Smoking and Death in Thai Diabetic Patients: The Thailand Diabetic Registry Cohort

Thongchai Pratipanawatr MD*, Petch Rawdaree MD*, Thanya Chetthakul MD*, Pongamorn Bunnag MD*, Chardpraorn Ngarmukos MD*, Yupin Benjasuratwong MD*, Rattana Leelawatana MD*, Natapong Kosachunhanun MD*, Nattachet Plengvidhya MD*, Chaicharn Deerochanawong MD*, Sompongse Suwanwalaikorn MD*, Sirinate Krittiyawong MD*, Sirima Mongkolsomlit BS*, Chulaluk Komoltri PhD*, TDR Working Group*

** Division of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol Universty, Bangkok, Thailand*

Objective: *To determine the impact of smoking and quit smoking on mortality rate.*
Material and Method: *This prospective cohort was a three-year follow-up of Thai Diabetes Registry project that registered 9,370 diabetic patients from 10 diabetic clinics in tertiary medical centers in Bangkok and major provinces between April 2003 and February 2006.*
Results: *The groups of 7,487 (80%), 1,315 (14%), and 568 (6%) patients were classified as non-smokers, ex-smokers, and current smokers. The crude death rate of ex-smokers (Hazard Ratio (HR) 1.52 (95% CI 1.19-1.95)) and current smokers (HR 1.55 (1.10-2.19)) were higher than death rate of non-smokers. After control for covariates, the HR comparing ex-smokers with non-smokers was not different (1.10 (0.81-1.50)), while the HR comparing current smokers with non-smokers remained statistical significant (1.74 (1.17-2.61)).*
Conclusion: *Smoking increases mortality rate in diabetic patients by about 74%. Quitting smoking decreased mortality rate to the same rate as of diabetic non-smokers.*

Keywords: *Diabetes, Smoking, Death rate, Cause of death*

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Smoking was recognized as an important health problem for more than a half century[1]. It is leading to increase death[2-5]. The World Health Organization now recognizes tobacco use as the major preventable cause of adult death, and about 5 million deaths worldwide each year (8.8% of all deaths annually) are attributed to smoking[6]. On a global scale, the death toll from tobacco use is increasing[7,8]. Thailand is also suffering to burden of smoking problem.

People with diabetes experience considerably worse health outcomes and have a shorter life expectancy than the general population. This is largely attributable to a two to four times greater risk of cardiovascular disease, which accounts for two-thirds of deaths among people with diabetes[9-11]. Cigarette smoking was shown to be a significant risk factor for death by coronary heart disease in type 2 diabetes[12-14]. Smoking is an important modifiable risk factor for cardiovascular disease and microvascular complications in people with diabetes[15]. Despite being at an increased risk of cardiovascular disease and cancer, many people with diabetes smoke, with the rate of smoking among people with diabetes approaching the rate in the general population[16,17].

Comprehensive tobacco control strategies have been an integral component of public health policy in Thailand for many years. These strategies aim to reduce overall tobacco use and exposure especially young people. Direct and indirect cigarette advertisements are prohibited. Sale of cigarettes to young people is illegal. Smoking in public is prohibited except in a smoking zone. However, despite evidence of success in tobacco control, the authors have no known evidence about risk of smoking and benefit of quit smoking in Thai diabetic people.

In this article, the authors present the findings of a longitudinal study of 9,370 Thai diabetic patients that examined the impact of smoking and quit smoking on mortality rate.

Correspondence to:
Pratipanawatr T, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Phone: 043-363-664
E-mail: thongcha@kku.ac.th

Material and Method

Setting and Subjects

The methods in detail of Thailand Diabetic Registry have been described previously[18]. In brief, the authors registered diabetic patients in diabetic clinics of eleven tertiary care hospitals across Thailand. The authors examined smoking status based on information recorded during registry periods (April 2003 and December 2003). The authors also included demographic data, pertinent parts of physical examinations, laboratory examinations performed over the 12 months prior to recruitment, medications (including insulin, oral hypoglycemic agents, antihypertensive agents, lipid lowering agents and aspirin), and diabetic complications verified by physician's reports. The patients were the diabetics being treated in these clinics and they gave informed consent before participating in the registry. The present study was approved by the Ethics Committees at each hospital.

