Articles

Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43 000 adult male deaths and 35 000 controls

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Summary

Background In India most adult deaths involve vascular disease, pulmonary tuberculosis, or other respiratory disease, and men have smoked cigarettes or *bidis* (which resemble small cigarettes) for several decades. The study objective was to assess age-specific mortality from smoking among men (since few women smoke) in urban and in rural India.

Methods We did a case-control study of the smoking habits of 27 000 urban and 16 000 rural men who had died in the state of Tamil Nadu, southern India, from medical causes (ie, any cause other than accident, homicide, or suicide), and of 20 000 urban and 15 000 rural male controls. The main analyses are of mortality at ages 25–69 years.

Findings In the urban study area, the death rates from medical causes of ever smokers were double those of never smokers (standardised risk ratio at ages 25–69 years 2·1 [95% CI 2·0–2·2]). The risks were substantial both for cigarette smoking (the main urban habit) and for *bidi* smoking. Of this excess mortality among smokers, a third involved respiratory disease, chiefly tuberculosis (4·5 [4·0–5·0], smoking-attributed fraction 61%), a third involved vascular disease (1·8 [1·7–1·9], smoking-attributed fraction 24%), 11% involved cancer (2·1 [1·9–2·4], smoking-attributed fraction 32%), chiefly of the respiratory or upper digestive tracts, and 14% involved alcoholism or cirrhosis (3·3 [2·9-3·8], not attributed to smoking). Among ever smokers, the absolute excess mortality from tuberculosis was substantial throughout the age range 25–69 years. (A separate survey of 250 000 men living in the urban study area found that ever smokers are three times as likely as never smokers to report a history of tuberculosis, corresponding to a higher rate of progression of chronic subclinical infection to clinical disease.) The proportional excesses of respiratory, vascular, and neoplastic mortality at ages 25–69 years among ever smokers in the urban study area were replicated, each with similarly narrow CI for the risk ratio, in the rural study area (where *bidi* smoking predominated), and are taken to be largely or wholly causal. For urban and for rural death from medical causes at older ages (⩾70 years), the standardised risk ratio was 1·3.

Interpretation Smoking, which increases the incidence of clinical tuberculosis, is a cause of half the male tuberculosis deaths in India, and of a quarter of all male deaths in middle age (plus smaller fractions of the deaths at other ages). At current death rates, about a quarter of cigarette or *bidi* smokers would be killed by tobacco at ages 25–69 years, those killed at these ages losing about 20 years of life expectancy. Overall, smoking currently causes about 700 000 deaths per year in India, chiefly from respiratory or vascular disease: about 550 000 men aged 25–69 years, about 110 000 older men, and much smaller numbers of women (since few women smoke).

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Introduction

Smoking has been widespread for many decades among men in India,[1–4] where most adult deaths involve vascular disease, tuberculosis, or other respiratory disease. However, we know of no substantial completed studies of the extent to which smoking is causing death from these or other diseases, or of how the hazards vary between urban and rural India. In rural areas most smoking involves not cigarettes but *bidis*, which are smaller and consist of 0·2–0·3 g tobacco rolled in the leaf of another plant, *temburni*. Large prospective studies are in progress,[5–10] but will take many years to accumulate sufficient numbers of deaths from particular causes. We report two large case-control studies of smoking and cause-specific mortality in southern India, one urban and one rural. In both study areas large population surveys of tobacco use were also carried out (chiefly for other purposes[7]). Although many women in these particular parts of India chew tobacco, fewer than 0·1% smoke it. Hence, the present analyses of the effects of smoking involve only men.

Methods

Case-control studies in urban and in rural areas among men aged 25 years and older

The urban study area is the whole of the city of Chennai, formerly Madras (population 4 million), the capital of the state of Tamil Nadu. Elsewhere in that state the rural study area is (the whole of the district of Vilippuram, population 2·5 million, in 2000 villages) in the former district of South Arcot. The cases are all the men (27 000 urban, 16 000 rural) who died of disease in those areas in particular years (1995–97 urban, 1997–98 rural) and whose household could be visited by interviewers to determine from the surviving family members the smoking habits of the dead man, and to check that death was from disease, not from accident, suicide, or homicide. The controls (20 000 urban, 15 000 rural) are men aged 25 years or older living in a household where a female member had died during those same years. The methods

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of case identification and the reliability of cause of death assignment, however, were somewhat different in the urban and in the rural study areas.

Urban case-control study

The death records for 1995–97 in the Chennai Vital Statistics Department, which are fairly complete[11] (but cover only the urban study area), were searched to identify all deaths in those years at age 25 years or above. Of 72 000 found, 5000 were attributed in the city records to non-medical causes (unintentional injuries, suicide, or homicide), and were excluded. For the 67 000 remaining, the households were to be visited in 1998–99 for collection of data on the smoking habits of the dead person and on the medical circumstances of death. 19 000 of the homes could not be visited successfully, usually because the address was missing or inadequate, the house no longer existed, or the family had moved. The remaining 48 000 families provided information on the disease that had caused death and on the dead person's smoking habits, tobacco chewing habits, and educational status. After exclusion of 1000 people for whom the cause of death was found from the family to have been non-medical, 47 000 dead adults remained (27 000 men [urban cases] and 20 000 women [not analysed here]). The families were also asked to provide information on the tobacco smoking and chewing habits of a living family member of the opposite sex to the dead person, preferably the surviving spouse, and 47 000 of the 48 000 did so (20 000 men [urban controls] and 27 000 women [not analysed here]). Smokers and ex-smokers were combined into a single category, to allow comparison of ever versus never smokers to be unaffected by any disease-related changes in smoking prior to death among the cases.

