Smoking adversely affects treatment response, outcome and relapse in tuberculosis

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ABSTRACT The impact of smoking on tuberculosis outcome was evaluated in a territory-wide treatment programme.

16 345 consecutive patients undergoing chemotherapy for active tuberculosis in government chest clinics in Hong Kong from 2001 to 2003 were followed up prospectively for 2 years for treatment outcome and subsequently tracked through the territory-wide tuberculosis notification registry for relapse until the end of 2012.

Smoking was associated with more extensive lung disease, lung cavitation and positive sputum smear and culture at the baseline. In both current smokers and ex-smokers, sputum smears and cultures were significantly more likely to remain positive after 2 months of treatment. Both categories of smokers were significantly less likely to achieve cure or treatment completion within 2 years. Overall, 16.7% of unsuccessful treatment outcomes were attributable to smoking, with the key contributor being default in current smokers and death in ex-smokers. Among successful treatment completers, there was a clear gradient (hazard ratios of 1.00, 1.33 and 1.63) of relapse risk from never-smokers to ex-smokers and current smokers, with an overall population attributable risk of 19.4% (current smokers: 12.2%; ex-smokers: 7.2%).

Smoking adversely affects baseline disease severity, bacteriological response, treatment outcome and relapse in tuberculosis. Smoking cessation likely reduces relapse and secondary transmission.

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Introduction

The association between smoking and tuberculosis (TB) was investigated as early as 1918 [1]. In recent years, active smoking has been shown to be associated with TB after controlling for a series of potential confounders in a number of prospective cohort studies [2–4]. Active smoking has also been associated with TB infection [5, 6] and mortality [7–10], albeit with more heterogeneous effect sizes and/or lesser degrees of certainty [11–13]. However, the full impact of smoking on the TB patients has not been evaluated in sufficient depth, especially in the setting of a national or territorial TB control programme.

In Hong Kong, the annual TB notification rate remains high at ~70 per 100 000 in recent years [14]. 18 government chest clinics offer free programmatic case-finding and treatment services for TB patients under a centralised TB and Chest Service of the Dept of Health, with estimated programme coverage of over 80%. Standard short-course regimens are used in line with the recommendations of the World Health Organization (WHO). Baseline smoking status is regularly captured at initiation of TB treatment. Brief advice on smoking cessation is given during health education, and referral for further nonpharmacological and/or pharmacological interventions is made, as deemed appropriate. Patients are regularly followed up for 2 years after initiation of TB treatment to facilitate cohort analysis of treatment outcome. A statutory TB notification system is in place, whereby medical practitioners are required to notify all diagnosed TB cases to the Dept of Health. With the availability of appropriate service infrastructure, a prospective cohort study was, therefore, conducted to examine the impact of smoking on disease severity, bacteriological response, treatment outcome and relapse among consecutive patients managed under the centralised TB programme.

Materials and methods

Consecutive patients who underwent chemotherapy for active TB at the 18 clinics of the Hong Kong TB and Chest Service from January 1, 2001 to December 31, 2003 were followed up prospectively in clinics to assess treatment progress and outcome for up to 2 years. Those who successfully completed treatment were then tracked by linking with the territory-wide TB registry and death registry using identity card number as the unique identifier for relapse, death or until December 31, 2012, whichever was the earliest. Patients who were not local residents (and, thus, without a valid local identity card number) were excluded to minimise loss to follow-up through population movement. Patients whose subsequent culture isolates showed drug resistance to either isoniazid and/or rifampicin were also excluded because of their small numbers and potential confounding effects. The diagnosis and clinical information of all identified relapse TB cases were verified by reviewing the medical records retrieved from the chest clinics and other relevant sources.

An ever-smoker was defined as one who had smoked the equivalent of at least one cigarette a day for a period of 1 year. An ex-smoker was defined as an ever-smoker who had stopped smoking for at least 1 year before the current TB episode, and a current smoker as an ever-smoker who was still smoking or had stopped smoking for less than 1 year. Patients who did not fulfil the criterion of an ever-smoker were classified as never-smokers. Relapse was defined as recurrence of TB after successful completion of treatment, either proven by isolation of *Mycobacterium tuberculosis*, or in the absence of bacteriological confirmation, recurrence diagnosed on clinical, radiological and/or histological grounds together with an appropriate response to treatment.

