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IMPACT OF CIGARETTE SMOKING ON RATES AND CLINICAL PROGNOSIS OF PULMONARY TUBERCULOSIS IN SOUTHERN MEXICO

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Abstract

Objectives—To examine the relationship between cigarette smoking and incidence and mortality rates of pulmonary tuberculosis (TB) and treatment outcomes.

Materials—From 1995-2010, we analyzed data from 1062 patients with TB and from 2001-2004, 2951 contacts in Southern Mexico. Patients with acid-fast bacilli or Mycobacterium tuberculosis in sputum samples underwent epidemiological, clinical and mycobacteriological evaluation and received treatment by the local DOTS program.

Results—Consumers of 1-10 (LS) or 11 or more (HS) cigarettes per day incidence (1.75 and 11.79) and mortality (HS,17.74) smoker-nonsmoker rate ratios were significantly higher for smokers. Smoker population was more likely to experience unfavorable treatment outcomes (HS, adjusted OR 2.36) and retreatment (LS and HS, adjusted hazard ratio (HR) 2.14 and 2.37). Contacts that smoked had a higher probability of developing active TB (HR 2.38) during follow up.

Conclusions—Results indicate the need of incorporating smoking prevention and cessation, especially among men, into international TB control strategies.

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Conflict of Interest
None

Introduction

Tuberculosis (TB) continues to be one of the great infectious disease challenges of our time, responsible for an estimated 2 billion infected people worldwide. In 2010, TB accounted for 8.8 million incident cases and 1.1 million deaths (1). TB is devastating because it burdens primarily young adults during their most productive years, precipitating significant social and economic harm. Recent TB control efforts primarily have focused on case detection and treatment, but the WHO's redesigned Stop TB strategy recognizes the imminent importance of preventing frequent risk factors (2).

Among the most common risk factors, tobacco smoking is prominent. Over 1.3 billion people smoke or consume tobacco products. Tobacco consumption accounts for over 5 million deaths per year, making it the second major cause of death worldwide (2). Similar to TB, the disease burden from tobacco use falls primarily on low and middle-income countries (2).

The association between smoking and TB has been recently reviewed (3-5). Previous literature examining the risk of smoking for treatment outcomes and retreatment shows important limitations. For unfavorable treatment outcomes, studies show unclear results (6-9), and for retreatment, significant study design limitations may not be generalizable to general population due to focus on high-risk groups, case-control design, or not controlling for important confounders (10-12).

Further, recent studies have suggested that among non-smokers, environmental tobacco smoke (ETS) exposure is a risk factor for development of active TB in people without previous infection. The results of those studies are neither conclusive nor generalizable because their study populations are mainly those younger than 15 or older than 65 years old (13, 14).

In this study, we analyzed data from a population based molecular epidemiologic study conducted in Southern Mexico from 1995 to 2010. We describe whether, among smoking and non-smoking individuals, there were differences in bacteriologically proven pulmonary TB incidence and mortality rates. Among TB patients, we analyze differences in treatment outcomes and retreatment according to smoking status.

Materials and Methods

Study site

Study site and enrollment procedures have been described previously (15). Briefly, the study area includes 12 municipalities in the Orizaba Health Jurisdiction in Veracruz State, Mexico. The study area is 618.11 km^2 and has 413 223 inhabitants, 14.4% of them in rural (fewer than 2500 residents) communities. We performed passive case finding supported by community health workers and screened persons ≥ 15 years of age who reported coughing for more than 15 days.

Recruitment and follow-up of TB patients

Between March 1995 and April 2010, patients with acid-fast bacilli or Mycobacterium (M) tuberculosis in sputum samples underwent epidemiological, clinical (standardized questionnaire, physical examination, chest radiography, and HIV test), mycobacteriological and molecular evaluations. We performed cultures on smear positive sputa from 1995 to 2000; on all sputa (both smear positive and smear negative) from 2000 to 2005; and on sputa from all previously treated TB patients, as well as any new TB patients considered at high risk of having drug resistant TB from 2005 to 2010. Treatment was provided per official

norms of Mexico's TB control program (16). Annual follow up was performed to ascertain treatment outcome, vital status, and cause of death, as previously described (15). We used the Program's operational definitions for treatment outcomes except that defaulting and death were defined according to international definitions (17). As previously described (18), deaths were attributed to tuberculosis based on two of the following: death certificate with tuberculosis as the main cause of death; interview with a close caregiver who identified tuberculosis as a probable cause of death; or bacteriologically confirmed tuberculosis at the time of death. Retreatment was defined as medically prescribed treatment occurring during follow up in a patient with a history of prior treatment for TB. Unfavorable treatment outcomes were defined as default, failure, or death during treatment.