More than half the medical causes of death recorded by the Vital Statistics Department were non-specific, and in all cases the information from those records was to be supplemented by a so-called verbal autopsy, based on the home visit.[11] Trained non-medical field interviewers (graduates with at least 15 years of formal education) asked family members or other associates of the deceased about symptoms and signs of illness prior to death, about where the deceased had been treated (eg, tuberculosis hospital, cancer hospital, coronary care unit, etc), about what treatments had been given, and about any history of past treatment or admission to hospital for any similar episode. A half-page written summary (generally in Tamil) of each interview was reviewed independently by two locally experienced medical doctors unaware of the deceased's habits (VG and TSK), both of whom coded the probable underlying cause of death according to the three-digit categories of the *International Classification of Diseases*, ninth revision (ICD-9).[12] Discrepancies were discussed and resolved soon after they arose, which quickly led to the establishment of consistent coding conventions. Finally, the probable cause of death arrived at by this verbal autopsy was linked with the patient's hospital records[13] to help determine the site of any cancer. Probable underlying causes were assigned to 95% of the urban male deaths from disease at ages 25–69 years, but to a smaller proportion (and with less confidence) of those at older ages.

Five supervisors monitored the daily numbers interviewed by the 25 interviewers and checked the field visit reports for plausibility. The reports were further validated by re-interview of 5% of the households by one or other of two special interviewers, with random selection for re-interview taking place about 1 week after completion of the main interview, and blind to its results. The questionnaires were checked centrally for consistency and missing values, and were double-entered into the computer.

Rural case-control study

In the rural study area all formal or informal village records were to be sought to identify all deaths at any age during 1997–98. 41 000 such deaths were identified, and 39 000 of the households were successfully visited during 1999–2000, to try to assign causes of death by verbal autopsy and to get information on the smoking habits of those who had died of a medical cause at age 25 years or older. 7000 of the deaths were before age 25 and another 5000 were from non-medical causes, so 27 000 dead adults remained (16 000 men [rural cases] and 11 000 women [not analysed here]). The 39 000 households were also asked for information on the smoking habits of a household member aged 25 years or older, either the surviving spouse or someone else of opposite sex to the dead person, yielding 36 000 live respondents (15 000 men [rural controls] and 21 000 women [not analysed here]). Survey methods and quality control were as in the urban study area, but generally without any cancer registry or other medical records available. Probable underlying causes were assigned by the verbal autopsy to 83% of the rural male deaths from a medical cause at ages 25–69 years.

Population surveys in same urban and rural study areas among men aged 35 years and older

Urban population survey

For purposes other than this study,[7] a population survey was undertaken during 1998–2001 that covered almost half the urban study area. We sought to visit all the houses in two of the ten administrative zones of the study area, and in a randomly chosen sample of 50% or of 30% of the streets in five more of the zones. The men and women aged 35 years or over who lived in these houses were to be interviewed at home. Precautions similar to those in the case-control studies were taken to ensure strict quality control of fieldwork, coding, and data entry. Information has been entered and checked on 250 000 men (used to validate the urban controls) and 225 000 women (not used here). Among the items recorded in this population survey were smoking, age, sex, tobacco chewing, educational status, and whether the adult being interviewed had ever been diagnosed as having tuberculosis. The results among the men are used in the present report both to help validate the age-specific prevalence of smoking among the controls in the urban case-control study, and to help interpret any relationship between smoking and tuberculosis.

Rural population survey

A similar population survey was performed at the same time that covered almost a quarter of the rural study area, seeking to interview all people aged 35 years or over in five of the 22 rural administrative blocks that make up the study area. For 55 000 men (used to validate the rural controls) and 45 000 women (not used here) this survey recorded the smoking habits, but it did not record whether the rural interviewees had ever had tuberculosis.

Statistical methods

The urban and the rural case-control studies of male smoking and mortality are analysed separately. For each category of disease the cases are the men who had died of it, and the controls are men living in a household in which a female member had died, irrespective of her cause of death and age. Thus, particular cases are not matched to particular controls (indeed, the age distribution of the cases differs from that of the controls), and for each different category of disease the control group is always the same. Hence, the main analyses involve unmatched comparisons between the relevant cases and all the

	Number of men and proportion smoked (%)		Risk ratio, ever to never smoked (95% CI)*	Smoking-associated deaths (% of cases)*	Expected years lost per death*
	Cases (deaths)	Controls			
Age range (years)					
Urban (Chennai; 27 043 cases *vs* 20 162 controls)					
25–34	1095 (55·3)	1787 (31·7)	2·4 (2·1–2·9)	359 (33%)	38·0
35–44	2206 (67·2)	3847 (40·7)	2·7 (2·4–3·0)	928 (42%)	29·5
45–54	3697 (65·5)	5079 (41·5)	2·4 (2·2–2·6)	1410 (38%)	21·4
55–64	5614 (57·7)	4171 (39·8)	1·9 (1·7–2·1)	1517 (27%)	14·6
65–69	3464 (52·9)	1604 (36·3)	1·8 (1·6–2·0)	807 (23%)	10·6
70–74	3623 (47·1)	1570 (37·8)	1·4 (1·2–1·6)	474 (13%)	8·2
⩾75	7344 (35·1)	2104 (30·8)	1·3 (1·1–1·4)	517 (7%)	5·5
Subtotal 25–69	16 076 (59·6)	16 488 (39·0)†	2·1 (2·0–2·2)	5021 (31%)	20·3
Rural (South Arcot; 15 998 cases *vs* 15 128 controls)					
25–34	679 (46·1)	2738 (43·1)	1·1 (1·0–1·4)	39 (6%)	38·0
35–44	1506 (62·0)	4068 (51·8)	1·6 (1·4–1·8)	350 (23%)	29·5
45–54	2720 (58·1)	3510 (47·8)	1·7 (1·6–2·0)	687 (25%)	21·4
55–64	3331 (49·6)	2183 (39·4)	1·7 (1·5–1·9)	687 (21%)	14·6
65–69	1885 (43·0)	864 (34·3)	1·6 (1·3–1·9)	294 (16%)	10·6
70–74	2031 (39·7)	794 (36·1)	1·2 (1·0–1·5)	147 (7%)	8·2
⩾75	3846 (34·7)	971 (29·4)	1·3 (1·1–1·6)	343 (9%)	5·5
Subtotal 25–69	10 121 (52·2)	13 363 (42·8)†	1·6 (1·5–1·7)	2057 (20%)	19·3

*Cases (deaths from all medical causes: excludes accident, suicide, and homicide) *vs* controls, standardised for age, educational level, and tobacco chewing. Smoking-associated number of medical deaths calculated as (1–1/risk ratio)×number of cases. Current and ex-smokers combined. Expected loss per smoking-associated death is all-India year 2000 male life expectancy (reference 34) in middle of age range (or at age 80 years); that at ages 25–69 years is weighted average. †Percentages among urban and rural controls aged 25–69 years standardised to age distributions of corresponding cases.