The clinical parameters were compared by smoking status at the baseline. For those with positive sputum smears or cultures, the bacteriological response was assessed by smear and/or culture conversion at 2 months after initiation of treatment. The proportion of patients who successfully completed treatment (cure or treatment completion) within 24 months were then compared by baseline smoking status, with control of the potentially confounding baseline parameters of sex, age, ethnicity, residency status, employment status, housing situation, alcohol dependence, drug abuse, diabetes mellitus, HIV status, retreatment *versus* new case, extent of lung involvement, lung cavity, and sputum status. For successful treatment completers, the effect of smoking on subsequent relapse was assessed, with adjustment for other baseline characteristics.

Chi-squared was used for categorical variables and ANOVA was used for numerical variables in univariable analysis. Logistic regression analysis was used for multivariable analysis of treatment outcome within an uncensored time-interval of 2 years. Kaplan–Meier analysis was used for univariable analysis of relapse and Cox proportional hazards modelling was used in multivariable analysis to adjust for potential confounding baseline parameters, using the backward conditional approach with probability to retain being 0.05 and probability to remove being 0.10. The proportional hazard assumption of the Cox model was assessed by inspection of the log minus log curve. A two-tailed p-value of <0.05 was taken as statistically significant.

The population attributable risk was estimated by a modified version of the Levin's formula as follows [2, 15]:

$$\begin{aligned}\text{Population attributable risk} &= (\text{observed rate} - \text{unexposed rate})/\text{observed rate}\\ &= 1-(\text{unexposed rate}/\text{observed rate})\\ &= 1-((N_1+N_2+N_3)\times 1/(N_1HR_{13}+N_2HR_{23}+N_3\times 1))\end{aligned}$$

where N_1, N_2 and N_3 were the number of current smokers, ex-smokers and never-smokers, respectively, and HR_{13} and HR_{23} were the adjusted hazard ratios of current smokers *versus* never-smokers and ex-smokers *versus* never-smokers, respectively. Never-smokers were used as the reference group with a hazard ratio of 1.

The study was approved by the Ethics Committee of the Dept of Health of Hong Kong (Hong Kong, China).

Results

Out of 17 415 consecutive TB patients, 212 (1.2%) with subsequently revised diagnosis, 540 (3.1%) with isoniazid or rifampicin resistance and 318 (1.8%) with unknown smoking status at initiation of treatment were excluded, leaving 16 345 patients for analysis. Table 1 summarises their baseline characteristics by smoking status. Smoking was significantly associated not only with sociodemographic variables but also with history of previous TB treatment, extent of lung disease, lung cavity, and positive sputum bacteriology at the baseline.

Table 2 shows the bacteriological status at 2 months among patients with positive bacteriology at the baseline. Both ex-smokers and current smokers were significantly more likely to have persistently positive sputum smear and culture after 2 months of treatment, and a clear gradient was seen in increasing rates of positive sputum culture from never-smokers to ex-smokers and current smokers.

Table 3 summarises the treatment outcomes at 24 months after initiation of treatment. Among the cohort, a total of 13 349 (81.7%) patients were successfully treated (cure or treatment completion) within 2 years. The major contributor to unsuccessful treatment outcome (outcome other than cure or treatment completion) was default among current smokers, while death was key reason for the poorer outcome among ex-smokers. Table 4 summarises the relationship between smoking status and treatment success in both univariable analysis and multivariable analysis. On applying the modified Levin formula to the reciprocals of the adjusted odds ratios for treatment success (equivalent to the adjusted odds ratios for

TABLE 1 Baseline characteristics of the cohort by smoking status

	Smoking status			p-value
	Never-smokers	Ex-smokers	Current smokers	
Subjects n	7687	4708	3950	
Male sex	36.8	89.9	91.3	<0.001
Mean±SD age years	47.0±21.7	63.8±17.4	49.9±16.8	<0.001
Chinese	91.4	98.3	97.6	<0.001
Permanent residents	89.3	98.0	97.5	<0.001
Unemployment	4.5	4.5	12.2	<0.001
Homeless/overcrowded[#]	6.8	10.1	5.4	<0.001
Alcohol dependence	0.4	1.4	4.4	<0.001
Drug abuse	0.1	0.7	4.1	<0.001
Diabetes mellitus	11.4	17.3	9.2	<0.001
HIV	0.3	0.5	0.6	0.034
Retreatment	9.3	18.3	14.0	<0.001
Lung involvement				<0.001
Extrapulmonary only	17.7	5.9	5.7	
⩽right upper lobe[¶]	56.4	53.5	56.8	
>right upper lobe[¶]	25.9	40.6	37.5	
Lung cavity	8.8	13.8	17.2	<0.001
Sputum status				<0.001
Smear and culture negative	45.0	29.7	34.5	
Culture positive only	25.8	30.8	28.8	
Smear positive	29.2	39.6	36.7	