Recruitment and follow-up of household and neighborhood contacts

From February 2001 to November 2004, all persons living in the same household as a bacteriologically-confirmed TB patient, diagnosed as outlined above, were invited to participate in the study (household contacts). For each patient, we also randomly selected a household on the same block where no TB patients had been diagnosed and invited the inhabitants to participate in the study (neighborhood contacts). We administered a standardized questionnaire investigating clinical and epidemiological variables to consenting individuals. Follow up was performed to ascertain development of active TB. The register of tuberculosis patients was reviewed periodically to identify patients with pulmonary tuberculosis who might have been missed by recruiters.

Ethical aspects

We obtained written informed consent from each individual prior to enrollment. The study was approved by appropriate institutional review boards.

Mycobacteriology and genotyping

Sputum samples were processed for M. tuberculosis following standardized procedures and isolates were genotyped and compared using IS6110-based restriction fragment length polymorphisms (RFLP) and spoligotyping, if the isolate's IS6110 RFLP patterns had fewer than 6 bands (19). We used previously standardized criteria to classify cases as "clustered" within one year of diagnosis.(19). We used this 12 month interval between clustered cases to prevent those patients harboring a strain with the same RFLP pattern belonging to a large cluster that has been circulating for years to be considered in the same cluster.

National Survey of Addictions

We used the National Survey of Addictions (NSA) to obtain smoking statistics in the general population. The NSA was a probabilistic, multi-stage, stratified, cluster household survey conducted by the Mexican Secretariat of Health during the months of April to October, 2008. Research design and methods have been described previously.(20) As part of this survey, 1522 individuals were randomly selected in the state of Veracruz to be representative of the civilian, non-institutionalized population at the state level. The study was done in accordance with the Helsinki Declaration of Human Studies.

Statistical Analysis

We used the same definitions for smoking as in the NSA (20). A non-smoker was any person that had not smoked cigarettes at least once in the 12 months prior to TB diagnoses. Smokers were classified as consumers of 1-10 (light smokers) or 11 or more cigarettes (heavy smokers) per day in that time period. We estimated the incidence rate of bacteriologically proven pulmonary TB by non-smoker, light and heavy smoker population, stratifying by sex, rural or urban residence, and clustered or unique genotype patterns using

non-smoker, light or heavy smoker TB patients from our patient cohort as numerators and estimation of the same three categories of non-smoker and smoker adult population (≥ 15 of age) for the study area from the NSA as denominators (20). We also estimated the TB mortality rate by non-smoker, light and heavy smoker population using the same three categories of non-smoker and smoker members of our cohort of patients who had died from TB as numerators and estimation of non-smoker, light and heavy smoker adult population for the study area as described above. Population data was obtained from census data (21). The ratio of smoking to non-smoking TB incidence and mortality rates were calculated and 95% CI were estimated. Statistical significance was calculated using the chi square test for trends to detect significant trends. Population attributable risk percent for tuberculosis due to light and heavy smoking was calculated.

Crude analyses were used to compare sociodemographic, behavioral, and clinical characteristics of non-smokers and consumers of 1-10 or 11 or more cigarettes per day. The bacteriological characteristics of M. tuberculosis isolates (drug susceptibilities, genotype patterns) were compared among groups. To evaluate health care access, we assessed the frequency of symptoms and disease at diagnosis, distance to nearest health center, and time elapsed between onset of symptoms and starting treatment. We used the chi-square test for trends to detect significant trends and the chi-square test with R x C contingency tables to detect significant differences between groups.

Associations between non-smokers, light or heavy smokers and unfavorable treatment outcome were investigated by multivariate unconditional logistic regression. We tested the association of smoking with a combined variable (unfavorable treatment outcome) that included either of three outcomes (default, failure or death) because the resulting p value when testing some of the individual outcomes was above the cut-off value (0.2) that we established to include in the multivariate analyses. We constructed Cox proportional hazards models to assess the association of non-smokers, light or heavy smokers with retreatment for TB among patients.