Table 1: **Death from all medical causes, by smoking and age, among men in urban and in rural India**

controls, using logistic regression to obtain death rate ratios (relative risks) that are standardised for age, educational level, and tobacco chewing. We used EGRET statistical software (version 4). For any particular age range, such as 25–69 years, calculation of the excess deaths among smokers (ie, the deaths that would have been avoided if the men who had ever smoked had had non-smoker death rates) involves multiplying the overall number of deaths among smokers by 1–1/RR, in which RR is the standardised risk ratio.

To estimate the absolute death rates in a particular 5-year age range for smokers and for non-smokers, the standardised relative risk in that age range from the case-control study of all medical deaths (r) is combined with m and n, the death rates from medical and from non-medical causes respectively in that age range, as provided by the Chennai Vital Statistics Department.[11] If the prevalence of smoking among the controls in this age range is p then the absolute death rates are rm/[1+(r–1)p]+n for smokers and m/[1+(r–1)p]+n for non-smokers. (This yields smoker and non-smoker death rates that are standardised for educational level, for tobacco chewing and for any differences in mortality from non-medical causes.) From these age-specific death rates the cumulative risks of death since age 25 years are calculated and plotted against age for smokers and for non-smokers.

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Since chronic illness may make some smokers stop, the term smoker is consistently used to mean ever smoker. Assignment of causes by verbal autopsy is likely to have been more reliable in urban than in rural areas, and more reliable at ages 25–69 years than at older ages; moreover, deaths before age 70 years involve a substantially greater loss of life expectancy than deaths at older ages. Hence, detailed analyses of urban mortality are presented first, with particular emphasis on the age range 25–69 years.

Urban male mortality

In the urban study area there were 27 000 cases and 20 000 controls, of whom 16 000 cases and 16 000 controls were aged 25–69 years.

All-cause mortality

At ages 25–69 years, 59·6% of the men who had died from medical causes (cases) had been smokers, as against only 39·0% of the corresponding age-matched controls (table 1). There was an excess of 5021 deaths at ages 25–69 years among the smokers, and the average loss of life expectancy per smoking-associated death at these ages was 20 years. After standardisation for educational level and tobacco chewing as well as for age, this difference between the urban cases and the controls corresponds to a standardised risk ratio of 2·1, with a narrow CI (2·0–2·2), indicating that in middle age smokers have about twice the death rate of non-smokers from all medical causes combined. The relative risks were slightly more than 2 at ages 25–54 years, and almost 2 at ages 55–69 years. In old age (70–74, ⩾75 years), however, the smoker versus non-smoker risk ratios were less extreme, although still significant.

Disease-specific hazards

Table 2, which is restricted to urban men aged 25–69 years, gives the separate findings for particular diseases, or groups of diseases. For each catergory, the standardised risk ratio comparing smokers with non-smokers is followed by calculation of the smoking-associated number of deaths.

Respiratory disease—The relative risk for death from tuberculosis was 4·5 (95% CI 4·0–5·0). Of the 1840 deaths from tuberculosis among men aged 25–69 years, 79% involved smokers, and 1127 (61%) would have been avoided if the smokers had had non-smoker tuberculosis death rates. For other respiratory diseases, chief among which was chronic obstructive lung disease, the relative risk was 2·9 and the smoking-associated proportion was 45%. Overall, tuberculosis and other respiratory diseases accounted for a substantial proportion of all smoking-associated mortality.

	Number of deaths (cases)	Proportion ever smoked (%)	Risk ratio, ever to never smoked (95% CI)*	Smoking-associated deaths (% of cases)*
Cause of death (ICD-9 codes)				
Respiratory	2761	76	3·8 (3·5–4·2)	1538 (56%)
Tuberculosis (011, 012, 018)	1840	79	4·5 (4·0–5·0)	1127 (61%)
Other respiratory (416-7, 460–519)	921	69	2·9 (2·5–3·3)	411 (45%)
Vascular	7148	54	1·8 (1·7–1·9)	1709 (24%)
Stroke (430–38)	745	54	1·6 (1·3–1·9)	152 (20%)
Cardiac and other vascular (390–415, 420–29, 440–59)	6403	54	1·8 (1·7–1·9)	1557 (24%)
Neoplastic	1704	60	2·1 (1·9–2·4)	539 (32%)
Lung (162)	235	71	3·6 (2·7–4·9)	121 (52%)
Mouth, pharynx (except nasopharynx), larynx (140–46, 148–49, 161)	350	73	3·6 (2·8–4·6)	184 (52%)
Oesophagus (150)	150	63	2·3 (1·6–3·3)	54 (36%)
Stomach (151)	288	65	2·6 (2·1–3·4)	116 (40%)
Liver (155)	86	56	2·0 (1·3–3·1)	24 (28%)
Other specified site (rest of 140–94, 200–08)	500	43	1·2 (1·0–1·4)	20 (4%)
Unspecified site (195–99)	95	54	1·5 (1·1–2·5)	20 (21%)
Other medical	4463	58	2·0 (1·9–2·1)	1235 (28%)
Peptic ulcer (531–33)	58	72	3·3 (1·8–5·9)	29 (51%)
Alcoholism or cirrhosis (303, 305, 570–73)	1378	71	3·3 (2·9–3·8)	687 (50%)
Other specified medical (rest of 000–799)	2171	52	1·5 (1·4–1·6)	414 (19%)
Unspecified medical (780–89, 797–99)	856	51†	1·3 (1·1–1·5)	105 (12%)
All medical causes	16 076	60	2·1 (2·0–2·2)	5021 (31%)

*Cases (deaths from all medical causes: excludes accident, suicide, and homicide) *vs* controls, standardised for age, educational level, and tobacco chewing. Smoking-associated numbers of deaths calculated by subtraction. Current and ex-smokers combined. †9138 (60%) of 15 220 men with specified medical cause of death ever smoked, with 3786 (41%) of these 9138 deaths due to excess mortality among smokers from respiratory, vascular, and neoplastic disease.