Data are presented as %, unless otherwise stated. [#]: street sleeper, institutional clients, or living in bed spaces or cubicles; [¶]: total area of observable lung lesions as compared with that of the right upper lobe.

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TABLE 2 Smear and culture conversion at the end of 2 months

	Baseline smoking status			p-value
	Never-smokers	Ex-smokers	Current smokers	
Smear				<0.001
Subjects n	2246	1864	1450	
Not available	26.5	26.7	22.1	
Converted	67.7	62.3	64.7	
Not converted	5.8	11.1	9.4	
Culture				<0.001
Subjects n	3919	3102	2473	
Not available	31.0	30.7	26.4	
Converted	64.1	62.2	64.1	
Not converted	4.9	7.2	9.4	

Data are presented as %, unless otherwise stated.

unsuccessful treatment outcome) with respective baseline smoking status, 16.7% (95% CI 10.4–22.5%) of unsuccessful treatment outcome was attributable to smoking.

Among the 13 349 patients who were successfully treated, 426 relapses were detected after 107 686 person-years of post-treatment follow-up, at a rate of 396 per 100 000 person-years. Of these relapses, 349 (81.9%) involved the lung alone, 66 (15.5%) involved extrapulmonary sites alone and 11 (2.6%) involved both. Overall, 204 (47.8%) of these relapses were bacteriologically confirmed. Table 5 summarises the results of univariable and multivariable survival analyses of the effect of baseline smoking status on TB relapse. A clear gradient of increasing risk of relapse was observed from never-smokers to ex-smokers and current smokers in both analyses. Consistent results were also obtained in sensitivity analyses with respect to bacteriologically confirmed relapses. Figure 1 shows the cumulative hazard curves by baseline smoking status in Cox proportional hazards modelling using the backward conditional approach. On applying the modified Levin formula to the adjusted hazard ratios for TB relapse with respective baseline smoking status, 19.4% (95% CI 7.5–30.9%) of TB relapse among the successful treatment completers was attributable to smoking, with current smoking accounting for 12.2% (95% CI 6.5–17.7%) and ex-smoking accounting for 7.2% (95% CI 1.0–13.3%).

Discussion

In this study, both current smokers and ex-smokers were associated with more extensive lung disease, lung cavitation and positive sputum bacteriology at baseline (table 1) and increased risks of persistently positive smear and culture after 2 months of treatment as compared with never-smokers (table 2). While both categories of smokers were less likely to achieve cure or treatment completion within 2 years in both univariable and multivariable analysis (table 3 and 4), the key contributor for the poorer treatment outcome was default in current smokers and death in ex-smokers (table 3). Among successful treatment completers, there was a clear gradient (hazard ratio: 1.00, 1.33 and 1.63, respectively) of relapse risk from never-smokers to ex-smokers and current smokers.

TABLE 3 Treatment outcomes measured at 24 months after initiation of treatment

	Smoking status			p-value
	Never-smokers	Ex-smokers	Current smokers	
Treatment success[#]	6517 (84.7)	3611 (76.7)	3221 (81.5)	<0.001
Still on treatment	17 (0.2)	19 (0.4)	16 (0.4)	
Transfer out	279 (3.6)	95 (2.0)	80 (2.0)	
Defaulted	531 (6.9)	374 (7.9)	457 (11.6)	
Death (all causes)	343 (4.5)	609 (12.9)	176 (4.5)	
Subtotal	7687 (100)	4708 (100)	3950 (100)	

Data are presented as n (%), unless otherwise stated. [#]: cure or treatment completion (successfully completed treatment of ⩾6 months for new cases and ⩾8 months for retreatment cases), irrespective of subsequent relapse or death or loss to follow-up.