Among contacts, we classified the exposure to tobacco as follows: 1) “No one smokes in the household” when the contact and all other inhabitants of the household had not smoked cigarettes at least once in the 12 months prior to recruitment; 2) “Contact does not smoke but someone else smokes in the household” when the contact had not smoked cigarettes at least once in the 12 months prior to recruitment but another inhabitant of the household had smoked cigarettes at least once in that time period and 3) “Contact smokes” when the individual had smoked cigarettes at least once in the 12 months prior to recruitment. We constructed Cox proportional hazards models to assess the association of active and passive smoking and development of active TB among contacts. All data analysis was performed using STATA 10.0 (StataCorp LP, Texas, USA).

Results

Smoking status in tuberculosis patients

We screened 15160 individuals with a cough lasting > 2 weeks during the 15 year study period. Of these, 1101 patients were diagnosed with pulmonary TB, and 1063 patients consented to participate in the study. Smoking data was available for 1062 enrolled patients and were thus included for analysis. Of the 1062 pulmonary TB patients, 260 (24.4%) were smokers. Of the 1062 enrolled patients, on 946 (89.0%) DNA was available to perform RFLP and therefore we have genotyping information on them. There were no significant differences between patients with genotype as compared to patients on whom we were unable to perform genotype.

Incidence and mortality rates and rate ratios by smoking status

After adjustment for design effect, estimated prevalence of non-smoker, light and heavy smoker for adult population of the study area was of 87.3%, 12.1% and 0.6% respectively. We observed significantly increasing trends for overall, urban, rural, clustered and reactivated TB incidence rates when male non-smokers, light and heavy smokers were compared. Although overall incidence rates among smoking females were higher, small numbers did not allow reaching statistical differences. With the exception of females and rural light smokers, the ratio of tuberculosis incidence rates among smoker and non-smoker populations was significantly above unity for all groups (Table 1).

Trends for TB mortality rates for non-smokers, light and heavy smokers significantly increased with more frequent usage of tobacco. The ratio of tuberculosis mortality rates among smoker and non-smoker populations was significantly above unity for the heavy smoker group (17.74 (5.47-44.86), (Table 1).

Based on the population attributable risk, the proportion of tuberculosis attributable to smoking was higher for men, particularly for those living in urban settings. Overall, risk of tuberculosis among men attributable to light and heavy smoking was 12.01% and 12.61%, respectively (Table 1). When attributable risk was calculated comparing smokers (both light and heavy smokers) versus non-smokers it was found to be 20.05%.

Characteristics of patients by smoking status

Comparison characteristics of the non-smoker, light smokers and heavy smokers in the study population are shown in Table 2. We observed significant increasing trends between the groups of non-smokers, light smokers and heavy smokers to be male, younger, homeless or imprisoned, urban residents and of a higher socioeconomic level (determined by household characteristics) and with employment outside of the home. They were also increasingly more likely to report usage of alcohol and illegal drugs. We also observed significant differences between groups for age, sex, any formal education, employment outside the home, alcohol consumption, illegal drug use, homelessness or imprisonment, rural residence, and household with earthen floor.

When clinical characteristics were compared between non-smokers, light smokers and heavy smokers, we observed increased likelihood among light and heavy smokers to more frequently report hemoptysis and fever. There was no significant difference in distance from home to the nearest healthcare service. Heavy smokers had longer median time intervals between onset of symptoms, diagnosis and start of treatment.

Treatment outcomes by smoking status

Eleven patients refused treatment. Of the 1034 patients for whom treatment completion data could be evaluated, 1008 (97.4%) received directly observed therapy (DOTS). The association between smoking and failure or death during treatment was not statistically significant when each variable was examined, but the combined outcome (default, failure and death) was significant. Overall 14.7% (152/1034) had unfavorable treatment outcomes as indicated by default, failure or death during treatment. Crude analyses revealed a significant increasing trend between non-smokers, light and heavy smokers to suffer higher proportion of unfavorable treatment outcomes with significant differences between groups (Table 3).

Controlling for potential confounders in a multivariate model (Table 4), heavy smokers were significantly more likely than non-smokers to experience unfavorable treatment outcomes. Patients were followed for a median of 61 (IQR 25-91) months. One hundred and two

patients (10.2%) were retreated for TB during the study. Crude and adjusted analyses revealed that smoking was significantly associated with retreatment for TB (Tables 3 and 4). After adjusting for potential confounders in the Cox proportional hazards model, risk for retreatment among light and heavy smokers doubled the risk of non-smokers (Table 4). Inclusion of sex and usage of alcohol as covariables did not modify observed associations.