Table 2: **Death from specific medical causes, by smoking, among men aged 25–69 years in urban India (Chennai)**

Vascular disease—Although the smoker versus non-smoker relative risks were less extreme for vascular than for respiratory disease (stroke: standardised risk ratio 1·6 [1·3–1·9]; cardiac and other vascular: 1·8 [1·7–1·9]), there were more than twice as many vascular as respiratory deaths among middle-aged men in Chennai. Hence, vascular disease also accounted for a substantial proportion of all smoking-associated mortality.

Neoplastic disease—Most of the smoking-associated neoplastic deaths involved cancers of the respiratory or upper digestive tract, with relative risks of 3·6 for cancer of the lung, 3·6 for cancer of the mouth and throat, 2·3 for cancer of the oesophagus, and 2·6 for cancer of the stomach (each $p<0·001$). There was also a small but significant ($p<0·01$) absolute excess of liver cancer. In total, however, neoplastic disease accounts for only 11% of the deaths in table 2, and for a correspondingly small proportion of the smoking-associated deaths.

Other medical causes—There was a significant excess mortality among smokers from peptic ulcer (3·3 [1·8–5·9]). There was also a highly significant excess mortality among smokers from alcoholism and cirrhosis (3·3 [2·9–3·8]), perhaps because men who drink heavily tend to smoke tobacco. Urban male mortality from other specified medical conditions was also associated with smoking, as was mortality from unspecified medical conditions (much of which might actually have involved respiratory, vascular or neoplastic disease).

Cigarettes and bidis—In urban areas, cigarettes predominate: among urban controls aged 25–69 years, 4344 smoked only cigarettes and 798 only *bidis*. The risk ratios in table 2 therefore apply chiefly to cigarette smokers. Among the few urban men who did smoke only *bidis*, however, the standardised risk ratios were about as great (tuberculosis: 6·3 [5·3–7·5]; other respiratory: 3·7 [2·9–4·6]; vascular: 1·7 [1·5–1·9]; neoplastic: 2·0 [1·7–2·5]) as those in table 2.

Rural male mortality

In the rural study area there were 16 000 men who had died from medical causes (cases) and 17 000 controls, of whom 10 000 cases and 13 000 controls were aged 25–69 years.

All-cause mortality

At ages 25–69 years, 52·2% of the cases and 42·8% of the corresponding age-matched controls in the rural study area were smokers (chiefly of *bidis*; table 1). After standardisation for educational level and tobacco chewing as well as for age, this difference between the rural cases and controls corresponds to a standardised risk ratio of 1·6, with narrow CI (1·5–1·7), indicating that in middle age rural smokers have a 60% higher death rate than non-smokers from medical causes. This is true in each separate age group except the first (25–34 years; risk ratio 1·1, but with CI including 1·4). In old age the relative risks, although still significant, were less extreme than in middle age, and the numbers available for analysis are smaller.

Disease-specific hazards

Even at ages 25–69 years, the retrospectively assigned cause of death was less reliable in the rural than in the urban study area, since many of those who had died had had no proper medical diagnosis of the terminal illness, and family members were often the only useful source of information. Nevertheless, some events such as death from tuberculosis, death from vascular disease, and death from cancer (perhaps with an uncertain primary site) were often described quite clearly, and the numbers of deaths assigned to these broad categories of cause in the rural study area are given in table 3. Of the 10 121 deaths from medical causes of rural men aged 25–69 years, only 1764 (17%) had a completely unknown medical cause. Of the remaining 8357 deaths, 26% were assigned to respiratory disease, 36% to vascular disease, 5% to neoplastic disease and 34% to other specified diseases (eg, infection, diabetes, renal failure, etc).

Respiratory disease—Of the deaths from a specified medical cause in table 3, a quarter involved tuberculosis or other respiratory disease, and in the rural (as in the urban) study area there was a highly significant excess of smokers among those dying from these diseases. In particular, 73% of those who died of tuberculosis had smoked, yielding a highly significant risk ratio of 4·2 (3·7–4·8). Likewise, 68% of those who died of other respiratory disease had smoked (3·6 [3·0–4·3]). These two categories of respiratory disease account for more than half of the tobacco-associated excess mortality at ages 25–69 years in these rural men, and, taken

	Number of deaths (cases)	Proportion ever smoked (%)	Risk ratio, ever to never smoked (95% CI)*	Smoking-associated deaths (% of cases)*
Cause of death				
Rural†				
Tuberculosis	1529	73	4·2 (3·7–4·8)	853 (56%)
Other respiratory	604	68	3·6 (3·0–4·3)	298 (49%)
Vascular	3012	54	1·7 (1·6–1·9)	675 (22%)
Neoplastic	393	61	2·5 (2·0–3·1)	144 (37%)
Other medical	2819	42	1·0 (0·9–1·2)	..
Unspecified medical	1764	40‡	0·9 (0·8–1·1)	..
All medical causes	10 121	52	1·6 (1·5–1·7)	2057 (20%)

*Cases (deaths from all medical causes: excludes accident, suicide, and homicide) *vs* controls, standardised for age, educational level, and tobacco chewing. Smoking-associated numbers of deaths calculated by subtraction. Current and ex-smokers combined. †ICD codes as in table 2. ‡4576 (55%) of 8357 men with specified medical cause of death ever smoked, with 1970 (43%) of these 4576 deaths due to excess mortality among smokers from respiratory, vascular, and neoplastic disease.