The authors categorized smoking status as 1) current smokers - those who were still smoking on the day of examination or who had quit for less than one year, 2) ex-smokers - those who had stopped smoking for at least one year, and, 3) non-smokers - those who had never smoked.

Health care plan were categorized to Universal Coverage, Social Security Welfare, Civil Service health plan, private health insurance, and self-paid. Civil Service health plan is health plan for government officer and their family. It will pay for all health care cost. Social Security Welfare is the health care plan that worker and their company pay for their health insurance fee. Universal coverage health plan is provided by the government for all Thai people who had no coverage by other health care plan. It covers almost all essential health care but not the expensive care such as chronic kidney replacement.

At the end of February 2006, the vital statuses of 9,370 diabetic patients (99.5%) were determined by database of each participating hospitals and The Bureau of Registration Administration, The Ministry of Interior. The primary outcome was death from all causes. In order to avoiding inaccuracy of death certificates, the causes of death were defined by a panel of two independent physicians on reviewing of medical records. Disagreement was settled by consensus.

Outcome events

The primary outcome was death from all causes. Smoke-related death was defined as cardiovascular and cancer death. Death from cardiovascular disease included cardiac disease, stroke, and sudden death. Coronary artery disease was recognized as myocardial infarction - viz., serial electrocardiographic changes leading to development of Q waves, characteristic increase in serum myocardial markers with a suggestive clinical history or evidence at autopsy of new or recent infarction - while unstable angina pectoris was defined by a clinical history of acute coronary syndrome without definite criteria of myocardial infarction. Stroke was categorized into ischemic and hemorrhagic stroke by CT or MRI scan. Malignancy and infection were sub-categorized according to the primary organ of malignancy or infection.

Statistical methods

The patients were divided into three groups according to smoking status, current smoke, ex-smoke, and never smoke. Descriptive statistics were used. Proportions of studied variables were compared using the χ^2 and Fisher's exact tests. Differences in mean values of studied variables were compared using the t-test and the Mann-Whitney U test.

Cox proportional hazard models were used to calculate hazard ratios (HR) for all cause mortality and smoke-related mortality in relation to smoking status. The association between smoking status and all cause and smoke-related mortality was assess after controlling for covariates. Covariates factors were determined by applied multiple Cox regression models (backward elimination). Whenever two variables were very similar and had multi-co-linearity, only one of them was included in the model. For the final Cox proportional hazard model, assessment of the model adequacy was constructed. The proportional hazard assumption and goodness-of-fit were tested.

Statistical analyses were performed using STATA version 8.0 (Stata Corporation, College Station TX, US).

Results

The groups of 7,487 (80%), 1,315 (14%) and 568 (6%) patients were classified as non-smoker, ex-smoker, and current smoker. Table 1 shows the baseline characteristics of each group. Differences in treatment between each group are shown in Table 2.

The current smoker and ex-smoker were male predominant, meanwhile most of non-smoker group were female. Ex-smoker group were older, had longer duration of diabetes, and had more prevalence of

hypertension, previous history of coronary artery disease, cerebrovascular disease, and renal impairment that were reported as important risk factors of death. Ex-smoker group was taking more lipid lowering agent, aspirin, and anti-hypertensive agents than current smoker. These findings may reflect more chronic and severe disease in ex-smoker patients. These confounding factors in ex-smokers complicate the interpretation of the increased risk for death in ex-smokers compared with nonsmokers and current smokers. The issue is complex, and confounding might both inflate and deflate smoking and death associations.