Tuberculosis among household and neighborhood contacts

From February 2001 to November 2004, 1410 household and 1541 neighborhood contacts were recruited. The frequency of smoking was 16.3% (428/2618) overall. Contacts were followed for a median of 92 (IQR 80-111) months.

Thirty individuals were diagnosed with active TB during follow up. By Cox proportional hazards model, contacts who smoked had more than a twofold risk of developing active TB than non-smoking contacts, controlling for characteristics of the contact and of the TB case. Passive smoking was not associated with development of active TB (Table 5).

Discussion

In this prospective population-based study, we demonstrated higher incidence rates of bacteriologically proven pulmonary TB among male smokers than male non-smokers. By stratifying by consumers of 1-10 or 11 or more cigarettes per day we were able to document that male heavier consumers suffered from higher incidence rates of TB. We provide data showing these elevated incidence rates are due to both reactivated and recently transmitted infection and present in rural and urban zones. With the exception of females and rural light smokers, the ratio of tuberculosis incidence rates among smoker and non-smoker populations was significantly above unity for all groups. We determined that heavy smokers have higher mortality rates from TB than non-smokers. Additionally, heavy smoking was a strong and independent predictor of unfavorable treatment outcome. Light and heavy smoking was associated with subsequent retreatment. The higher risk for smokers was confirmed by follow up of household and neighborhood contacts among whom the risk for active tuberculosis was higher among people who referred smoking in the previous year. As these epidemics collide, international TB control strategies will need to place greater emphasis on smoking cessation among TB patients.

We show evidence of higher incidence rates of pulmonary TB among male smokers by two methods. First, taking advantage of our population based study, we estimated incidence rates of TB among nonsmokers and light and heavy smokers in the general population and showed increasing trends of incidence rates with more cigarettes consumed per day, particularly among males. Second, our follow-up data of household and neighborhood contacts revealed that individuals who smoke have a higher probability of developing active TB. Previous research has done little to document incidence rates among smokers and non-smokers for pulmonary TB. With few exceptions (22) most studies were conducted in high-risk populations or were predictive models, not stratifying for relevant variables (11, 23, 24). Here, we document that, the risk increases with consumption of more cigarettes per day among men in rural and urban zones as compared to male non-smokers and that, with the exception of rural residents smoking less than ten cigarettes per day, the ratio of tuberculosis incidence rates among smoker and non-smoker populations was significantly above unity for all groups. Further, we show increasingly higher incidence rates among male non-smokers, light and heavy smokers due to recent transmission and reactivation of latent infection. If confirmed in future studies, both disease pathways will have to be addressed by future TB reduction strategies. Among females, incidence rate ratios were not significant comparing smokers to non-smokers. We consider that this is likely due to the extremely low sample size of female smokers in our cohort, comprising only 2.8% (n=30) of patients.

Our study also revealed tuberculosis mortality rate ratio significantly above unity among the heavier smoking population. Previous studies have shown conflicting results mainly due to the fact that cause of death assignments were based on death certificates which has been shown to be often unreliable (3). We based our cause of death definition on two of three criteria: death certificate, verbal autopsy and positive bacteriological result in the six months prior to death as previously described (18). The estimate for mortality risk and its upper limit were higher than that of tuberculosis incidence which suggests there may be an additional contribution to TB mortality risk from smoking, most probably due to severity of disease and poor treatment outcomes among smoking TB patients.

We reported that in our cohort, smoker TB patients are of a higher socioeconomic status, with more formal education and employment outside of the home contrasting with the profile of smokers worldwide (25, 26); but consistent with information on Mexico, showing more pronounced smoking trends in wealthier quintiles (27). There was no significant difference in distance from home to the nearest healthcare service among smokers and non-smokers. Heavy smokers had longer median time intervals between onset of symptoms, diagnosis and start of treatment, although confidence intervals largely overlap between non-smokers, light and heavy smokers. Based on these indicators, we consider that smoking and non-smoking population have similar access to health care. This is consistent with our finding that TB patients who smoke demonstrate higher socioeconomic indicators, and we conclude that higher incidence and mortality rates of pulmonary TB among smokers are not due to lesser access to health care.

