dent GA, Weinberg CR, Yount B, Cerhan JR, Lynch CF, Schuman LM, Tolbert PE, Rothman N, Cantor KP and Blair A: A case-control study of tobacco use and other non-occupational risk factors for (t14;18) subtypes of non-Hodgkin’s lymphoma (United States). Cancer Causes Control 2002, 13:159–168.

111. Alguacil J and Silverman DT: Smokeless and other noncigarette tobacco use and pancreatic cancer: a case-control study based on disease interviews. Cancer Epidemiol Biomarkers Prev 2001, 10:413–414.

112. Bracci PM and Holly EA: Tobacco use and non-Hodgkin lymphoma: results from a population-based case-control study in the San Francisco Bay Area, California. Cancer Causes Control 2005, 16:333–346.

113. Rosenquist K, Wennerberg J, Schild E-B, Bladstrom A, Hansson BG and Andersson G: 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. Acta Otolaryngol 2005, 125:991–998.

114. Hassan MM, Abbruzzese JL, Bondy ML, Wolfit RA, Vauthey JN, Pisters PW, Evans DB, Khan R, Lenz R, Jiao L and Li D: Passive smoking and the use of noncigarette tobacco products in association with risk for pancreatic cancer: a case-control study. Cancer 2007, 109:2547–2556.

115. Breslow NE and Day NE: The analysis of case-control studies. [Statistical methods in cancer research.] Lyon: IARC; IARC Scientific Publication No. 32: Davis W 1980, I.

116. Fleiss JL and Gross AJ: Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: a critique. J Clin Epidemiol 1991, 44:127–139.

117. Greenland S and Longnecker MP: Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992, 135:301–1309.

118. Hamling J, Lee P, Weikkanut R and Ambühl M: Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008, 27:954–970.

119. Armitage P and Berry G: Statistical methods in medical research. Oxford: Blackwell Publishing; 31994.

120. Higgins JPT, Thompson SG, Deeks JJ and Altman DG: Measuring inconsistency in meta-analyses. BMJ 2003, 327:557–560.

121. Egger M, Davey Smith G, Schneider M and Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ 1997, 315:629–634.

122. US Surgeon General: Reducing the health consequences of smoking. 25 years of progress. A report of the Surgeon General Rockville, Maryland: US Department of Health and Human Services; Public Health Services; DHHS Publication No. (CDC) 89-8411; 1989 http://profiles.nlm.nih.gov/NN/B/B/X/S/.

123. World Health Organization: WHO Mortality Database. http://www3.who.int/whosis.

124. Inter-University Consortium for Political and Social Research (ICPSR): National Health Interview Survey, 2005. ICPSR Study No. 4606. Online analysis.U.S. Department of Health and Human Services, National Center for Health Statistics; http://www.icpsr.umich.edu/coconn/ICPSR/DAS/04606.xml (Accessed October 2008).

125. Spangler JG, Michielutte R, Bell RA and Dignan MB: Association between smokeless tobacco use and breast cancer among Native-American women in North Carolina. Ethn Dis 2001, 11:36–43.

126. Spangler JG, Michielutte R, Bell RA and Dignan MB: Correction to: Association between smokeless tobacco use and breast cancer among native-American women in North Carolina (Ethn.Disc.2001;11:36–43). Ethn Dis 2002, 12:158–159.

127. World Health Organization: International statistical classification of diseases and related health problems. Tenth revision Geneva: WHO; 1992, 1.

128. Nilsson R: De minimus non curat lex – virtual thresholds for cancer initiation by tobacco specific nitroamines – prospects for harm reduction by smokeless tobacco. Int J Oncol Environ Health 2006, 19:1–30 http://versitas.metapress.com/content/r3155663s202528cfulltext.pdf.

129. Peto R, Lopez AD, Boreham J, Thun M and Heath C Jr: Mortality from smoking in developed countries 1950–2000. Indirect estimates from national vital statistics Oxford, New York, Tokyo: Oxford University Press; 1994.

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