Table 3: **Death from selected medical causes, by smoking, among men aged 25–69 years in rural India (South Arcot district)**

together, they are causes of death that can probably be determined reasonably accurately in this age range.

Vascular disease—In the rural as in the urban study area, heart and other vascular disease again accounted for about a third of all smoking-associated mortality at ages 25–69 years, for although the relative risk for vascular disease (1·7 [1·6–1·9]) is less extreme than that for respiratory disease, vascular disease is the most common cause of death at these ages.

Neoplastic disease—Neoplastic disease was recorded as the underlying cause of only about 5% of the rural male deaths from a specified medical cause at ages 25–69 years, and accounted for only 7% of the smoking-associated deaths at these ages.

Other medical causes—In the rural study area there appeared to be little or no excess mortality among smokers from other specified medical causes or, surprisingly, from unspecified medical causes: only 40% of those with an unspecified cause of death were recorded to have been smokers. This may, however, be because incompleteness of information about the circumstances of death was correlated with incompleteness of information about the habits before death, for 55% of those with a specified cause of death were recorded to be smokers (table 3).

Cigarettes and bidis—In rural areas, *bidis* predominate: among rural controls aged 25–69 years, 679 smoked only cigarettes and 5024 only *bidis*. The risk ratios in table 3 therefore apply chiefly to *bidi* smokers. Among the few rural men who did smoke only cigarettes, however, the standardised risk ratios for the main smoking-related disease categories were also significant (tuberculosis: 2·1 [1·6–2·9]; other respiratory: 3·8 [2·6–5·5]; vascular: 2·5 [2·1–2·9]; neoplastic: 2·8 [1·8–4·1]), but each had a relatively wide CI because of the smaller numbers.

Tuberculosis in middle and old age

Tuberculosis mortality (from the case-control comparisons)

In both the urban and the rural areas the mortality rate from tuberculosis was about four times as great in ever smokers as in never smokers. In India, where tuberculosis is still a common cause of adult male death, the deaths attributed to tuberculosis by verbal autopsy are likely to have been correctly classified, even at older ages. Table 4 therefore provides age-specific comparisons not just in middle age but throughout adult life between the men whose deaths were attributed to pulmonary tuberculosis and the live male controls. In the urban study area the smoker versus non-smoker risk ratios decreased slightly with age, from 5·1 at ages 25–34 years to 3·4 at age 75 years and older, but in each age-group the excess tuberculosis mortality among smokers was substantial and highly significant. Likewise, in

	Tuberculosis deaths (cases)		Living men (controls)		Risk ratio, ever to never smoked (95% CI)*	Smoking-associated deaths (% of all tuberculosis deaths)
	Number of men	Proportion ever smoked (%)	Number of men	Proportion ever smoked (%)		
Age range (years)						
Urban (Chennai; 2231 tuberculosis deaths *vs* 20 162 controls)						
25–34	205	73·7	1787	31·7	5·1 (3·6–7·1)	121 (59%)
35–44	415	80·2	3847	40·7	4·6 (3·6–6·0)	261 (63%)
45–54	517	82·4	5079	41·5	5·2 (4·1–6·6)	344 (67%)
55–64	494	78·9	4171	39·8	4·4 (3·5–5·5)	301 (61%)
65–69	209	72·2	1604	36·3	3·4 (2·4–4·8)	107 (51%)
70–74	177	74·0	1570	37·8	4·1 (2·9–5·9)	99 (56%)
⩾75	214	64·0	2104	30·8	3·4 (2·5–4·6)	96 (45%)
Subtotal 25–69	1840	78·9	16 488	39·2†	4·5 (4·0–5·0)	1127 (61%)
Rural (South Arcot; 1841 tuberculosis deaths *vs* 15 128 controls)						
25–34	119	64·7	2738	43·1	2·4 (1·6–3·5)	44 (37%)
35–44	291	79·7	4068	51·8	4·1 (3·1–5·6)	176 (61%)
45–54	471	75·8	3510	47·8	4·0 (3·2–5·1)	268 (57%)
55–64	461	74·4	2183	39·4	5·5 (4·3–6·9)	280 (61%)
65–69	187	59·9	864	34·3	3·2 (2·3–4·6)	77 (41%)
70–74	139	51·1	794	36·1	2·2 (1·5–3·3)	39 (28%)
⩾75	173	49·1	971	29·4	2·5 (1·8–3·5)	51 (29%)
Subtotal 25–69	1529	73·3	13 363	44·0†	4·2 (3·7–4·8)	853 (56%)

*Cases (deaths from all medical causes: excludes accident, suicide, and homicide) *vs* controls, standardised for age, educational level, and tobacco chewing. Smoking-associated number of medical deaths calculated as (1–1/risk ratio)×number of cases. Current and ex-smokers combined. †Percentages among urban and rural controls aged 25–69 years standardised to age distribution of corresponding tuberculosis deaths.

Table 4: **Death from pulmonary tuberculosis, by smoking and age, among men in urban and in rural India**

	Number of men surveyed	Proportion ever smoked (%)	Proportion ever smokers with tuberculosis (%)	Proportion never smokers with tuberculosis (%)	Ratio of tuberculosis prevalences (95% CI)*
Age range (years)					
Urban (Chennai; 251 017 surveyed)					
35–44	114 086	37·5	0·54	0·19	2·4 (1·9–3·0)
45–54	69 489	39·3	0·93	0·29	2·7 (2·1–3·3)
55–64	39 321	38·6	1·41	0·30	3·9 (3·0–5·1)
65–69	12 205	34·2	1·63	0·31	4·6 (2·8–7·3)
70–74	8405	30·5	1·42†	0·46†	2·8 (1·9–4·0)†
⩾75	7511	25·1			
Subtotal 35–69	235 101	38·0‡	0·86	0·24	2·9 (2·6–3·3)
Rural (South Arcot; 54 802 surveyed)					
35–44	22 221	48·0	..	..	..
45–54	15 506	50·4	..	..	..
55–64	9760	42·0	..	..	..
65–69	3182	34·7	..	..	..
70–74	2233	29·4	..	..	..
⩾75	1900	28·6	..	..	..
Subtotal 35–69	50 669	46·7‡	..	..	..