Recent studies have proposed potential biological mechanisms to explain the association between smoking and TB development. Focused on pulmonary immune defenses, nicotinic suppression of intracellular TNF-α production could accelerate TB development (28). Other smoking related phenomena include reduced IFN-γ production by T cells (28, 29), inhibited phagocytic function of alveolar macrophages (30), iron loading of macrophages (31), and reduced pulmonary surfactant protein production (32). Systemically, nicotine and other compounds in cigarette smoke reduce peripheral blood mononuclear cell and T cell function that would account for increases in both unique and clustered TB cases (28).

We documented not only higher pulmonary TB incidence and mortality rates among smokers, but also that clinical manifestations such as hemoptysis and fever were more frequent. We observed that the risk of unfavorable treatment outcomes among consumers of more than 10 cigarettes per day doubled that observed among non-smokers, even though smokers were just as likely to undergo DOTS treatment and had similar healthcare services access. Importantly, this relationship persisted when controlling for independently significant confounders such as sex and alcohol usage. To date, studies that have examined unfavorable treatment outcomes for smokers have reported ambiguous results, and many are hindered by case-control designs (6-9). Previous studies on retreatment have primarily focused on relapse TB, and the few that look at recurrent TB have notable limitations and mixed results (10-12, 22, 33). We report that both light and heavy smokers have a greater than two-fold risk of retreatment for TB compared with non-smokers, even when controlling for potential confounders.

We did not find higher TB incidence rates among contacts exposed to ETS. Our results contrast with those reported by Leung et al.(14), where passive smoking was associated with the development of active TB (HR 1.49, 95%CI 1.01-2.19, p=0.05) and culture-confirmed TB (HR 1.70, 95%CI 1.04-2.80, p=0.04). However, it is important to consider that the lower limit of both CI is near the null value. The statistical significance of these results can be diluted due first to the non-smoker definition utilized (all people who have never smoked as much as 1 cigarette per day or the equivalent for the duration of 1 year), and second to not

considering proximity of a contact to a patient with active TB. The results we report are consistent with work by Den Boon et al., where passive smoking is not significant when controlling for proximity to a patient with active TB living in the same house (13). Our study reinforces the evidence of the impact of active cigarette smoking, rather than ETS exposure, as a principal risk factor for the development of active TB.

There are some potential limitations to this study. First, smoking status was self-reported during clinical history interview and was not measured via cotinine levels. However, past research indicates that for self-reported smoking, face-to-face interviews, such as ours, likely elicit accurate responses (34). Additional limitations include that among non-smokers, we did not differentiate between never and former smokers, which may confuse the association between smoking and TB. However, we would expect that this omission would bias results towards the null because former smokers, shown to have increased risk for TB (5), would be included in the non-smoking population and reduce the risk of smokers comparatively. On the other hand, we were able to differentiate between consumers of 1-10 (light smokers) or 11 or more cigarettes (heavy smokers) per day. This allowed us to document increasing incidence and mortality rates and a higher probability of unfavorable treatment outcomes and retreatment with heavier consumption. Small sample size also may have prevented us from identifying associations that were present but not detected by the power of the study particularly among female smokers. Smokers were more likely to deny having been treated before and therefore were more likely to be catalogued as “new patients” upon enrollment (although the difference was not statistically significant as compared to non-smokers). However, after treatment completion follow up revealed that they were more likely to require retreatment. We do not have an explanation for this discrepancy; however, we have observed that a fifth of patients tend to deny having been treated before, perhaps due to fear of being sanctioned by the health services. In the multivariate models we tested “any alcohol” use as we did not measure excessive alcohol use. Therefore our results may be confounded as heavy alcohol use or daily use is a marker for alcohol dependence and its related immunologic and behavioral consequences. Finally, we were unable to control for the effect of usage of biomass fuel for heating or cooking. We would expect that this effect would be more important in rural areas where its usage is more frequent in the study area (32% versus 8% in rural and urban areas, respectively).(21)

Since the characteristics of our study community are similar to others in low and medium resource regions, results may be generalizable to other settings. Based on the results of this study, there are many implications for international TB control strategies. Because both ongoing transmission and reactivation contribute significantly to disease among smokers, not only should strengthening of case detection and treatment via DOTS occur, but targeted testing and treatment for latent infection among high-risk populations such as smokers, particularly those in contact with bacteriologically proven cases, should also be considered. Our population attributable risk calculations indicate that almost a fifth of the burden of TB occurring among men could be prevented if tobacco exposure could be eliminated. Further, policy makers should consider smoking prevention measures and cessation support as necessary parts of a comprehensive national TB control program. TB and tobacco control programs need to increase communication and coordination with each other. Overall, male smokers should merit special consideration, as they represent a disproportionate total of TB patients and smokers worldwide.