The crude death rate of ex-smoker (25.4 per 1,000 patient-year) was the same as current smoker (25.9 per 1,000 patient-year) and higher than non-smoker (16.7 per 1,000 patient-year) (Table 4). After adjusting for age and sex that were considered an important confounders, age- and sex-adjusted HR (model 1) for all-cause mortality of ex-smoker was not significantly higher than the non-smoker group (1.22 (0.91-1.62)), while age- and sex-adjusted HR comparing current smoke with non-smoker was significant high (1.73 (1.19-2.52)). Age, health care plan, education, HbA1c, previous history of coronary artery disease, and cerebrovascular disease, metformin, insulin and lipid lowering agent treatment were independent risk factors for all causes of mortality. After control all these covariates (model 2), the HR comparing ex-smoke with non-smoker was not difference (1.10 (0.81-1.50)), while the HR comparing

Table 1. Patient characteristics at entry divided by smoking status

	Non-smokers (n = 7,487)	Ex-smokers (n = 1,315)	Current smokers (n = 568)	p-value
Age	59.2±13.9	62.7±10.8	54.9±12.2	<0.01
Male sex	1,571 (21.0)	1,136 (86.4)	489 (86.1)	<0.01
Duration of DM	10.5±7.7	11.0±7.5	8.0±6.7	<0.01
Height	155.8±8.4	163.6±7.6	164.7±8.0	<0.01
Weight	62.3±12.6	67.8±11.9	68.4±13.6	<0.01
BMI	25.6±4.4	25.3±3.9	25.2±4.4	NS
SBP	142.3±23.1	144.8±22.5	136.6±20.1	<0.01
DBP	78.6±11.3	79.4±11.7	79.3±11.5	NS
Education higher than BSc	1,255 (16.8)	321 (24.4)	110 (19.4)	<0.01
Hx of coronary artery disease	653 (7.4)	174 (13.3)	31 (5.5)	<0.01
Hx of cerebrovascular disease	305 (4.1)	91 (6.9)	14 (2.5)	<0.01
Hypertension	5,572 (74.4)	1,067 (81.1)	346 (60.9)	<0.01
FBS	153.4±56.2	151.2±54.1	161.0±67.2	<0.01
HbA1c	8.2±1.9	8.1±1.9	8.2±1.8	NS
Cr	1.1±0.8	1.4±1.3	1.2±0.7	<0.01
Cholesterol	198.1±42.3	192.0±41.3	196.4±46.5	<0.01
Triglyceride	147.5±92.3	156.7±125.2	179.6±182.4	<0.01
HDL	55.0±15.6	50.0±13.0	48.4±13.1	<0.01
LDL	114.9±36.0	112.3±33.4	114.5±38.0	<0.01
Serum Cr				<0.01
<1.5	6,278 (83.9)	967 (73.5)	469 (82.6)	
1.5 to 3.0	855 (11.4)	285 (22.7)	60 (10.6)	
>3.0	354 (4.7)	63 (4.8)	39 (6.9)	
Health care plan				<0.01
Government officer	4,150 (55.4)	826 (62.8)	280 (49.3)	
Self pay & insurance	2,133 (28.5)	327 (24.9)	167 (29.4)	
Social welfare	423 (5.7)	65 (4.9)	52 (9.2)	
Universal coverage	781 (10.4)	97 (7.4)	69 (12.2)	
Type 1 diabetes	370 (4.9)	29 (2.2)	24 (4.2)	<0.01