Tuberculsois prevalence not routinely sought in rural study area. *Tuberculosis prevalence ratio (and 95% CI), comparing tuberculosis prevalence among ever smokers *vs* tuberculosis prevalence among never smokers, standardised for age, education level, and tobacco chewing. †70–74 years and ⩾75 years combined. ‡Corresponding percentages among the controls aged 35–69 years, standardised to age distribution of those in corresponding population surveys, would have been 40·6% urban and 47·1% rural.

Table 5: **Prevalence of smoking, by age, and prevalences among smokers and non-smokers of self-reported pulmonary tuberculosis (past or current) in population survey of urban and rural men aged ⩾35 years**

the rural study area the excess mortality from tuberculosis was substantial, and highly significant, throughout adult life (table 4: when standardised to the age distribution of the rural tuberculosis deaths, the prevalence of smoking among the rural controls aged 25–69 years becomes 44% instead of 43%). Some additional deaths that were actually caused by tuberculosis may well have been misattributed to other respiratory causes, but this should not materially affect the smoker versus non-smoker risk ratios in table 4 for the deaths that were attributed to tuberculosis.

Tuberculosis prevalence (from a separate population survey)

If the main reason why mortality from tuberculosis is substantially higher among smokers is because smoking increases the incidence of clinical disease (either by facilitating infection or by helping subclinical infection progress to clinical disease), then the proportion of adults with a history of tuberculosis would be expected to be greater among ever smokers than among never smokers. A local population survey in 1998–2001 of the smoking habits of adults aged 35 years or over, done chiefly for other purposes,[7] included 250 000 men in the urban study area and 55 000 men in the rural study area, and in the urban area the men in it were also asked whether they had ever been diagnosed as having pulmonary tuberculosis (table 5). This self-reported prevalence of tuberculosis was, both in middle age and in old age, substantially greater among the ever smokers than among the never smokers. Both among smokers and among non-smokers the prevalence of pulmonary tuberculosis (past or current) increases with age, and by about 60 years of age (55–64) 1·4% of ever-smokers and 0·3% of never-smokers reported a history of tuberculosis, yielding a standardised prevalence ratio of 4 (table 5). Among ever smokers aged 35–69 years, the tuberculosis prevalence ratio is significantly ($p<0·002$) positively related to the daily consumption of cigarettes and of *bidis* (table 6).

Discussion

Smoking as a cause of tuberculosis

In this study the two most important associations with smoking, in terms of the absolute numbers of deaths involved, were the excess respiratory mortality, particularly that from tuberculosis, and the excess vascular mortality, particularly that from cardiac disease. Respiratory disease was the second most important cause of death in middle age, and was about four times as common among those who had smoked as among those who had not. Hence, even in the urban study area, the absolute excess of respiratory mortality among smokers was almost as great as the absolute excess of vascular mortality among smokers. In the rural study area it was substantially greater, and in both areas most of the tobacco-associated respiratory mortality involved death from tuberculosis.

Many of the previous studies of smoking were done in developed countries (such as the UK[14]) where tuberculosis had already become uncommon as a cause of death, or in developing countries (such as China[15,16]) where the main increase in smoking was too recent for the full hazards yet to have materialised. Hence, the potential importance of the association between persistent smoking and tuberculosis has been greatly underestimated. For example, the disease was not even indexed in two major reports by the US Surgeon General on smoking and health,[17,18] and two major reports from WHO on smoking and health[2,4] mentioned the association between smoking and tuberculosis chiefly to dismiss it. Yet in India, as in many other countries, tuberculosis still remains a major cause of premature death both in early adult life and in middle age, particularly among men who smoke. Of those who died from

	Prevalence of past or current tuberculosis (%)	Ratio of tuberculosis prevalences (95% CI)*
Smoking habit		
Urban (Chennai; 235 101 surveyed)		
Never smoked	355/145 665 (0·24)	1·0 (reference)
Cigarette smoker (cigarettes/day)†		
<10	103/22 039 (0·47)	1·7 (1·4–2·2)
⩾10	267/38 317 (0·70)	2·6 (2·2–3·1)
Bidi smoker (*bidis* per day)†		
<15	125/12 563 (0·99)	2·9 (2·4–3·6)
⩾15	170/10 553 (1·61)	4·5 (3·7–5·5)

*Standardised for age, educational level, and tobacco chewing. †Smokers or ex-smokers whose most recent habit involved only cigarettes or only *bidis*. Tests for positive trend in risk between higher and lower daily consumption among cigarette smokers and among *bidi* smokers both yield $p<0·002$.

Table 6: **Prevalence of self-reported pulmonary tuberculosis at ages 35–69 years, by amount of cigarettes or *bidis* smoked, in a population survey of men in urban India (Chennai)**

tuberculosis at ages 25–69 years, 79% in the urban and 73% in the rural study areas had been smokers, as against only about 39% and 44% of the general male population in those areas (ie, the age-matched controls; table 4). After standardisation for educational level and tobacco chewing as well as age, the results in both areas indicate a mortality ratio (smoker *vs* non-smoker) of about 4. This four-fold risk ratio is too great to be plausibly explained unless smoking itself makes death from tuberculosis more probable.

Chronic subclinical infection with the tubercle bacillus is widespread among men in India, and such infection often remains subclinical for many years, or indefinitely. Only a minority of these chronic infections progress to clinical disease.[19] In the general population survey, the proportion of adults who report a current or previous history of clinical tuberculosis is higher among those who have smoked (ie, current or ex-smokers) than among those who have never done so (table 5). This suggests that smoking acts more to increase the incidence of clinical disease, perhaps helping to convert chronic subclinical infection into clinical disease, than to increase the probability that clinical disease will lead to death from tuberculosis. For, an increased case-fatality rate among those with clinical disease would selectively remove smokers from the population of patients, and would therefore tend to reduce rather than increase the proportion of smokers with a history of clinical disease. Further evidence of causality is that the heavier the exposure (either to cigarettes or to *bidis*), the greater the prevalence of clinical disease among smokers (table 6).