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Table 1

Incidence and mortality rates of pulmonary tuberculosis in Orizaba, Veracruz, Mexico, 1995-2010.

	General	Non-smokers	Light smokers	Heavy smokers	P value §§	Incidence rate ratio Light smokers* vs Non-smokers	Population attributable risk Light smokers vs Non-smokers	Incidence rate ratio Heavy smokers† vs Non-smokers (%)	Population attributable risk Heavy smokers vs Non-smokers (%)
Incidence ‡									
Overall	29.07 (1062)	25.15 (802)	44.12 (195)	296.58 (65)	<0.001	1.75¶ (1.49-2.05)	8.41	11.79¶ (9.01-15.20)	6.86
Men	37.14 (627)	29.69 (397)	49.97 (167)	373.28 (63)	<0.001	1.68¶ (1.40-2.02)	12.01	12.57¶ (9.48-16.43)	12.61
Women	22.13 (435)	21.78 (405)	27.94 (28)	50.9 (2)	0.1	1.28 (0.84-1.88)	1.42	2.34 (0.28-8.49)	0.28
Incidence rates by zone of residence among men									
Rural cases	33.4 (79)	30.24 (59)	39.34 (16)	564.17 (4)	0.004	1.3 (0.70-2.29)	4.93	18.65¶ (4.92-50.34)	6.01
Urban cases	40.37 (548)	32.29 (338)	51.98 (151)	289.79 (59)	<0.001	1.61¶ (1.31-1.96)	11.7	8.97¶ (6.68-11.86)	13.21
Incidence rates by genotyping results among men §									
Clustered cases	2.65 (97)	1.88 (60)	5.88 (26)	50.19 (11)	<0.001	3.12¶ (1.89-5.03)	20.56	26.67¶ (12.64-51.20)	14.91
Reactivated cases	12.48 (456)	9.06 (289)	27.15 (120)	228.14 (50)	<0.001	2.99¶ (2.40-3.72)	19.54	25.17¶ (18.25-34.08)	14.16
Mortality due to TB§	1.53 (56)	1.28 (41)	2.26 (10)	22.81 (5)	<0.001	1.7 (0.78-3.57)	8.4	17.74¶ (5.47-44.86)	10.25

§§Chi-square test for trends

*Light smokers: Individuals smoking 1-10 cigarettes per day.

† Heavy smokers: Individuals smoking >10 cigarettes per day.

‡ Total rate per 100,000 person-years (n)

§ Clustering within 1 year of diagnosis.

¶ p value < 0.05.

Table 2

Characteristics of patients with pulmonary tuberculosis in Orizaba, Veracruz, Mexico, 1995-2010.