Table 2. Treatment at entry divided by smoking status

	Non-smokers (n = 7,487)	Ex-smokers (n = 1,315)	Current smokers (n = 568)	p-value
Insulin	2,140 (28.6)	404 (30.7)	169 (29.8)	NS
Sulfonamide	4,924 (65.5)	863 (65.2)	364 (63.6)	NS
Metformin	5,192 (69.4)	805 (61.2)	376 (66.2)	<0.01
TZD	400 (5.3)	77 (5.9)	28 (4.9)	NS
ACEi	2,580 (34.5)	547 (41.6)	169 (29.8)	<0.01
ARB	601 (8.0)	131 (10.0)	29 (5.1)	<0.01
B-Blocker	1,497 (20.0)	253 (19.2)	66 (11.6)	<0.01
Alpha-blocker	217 (2.9)	76 (5.8)	14 (2.5)	<0.01
Calcium channel blocker	1,662 (22.2)	299 (22.7)	84 (14.8)	<0.01
Diuretic	2,144 (28.5)	356 (26.9)	119 (20.8)	<0.01
Statin	3,286 (43.9)	640 (48.7)	212 (37.3)	<0.01
Fibrate	941 (12.6)	194 (14.8)	91 (16.0)	<0.01
Lipid lowering agent	4,054 (54.2)	777 (59.1)	281 (49.5)	<0.01
ASA	2,520 (33.7)	566 (43.0)	205 (36.1)	<0.01

Table 3. Causes of death categorized by smoking status

	Non-smokers (n = 7,487)	Ex-smokers (n = 1,315)	Current smokers (n = 568)	p-value
Total death	308 (4.1)	81 (6.2)	36 (6.3)	<0.01
CVD death	88 (1.2)	21 (1.6)	10 (1.76)	<0.01
Cancer death	61 (0.8)	17 (1.3)	5 (0.9)	<0.01
Infectious death	70 (0.9)	12 (0.9)	9 (1.6)	<0.01
Kidney death	29 (0.4)	10 (0.8)	1 (0.2)	<0.01

current smoke with non-smoker remained statistical significantly (1.74 (1.17-2.61)).

The age- and sex-adjusted HR (Table 5 (model 1)) for smoke-related mortality comparing ex-smoker with non-smokers was 1.27 (0.83-1.93), while the HR for smoke-related mortality comparing current smoker with non-smoker was 1.64 (0.92-2.92). Age, HbA1c, previous history of coronary artery disease and cerebrovascular disease, metformin and lipid lowering agent treatment were independent risk factors for smoke-related mortality. After control all these covariates (model 2), the HR comparing ex-smoker with non-smoker was not difference 0.93 (0.58-1.47). Although smoke-related mortality HR for smoke-related mortality comparing current smoker with non-smoker was not significant (1.76 (0.96-3.22)), it showed the same direction with all-cause mortality.

Among ex-smokers who were divided by duration of quit smoking in to two groups, recent quit smoking (<10 year) and quit smoking earlier (≥10 year) groups. Both groups had the same benefit. The age- and sex-adjusted HR for all-causes mortality comparing recent quit smoking and quit smoking earlier groups with non-smokers were 1.31 (0.91-1.67) and 1.13 (0.79-1.63). After adjusted for all covariates, they were 1.12 (0.74-1.68) and 1.07 (0.72-1.59).

For each smoking status, all-cause (Fig. 1A) and smoke-related (Fig. 2A) unadjusted mortality Kaplan-Meier survival estimates are illustrated for the follow-up period, as well as age-and sex-adjusted survival estimates (Fig. 1B, 2B).

Discussion

The authors demonstrated impact of smoking on mortality rate in Thai diabetic patients. Smoking increases mortality rate by about 74%. Quit smoking decreased mortality rate to the same rate as of non-smoker patients.

Despite being comprehensive tobacco control in Thailand for many years, about 6% of people with diabetes smoking. Death rate in smoking population was 74% higher than non-smoking. That

Table 4. Adjusted hazard ratios (and 95% CI) from multivariate Cox models for a given difference factors level for all cause-mortality