Thus, smoking is a cause, and an important cause, of death from tuberculosis. Smoking is not, of course, a necessary cause of death from tuberculosis (since some non-smokers die from the disease), nor is it a sufficient cause (since, even if infected with the tubercle bacillus, many smokers do not die from the disease). But, at least in this population, smoking is an important cause of death from tuberculosis (as more than half the male deaths from tuberculosis would have been avoided if, at each age, smokers had the tuberculosis mortality rate of non-smokers).

Smoking as a cause of other diseases

Both in the urban and in the rural study areas there is, among smokers, a definite excess mortality not just from tuberculosis but from respiratory disease as a whole, from vascular disease and from neoplastic disease (and, in the urban area, from peptic ulcer). These overall findings for respiratory, vascular, and neoplastic disease are reliable, for there is no good reason to believe smoking was over-reported among the cases, and comparison of tables 1 and 5 indicates that it was not under-reported among the controls. For each of these three main disease groupings the proportional excess mortality among smokers was of similar magnitude in the urban and the rural areas (tables 2 and 3). Studies in other populations have provided strong evidence that smoking can actually cause various types of respiratory, vascular and neoplastic disease (ie, that, among otherwise similar people of a given age, smoking increases the probability of developing the disease in the near future),[2–4,17–28] and that it can cause peptic ulcer.[4] Hence, in the present study it is reasonable to conclude that the observed excess mortality from such diseases among smokers is largely or wholly causal, especially since the relative risks were not materially altered by standardisation for education. Moreover, in the urban study area (where the site of origin of the dead person's cancer was often reliably recorded), the excess mortality from neoplastic disease chiefly involved seven types of cancer that are already known to be affected by smoking: lung, mouth, pharynx, larynx, oesophagus, stomach, and liver cancer.[2–4,21–27] In contrast, the association between smoking and death from alcoholism or cirrhosis probably merely reflects a tendency of those who drink heavily also to smoke tobacco.

Because assignment of specific causes of death by verbal autopsy is sometimes not possible,[11] particularly at older ages, more precise assignment of causes might well have sharpened some of these relationships. In addition, mis-classification of some current or ex-smokers as non-smokers might well be more likely for dead people than for live people, and any such under-reporting of the smoking habits of cases may have been even greater at interviews where the verbal autopsy did not yield adequate information about the cause of death. In table 3, for example, only 40% of those with an unspecified cause of death (many of whom must have died from respiratory, vascular, or neoplastic causes) were reported to have been smokers, as against 55% of those for whom the interview led to specification of the cause of death. This lack of apparent effect of smoking on mortality from an unspecified cause in table 3 may chiefly reflect incompleteness of information both about the circumstances of death and about the habits before death. Hence, the low relative risks for death from an unspecified cause in tables 2 and 3 do not necessarily imply that the relative risks for death from respiratory, vascular, or neoplastic disease are too large.

Numbers of deaths from smoking in all India

The prevalence of smoking among middle-aged men in India as a whole[1,29,30] is similar to the average of the prevalences in the urban and rural study areas (tables 1 and 5). Hence, the proportions of respiratory, vascular and neoplastic deaths that are caused by smoking among middle-aged men in India as a whole can reasonably be estimated as the averages of the corresponding proportions at ages 25–69 years in the urban and rural study areas (which were quite similar, tables 2 and 3). In table 7, these smoking-attributed proportions are multiplied by independent estimates of the nationwide numbers of deaths in the year 2000,[31] indicating that about a quarter of all male deaths in middle age are caused by smoking. Conservatively, no deaths at earlier ages, and no deaths from other diseases (except peptic ulcer,[4] table 2) are attributed to smoking. At older ages attributable proportions only a third as great are used in table 7 for each disease, because the proportion of all mortality from medical causes that is associated with smoking appears to be only about a third as great at older ages as at ages 25–69 years (table 1). Of the deaths attributed to smoking in table 7, 13% involve cancer, a third involve vascular disease and half involve tuberculosis or other respiratory disease.

Comparison of tables 2, 3, and 7 indicates that, for men aged 25–69 years, the proportions of deaths from a specified medical cause that involve respiratory, neoplastic, and vascular disease are much the same in the present study areas as in the WHO estimates for India as a whole, as are the proportions of men who smoke.[1,29,30] Hence, table 7 provides a reasonably trustworthy indication of tobacco-smoking-attributed mortality among Indian men in the year 2000. To this must be added perhaps a few tens of thousands of female deaths as, nationwide, about 3% of middle-aged Indian women smoke[1,29,30] (even though fewer than 0·1% did so in the present study areas). Overall, therefore, tobacco smoking caused about

	Thousands of deaths attributed to smoking/ total Indian male deaths (%)*		
	0–24 years	25–69 years	⩾70 years
Cause of death			
Tuberculosis	0/25	140/242 (58%)	5/26 (19%)
Other respiratory	0/314	133/284 (47%)	38/235 (16%)
Vascular/diabetic	0/37	192/800 (24%)	50/626 (8%)
Neoplastic	0/15	74/218 (34%)	14/124 (11%)
Peptic ulcer	0/4	13/26 (51%)	1/8 (17%)
Other medical causes	0/1018	0/512	0/190
Non-medical causes	0/155	0/343	0/61
All causes	0/1568	552/2425 (23%)	108/1270 (9%)

*Total deaths from WHO Global Burden of Disease unit (A D Lopez). At ages 25–69 years smoking-attributable percentages of deaths from respiratory, vascular and neoplastic causes obtained by averaging (generally similar) urban and rural smoking-associated percentages in tables 2 and 3; most of smoking-associated mortality from other medical causes not attributed to smoking. At older ages, smoking-attributed percentages estimated to be only a third of percentages at ages 25–69 years, as suggested by table 1.