Characteristic	n/Total * (%)	Non-smokers	Light smokers †	Heavy smokers ‡	P value §	P value §§
		n/Total (%)	n/Total (%)	n/Total (%)		
Sociodemographic characteristics						
Age (Years) (Mean, SD¶)	45.45 (17.61)	46.86 (18.71)	41.18 (15.91)	40.81 (11.87)	<0.001#	<0.001
Men	627/1062 (59.0)	397/802 (49.5)	167/195 (85.6)	63/65 (96.9)	<0.001	<0.001
Any formal education	338/1061 (31.9)	417/802 (52.0)	118/195 (60.5)	48/65 (73.25)	0.037	0.06
Work outside the home	583/1062 (54.9)	417/802 (52.0)	118/195 (60.5)	48/65 (73.25)	<0.001	<0.001
Access to Social Security	373/1062 (35.1)	288/802 (35.9)	66/195 (33.8)	19/65 (29.2)	0.5	0.4
Alcohol consumption	475/1062 (44.7)	259/802 (32.3)	159/195 (81.5)	57/65 (87.7)	<0.001	<0.001
Illegal drug use	58/1062 (5.5)	8/802 (1.0)	28/195 (14.4)	22/65 (33.8)	<0.001	<0.001
Homelessness or imprisonment	37/1060 (3.5)	19/800 (2.4)	13/195 (6.7)	5/65 (7.7)	0.002	0.001
Distance to nearest health center (meters), (Median, IQR **)	705 (422-1053)	726 (430-1127)	635 (398-972)	644 (374-900)	0.8 ††	0.007
Rural residence	137/1062 (12.9)	115/802 (14.3)	18/195 (9.2)	4/65 (6.2)	0.040	0.024
Household with earthen floor	234/1023 (22.9)	191/768 (24.9)	36/191 (18.8)	7/64 (10.9)	0.013	0.017
Crowding	336/1023 (32.84)	246/769 (32.0)	66/190 (34.7)	24/64 (37.5)	0.5	0.2
Clinical characteristics						
Body Mass Index < 18	241/1061 (22.7)	178/801 (22.2)	44/195 (22.6)	19/65 (29.2)	0.4	0.4
HIV Infection	21/1036 (2.0)	13/782 (1.7)	5/192 (2.6)	3/62 (4.8)	0.2	0.1
Diabetes	348/1062 (32.8)	281/802 (35.0)	51/195 (26.2)	16/65 (24.6)	0.021	0.1
More than 10 bacilli per oil immersion field	281/1062 (26.5)	203/802 (25.3)	50/195 (25.6)	28/65 (43.1)	0.007	0.1
New patient upon enrollment	929/1062 (87.5)	692/802 (86.3)	178/195 (91.3)	59/65 (90.8)	0.1	0.6
Hemoptysis	362/1058 (34.2)	252/799 (31.5)	82/194 (42.3)	28/65 (43.1)	0.006	0.038
Fever	300/777 (38.6)	207/577(35.8)	67/151 (44.37)	26/49 (53.1)	0.016	0.004
Weight loss	906/1039 (87.2)	682/782 (87.2)	165/192 (85.9)	59/65 (90.8)	0.6	0.9
Cavitations	391/930 (42.0)	307/707 (43.4)	58/166 (34.9)	26/57 (45.6)	0.1	0.5
Night sweating	754/1060 (71.1)	556/801 (69.4)	146/194 (75.3)	52/65 (80.0)	0.1	0.4

Characteristic	n/Total * (%)	Non-smokers	Light smokers †	Heavy smokers ‡	P value §	P value §§
		n/Total (%)	n/Total (%)	n/Total (%)		
Time elapsed between onset of symptoms and treatment (days), (Median, IQR **)	107(65-186)	110(67-193)	94 (55-168)	135 (77-180)	0.034 ††	0.4
Mycobacteriology						
Drug test						
Sensitive	147/919 (16.0)	108/688 (15.7)	25/170 (14.7)	14/61 (23.0)		0.4
Resistance other than joint resistance to isoniazid and rifampin	729/919 (79.3)	546/688 (79.4)	139/170 (81.8)	44/61 (72.1)	0.5	0.8
Joint resistance to isoniazid and rifampin	43/919 (4.7)	34/688 (4.9)	6/170 (3.5)	3/61 (4.9)		0.6
IS6110 cluster	175/946 (18.5)	135/712 (19.0)	29/171 (17.0)	11/63 (17.5)	0.8	0.6

*Because there were missing values for the characteristics of some of the tuberculosis patients, several of the numbers below do not sum to the group total.

†Light smokers: Individuals smoking 1-10 cigarettes per day.

‡Heavy smokers: Individuals smoking >10 cigarettes per dya.

§Chi-square test with R × C contingency tables

§§Chi-square test for trends

¶D: Standard deviation.

#Kruskal-Wallis test

**IQR: Inter-quartile range.

††One way ANOVA.

Table 3

Treatment outcomes of pulmonary tuberculosis in Orizaba, Veracruz, Mexico, 1995-2010.

	Total *	**Non-smokers**	**Light smokers** †	**Heavy smokers** ‡	**P value** §	**P value** §§
	n/Total (%)	**n/Total (%)**	**n/Total (%)**	**n/Total (%)**		
Initiation of treatment < 10 days after diagnosis	734/980 (74.9)	538/732 (73.5)	143/185 (77.3)	53/63 (84.1)	0.1	0.5
Cure	870/1034 (84.1)	663/779 (85.1)	161/191 (84.3)	46/64 (71.9)	0.021	0.5
Default	94/964 (9.7)	66/729 (9.0)	15/176 (8.5)	13/59 (22.0)	0.004	0.041
Failure	33/903 (3.6)	23/686 (3.3)	8/169 (4.7)	2/48 (4.1)	0.7	0.5
Death during treatment	37/907 (4.0)	27/690 (3.9)	7/168 (4.1)	3/49 (6.1)	0.7	0.5
Unfavorable treatment outcome	152/1034 (14.7)	106/779 (13.6)	28/191 (14.7)	18/64 (28.1)	0.007	0.030
Follow up after treatment completion (Months) (Median, IQR ¶)	61(25-91)	61(25-87)	62 (28-92)	64 (24-124)	0. 2 #	0.09
Retreatment	102/997 (10.2)	68/752 (9.0)	23/184 (12.5)	11/61 (18.0)	0.044	0.029
Death due to any cause	253/1062 (23.8)	190/802 (23.7)	45/195 (23.1)	18/65 (27.7)	0.7	0.7
Death due to TB	76/1062 (7.2)	58/802 (7.2)	13/195 (6.7)	5/65 (7.7)	0.9	0.9
Death due to cause different from TB	177/1062 (16.6)	132/802 (6.4)	32/195 (16.4)	13/65 (20.0)	0.7	0.5