TABLE 4 Univariable analysis and multiple logistic regression analysis on successful treatment completion by baseline smoking status

	Subjects n	Treatment success[#]%	OR (95% CI)	p-value	Adjusted OR (95% CI)[¶]	p-value
Baseline smoking status				<0.001		<0.001
Never-smokers	7687	84.8	Reference		Reference	
Ex-smokers	4708	76.7	0.59 (0.54–0.65)		0.73 (0.65–0.82)	
Current smokers	3950	81.5	0.79 (0.72–0.88)		0.72 (0.64–0.82)	
Overall	16 345	81.7				

[#]: cure or treatment completion (successfully completed treatment of ⩾6 months for new cases and ⩾8 months for retreatment cases), irrespective of subsequent relapse or death or loss to follow-up. [¶]: adjusted for all potential confounding variables as listed in table 1, with all variables forced into the model; age was included as a continuous variable because of its reverse linear association with treatment success.

Our observations of more extensive lung disease, lung cavitation and positive sputum smears among current smokers and ex-smokers corroborate those reported in previous studies [16–18] and point to potentially enhanced secondary transmission risk [19]. In this study, both current smokers and ex-smokers were 1.5–2 times as likely to remain smear-positive and culture-positive after 2 months of treatment, closely parallel to the observation in a previous Brazilian case–control study that ever-smokers who smoked >20 cigarettes per day were also reported to be two-fold as likely to remain culture-positive after 2 months of treatment [20]. The slower bacteriological response raises concern over persistent transmission risk after the initiation of treatment, even for patients with initially fully drug-sensitive TB as included in the current study.

Similar to previous studies [21, 22], smoking was negatively associated with cure or treatment completion in this study, even after controlling for baseline sociodemographic variables, comorbidities, extent of lung disease, lung cavitation and bacteriology. As expected for the use of standard four-drug short course regimens for drug-susceptible TB, under a fully functioning treatment programme setting that also allowed individualised regimen modification and treatment prolongation, treatment failure was not an expected event. However, the default rate was as high as 11.6% among current smokers, which is double that in never-smokers. This finding further substantiates the significant association between smoking and treatment default as reported in previous studies [23, 24]. A major difference in mean age was observed between ex-smokers and current smokers. The high mortality rate among ex-smokers probably reflected the combined effects of smoking [7–10] and age-related comorbidities [25, 26]. It also remained a possibility that some of these comorbidities could have promoted the motivation for smoking cessation in the first place, and then increased the higher mortality on later follow-up.

While the independent association between smoking and TB relapse in this study corroborates those reported in previous smaller scale studies [27–29], a clear gradient of effect was seen from never-smokers to ex-smokers (adjusted hazard ratio: 1.3) and current smokers (adjusted hazard ratio: 1.6), and these

TABLE 5 Univariable and multivariable of risk of tuberculosis relapse by baseline smoking status

	Subjects n	All relapse				Bacteriologically confirmed relapse			
		Cases n (%)	p-value[#]	Adjusted HR (95% CI)[¶]	p-value	Cases n (%)	p-value[#]	Adjusted HR (95% CI)[¶]	p-value
Baseline smoking status			<0.001		0.001[+]		<0.001		<0.001[+]
Never-smokers	6517	166 (2.5)		Reference		63 (1.0)		Reference	
Ex-smokers	3611	124 (3.4)		1.33 (1.04–1.71)		65 (1.8)		1.46 (1.01–2.10)	
Current smokers	3221	136 (4.2)		1.63 (1.29–2.06)		76 (2.4)		2.10 (1.50–2.94)	
Overall	13 349	426 (3.2)				204 (1.5)			

HR: hazard ratio. [#]: Kaplan–Meier analysis, log-rank test. [¶]: adjusted for all variables listed in table 1, using the backward conditional approach with probability to retain being 0.05 and probability to remove being 0.10; age was included as a continuous variable because of its linear association with relapse; besides baseline smoking status, only age, retreatment case, extent of lung involvement and baseline sputum status were retained in the final model. [+]: p-value for trend across categories of never-smokers, ex-smokers and current smokers <0.001.