Table 7: **National numbers (year 2000) of male deaths attributed to smoking in all India, urban and rural**

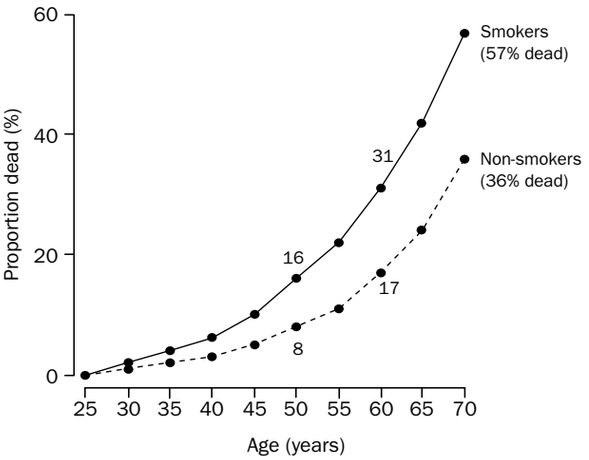
700 000 Indian deaths in the year 2000, chiefly among middle-aged men.

Comparison of table 7 with tables 1, 2, 3, and 4 suggests that, among adult respiratory deaths, WHO may, both in middle age and, particularly, in old age, have underestimated the proportion with tuberculosis as the underlying cause. Likewise, previous reports from the Registrar General of India indicate that the proportion of adult male deaths in middle age that is attributable to tuberculosis is a third greater than in table 7 and that the proportion in old age attributable to tuberculosis is twice as great as in table 7.[32,33] If this is the case, then as more reliable direct estimates (particularly from the Registrar General of India's new Sample Registration System Prospective Study[9–11]) replace the WHO indirect estimates of the numbers of deaths from particular diseases, table 7 will require recalculation. If this leaves the age-specific numbers of adult male deaths attributed to respiratory, vascular and neoplastic causes largely unchanged then the number of tobacco-attributed deaths will also be largely unchanged. If, however, within these respiratory deaths the number with tuberculosis given as the underlying cause is increased from about 300 000 to about 400 000 then the number of tobacco-attributed tuberculosis deaths will increase to about 200 000 per year, and the number of tobacco-attributed other respiratory deaths will correspondingly decrease.

Risks for the individual smoker in India

At year 2000 all-India male death rates,[33,34] about half of those aged 25 years would die from medical causes at ages 25–69 years, so about 60% of male smokers would do so. Among smokers in the present study, about 42% (41% urban, 43% rural, tables 2 and 3) of the deaths at these ages from a specified medical cause were accounted for by the smoking-attributed excesses of respiratory, vascular, and neoplastic mortality. If the same is true among smokers in India as a whole, then at current death rates about a quarter (0·42 of 60%) of the 25-year-old smokers in India would be killed by their habit at ages 25–69 years, and those killed by tobacco at these ages would, on average, lose about 20 years of life expectancy.

The figure illustrates the overall death rates among smokers and non-smokers in Chennai that would correspond to the standardised mortality ratios in table 1. At these death rates, the probability that a 25-year-old man would die before age 70 years is 57% for smokers and 36% for non-smokers. The corresponding probabilities of death just from medical causes would be 54% and 32%. The smoking-attributed excesses of respiratory, vascular or neoplastic mortality account for 41% of the deaths at these ages among smokers from medical causes—ie, for a risk of 22% (0·41 of 54%). Since the absolute death rates are somewhat lower in Chennai than in India as a whole, however, so too could be the hazards for smokers. Table 2 shows that this risk of 22% includes a risk of 6% of death from tuberculosis at ages 25–69 years in the urban study area (8% in smokers minus 2% in non-smokers). Table 3, together with the generally higher overall mortality rates in rural India, shows that the corresponding risks in the rural study area would be somewhat larger (eg, 9%—12% in smokers minus 3% in non-smokers). This finding is consistent with emerging[6] and previous[35,36] evidence from other locations.



Mortality of male smokers and non-smokers at ages 25–69 years in urban India (Chennai), at 1995–97 death rates
Standardised for educational level and tobacco chewing, and assuming no differences in mortality from non-medical causes. (Exclusion of mortality from non-medical causes would multiply both survival probabilities by 1·06, yielding 54 *vs* 32% mortality by age 70 years.)

Conclusions

About a quarter of all persistent smokers of cigarettes or of *bidis* are killed by tobacco before age 70 years, losing about 20 years of life expectancy. A third of the deaths caused by smoking are from vascular disease and half are from tuberculosis or other respiratory disease. Mortality from tuberculosis is four times as great among smokers as among non-smokers.

Among Indian male smokers and non-smokers together, smoking causes half of all deaths from tuberculosis and a quarter of all deaths from any disease in middle age. Smoking probably caused about 700 000 deaths in India during the year 2000, including about 550 000 among middle-aged men and about 110 000 among older men (with much smaller numbers among women, due to their low prevalence of smoking). The annual number of deaths from smoking must be expected to double between 2000 and 2025, partly because the population of India in early middle age will increase by half (and the populations in later middle age and in old age will both double during the period 2000–25),[37] partly because factors such as obesity and diabetes may become more widely prevalent and partly because *bidi* consumption per adult appears to have increased somewhat since the 1970s. (Annual consumption per adult age ⩾15 years was estimated by WHO[1] to have been 170 cigarettes plus 840 *bidis* in 1970–72, and 150 cigarettes plus 1200 *bidis* in 1990–92, and the full health effects of any such increase in smoking may not yet be apparent.) Thus, the number of deaths from tobacco

among Indian men just at ages 25–69 years will, if present smoking patterns persist, reach 1 million per year by about 2025, with an average of about 20 years of life lost for each such death. The annual number of deaths that will be caused by smoking at older ages is, however, less reliably predictable from the present study.

Contributors

Study planning and analysis was by V Gajalakshmi and R Peto. Fieldwork and data management were done by V Gajalakshmi, and verbal autopsy review by V Gajalakshmi and T S Kanaka. V Gajalakshmi, R Peto, and P Jha were responsible for interpretation and preparation of the report.

Conflict of interest statement

None declared.

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