*Because there were missing values for the characteristics of some of the tuberculosis patients, several of the numbers below do not sum to the group total.

†Light smokers: Individuals smoking 1-10 cigarettes per day.

‡Heavy smokers: Individuals smoking >10 cigarettes per day.

§Chi-square test with R x C contingency tables

§§Chi-square test for trends

¶IQR: Inter-quartile range.

#Mann Whitney Test

Table 4

Results of the multivariate analysis of the risk factors for default, failure or death and retreatment for tuberculosis among bacteriologically confirmed tuberculosis patients, 1995-2010.

	Default, Failure, Death Odds Ratio* (95%CI)	P-value	Retreatment Hazard Ratio† (95%CI)	P-value
Non-smokers	1		1	-----
Light smokers	1.46 (0.81-2.63)	0.2	2.14 (1.18-3.89)	0.012
Heavy smokers	2.36 (1.1-5.05)	0.026	2.37 (1.12-4.98)	0.023
Men	1.97 (1.18-3.28)	0.009	-----	-----
Age	1.01 (1-1.03)	0.014	-----	-----
Age >55 years-old	-----	-----	1.94 (1.12-3.36)	0.017
Body Mass Index ≤ 18	-----	-----	2.07 (1.20-3.56)	0.008
Social Security	0.61 (0.37-1.01)	0.06	0.57 (0.32-1.01)	0.06
Crowding	1.98 (1.25-3.12)	0.003	-----	-----
Rural residence	1.8 (0.95-3.41)	0.07	-----	-----
New patient upon enrollment	0.3 (0.17-0.52)	<0.001	-----	-----
HIV Infection	12.79 (3.73-43.82)	<0.001	6.43 (1.49-27.74)	0.013
Any resistance to isoniazid or rifampin	0.29 (0.18-0.47)	<0.001	-----	-----
Diabetes	-----	-----	1.86 (1.09-3.17)	0.022
Joint resistance to isoniazid or rifampin	-----	-----	5.09 (2.08-12.46)	<0.001
Hemoptysis	0.56 (0.34-0.92)	0.024	1.71 (0.99-2.94)	0.06
Weight loss	0.89 (0.47-1.69)	0.7	-----	-----
Cavitations	-----	-----	1.89 (1.15-3.11)	0.011
Initiated treatment ≤ 10 days after diagnosis	0.41 (0.26-0.66)	<0.001	-----	-----
Treatment default	-----	-----	3.65 (2.01-6.60)	<0.001

*Logistic regression analysis.

†Cox proportional hazard model.

Table 5

Results of the multivariate analysis of the risk factors for development of active tuberculosis among contacts of bacteriologically confirmed tuberculosis patients

Variable	Adjusted Hazard Ratio (95% CI)	p-value *
Exposure to tobacco		
No one smokes in the household	1	-----
Contact does not smoke but someone else smokes in the household	1.19 (0.39-3.65)	0.7
Contact smokes	2.38 (1.03-5.50)	0.042
Age, (Years) (Mean SD) †	1.02 (1.00-1.04)	0.015
Diabetes	6.78 (2.90-15.86)	<0.001
Proximity with index case		
Same Neighborhood	1	-----
Sharing house	0.94 (0.24-3.68)	0.9
Sharing room	2.42 (0.8-7.29)	0.116
Sharing bed	5.93 (2.36-14.92)	<0.001
Index case with negative AFB in sputum and M. tuberculosis		-----

*Cox proportional hazard models.

†SD: Standard deviation.

‡None of the contacts living in households in which the index case had negative AFB in sputum and M. tuberculosis in culture developed TB.