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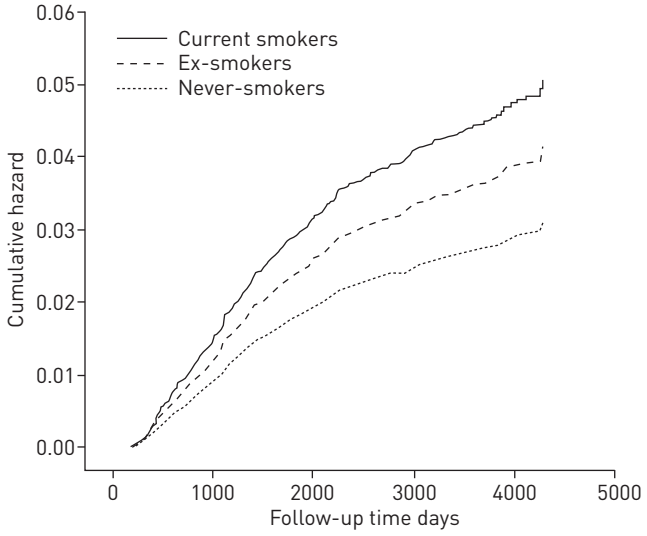

FIGURE 1 Cumulative hazards for tuberculosis relapse by smoking status in Cox proportional hazards analysis.

effect sizes were substantially lower than the two- to three-fold risks reported in the previous studies. Our observed effect sizes closely paralleled the estimated effect size of 1.5 for the effect of smoking on progression from latent TB infection to active disease (overall effect on disease/effect on infection) [10, 30] and the differences from previous observations could be attributable to our adjustment for baseline disease severity in addition to other potential confounding factors.

The effects of smoking on baseline disease parameters (lung cavitation, positive sputum smear and culture), and slower smear and culture conversion after initiation of treatment highlight a critical need for prevention of nosocomial transmission. Even for patients with initially drug-sensitive TB, the treatment completion rates fell substantially below the WHO target of 85% [31] among both current smokers and ex-smokers in this study. The high percentage of current smokers who default treatment also raises concern over the emergence of drug resistance and secondary spread within the community. Even among those who were successfully treated, they still ran a substantially higher risk (396 per 100 000 person-years) for developing active TB again than overall TB risk (70 per 100 000 person-years) in the general population [14]. Smoking contributed substantially to such relapses, with a major part of the excess risk occurring among those who continued to smoke. Passive smoking has also been shown to increase the risk of both TB infection [32] and disease [33]. Patients who continue to smoke, therefore, pose a risk not only to themselves, but also to every other person simultaneously exposed to their infection and cigarette smoke. The situation is expected to be even worse for drug-resistant TB as the effect of smoking is probably compounded by the generally poorer response to available drugs. Smoking cessation is, therefore, called for in all TB patients who smoke to protect everyone from healthcare facilities to the general community.

The number of cigarettes smoked per day or the duration of smoking was not regularly captured in this study, thus preventing the establishment of a dose–response relationship. However, the considerable size of our cohort helped to overcome the power limitations of previous studies, especially in discerning the differential effects of current smoking and previous smoking. Data capture was also facilitated by the well-developed health infrastructure with a freely accessible TB service and regular follow-up of TB patients, as well as the statutory TB notification system and death registration using the identity card number as the common unique identifier. In addition to patients with only extrapulmonary disease, quite a large number of patients failed to produce sputum spontaneously for examination at 2 months with improvement in their clinical condition, and sputum induction was not normally performed for disease monitoring in the regular service setting. While incomplete case ascertainment or misclassification could occur as in other similar studies, good validity is still expected for internal comparison among different subcategories of smokers within the same cohort. Only 47.8% of TB relapses were bacteriologically confirmed in this study. However, as shown in the first smear-active study in Hong Kong [34], joint decision by experienced physicians in clinical meetings was useful in achieving a high standard in active disease categorisation. Consistent results were also obtained on restricting the analyses to bacteriologically confirmed relapses. As data on change of smoking status was not systematically captured during treatment, we were not able to assess the impact of smoking cessation during treatment on treatment outcome. However, a cause–effect relationship might be difficult to delineate in the absence of a clear time sequence

between change in smoking status and treatment effect. Treatment adherence and other causes of loss to follow-up could also confound any observed relationship. The introduction of brief tobacco cessation advice for TB patients has been shown to be feasible in a programme setting [35]. A recent randomised controlled trial in Africa also demonstrated that motivational interviewing by lay counsellors doubled sustained smoking abstinence for at least 6 months among TB patients compared with brief advice alone [36]. A randomised controlled trial assessing the effect of smoking cessation on TB treatment outcome under a programme setting would be worth exploring to definitively answer this question.

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