Variables	Crude HR	Model 1	Model 2
Smoking			
Non-smokers	1	1	1
Ex-smokers	1.52 (1.19-1.95)	1.22 (0.91-1.62)	1.10 (0.81-1.50)
Current smokers	1.52 (1.19-1.95)	1.73 (1.19-2.52)	1.74 (1.17-2.61)
Age (10 years)		1.60 (1.47-1.75)	1.55 (1.40-1.70)
Female gender		0.84 (0.66-1.06)	0.93 (0.72-1.21)
Health plan			
Civil Service			1
Self pay & insurance			1.07 (0.83-1.39)
Social welfare			1.04 (0.58-1.85)
Universal coverage			1.96 (1.48-2.58)
Education			
Below BSc.			1
BSc. or Higher			0.65 (0.45-0.94)
Serum creatinine			
<1.5			1
1.5-3.0			1.82 (1.40-2.37)
>3.0			6.85 (4.86-9.66)
Previous history of coronary artery disease			1.97 (1.52-2.56)
Previous history of cerebrovascular disease			1.78 (1.24-2.54)
Using lipid lowering agent (statin and/or fibrate)			0.56 (0.45-0.69)
Insulin			1.49 (1.18-1.87)
Metfomin			0.59 (0.47-0.74)
Hba1c (1%)			1.06 (1.01-1.12)

Table 5. Adjusted hazard ratios (and 95% CI) from multivariate Cox models for a given difference factors level for smoke-related mortality

Variables	Crude HR	Model 1	Model 2
Smoking			
Non-smokers	1	1	1
Ex-smokers	1.48 (1.03-2.10)	1.27 (0.83-1.93)	0.93 (0.58-1.47)
Current smokers	1.34 (0.79-2.27)	1.64 (0.92-2.92)	1.76 (0.96-3.22)
Age (10 years)		1.66 (1.46-1.89)	1.59 (1.38-1.82)
Female gender		0.95 (0.67-1.34)	1.02 (0.70-1.49)
Serum creatinine			
<1.5			1
1.5-3.0			1.72 (1.19-2.48)
>3.0			2.43 (1.36-4.36)
Previous history of coronary artery disease			2.05 (1.37-3.06)
Previous history of cerebrovascular disease			2.13 (1.30-3.49)
Using lipid lowering agent (statin and/or fibrate)			0.56 (0.41-0.76)
Metfomin			0.56 (0.41-0.76)
Hba1c (1%)			1.12 (1.04-1.20)

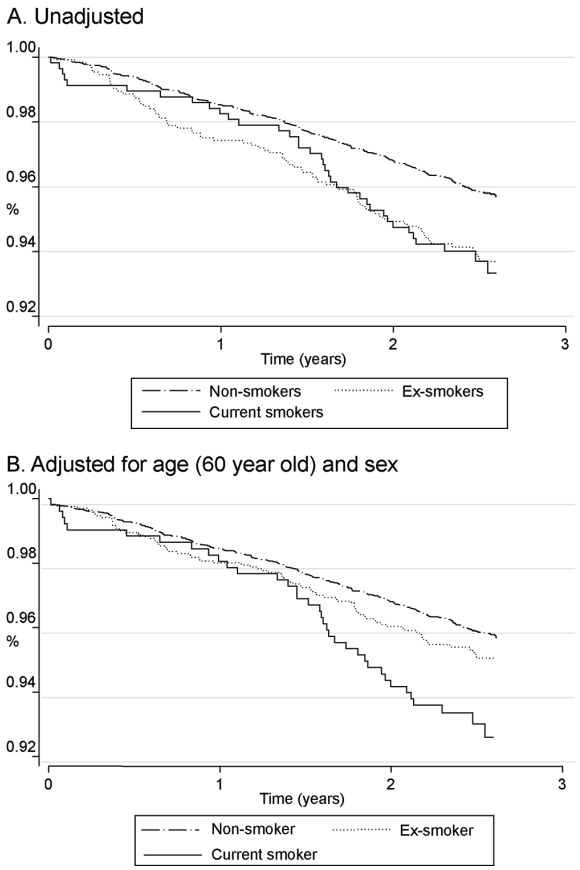

Fig. 1 Kaplan-Meier all cause survival estimates for smoking status.
A. Unadjusted
B. Adjusted for age (60 year old) and sex

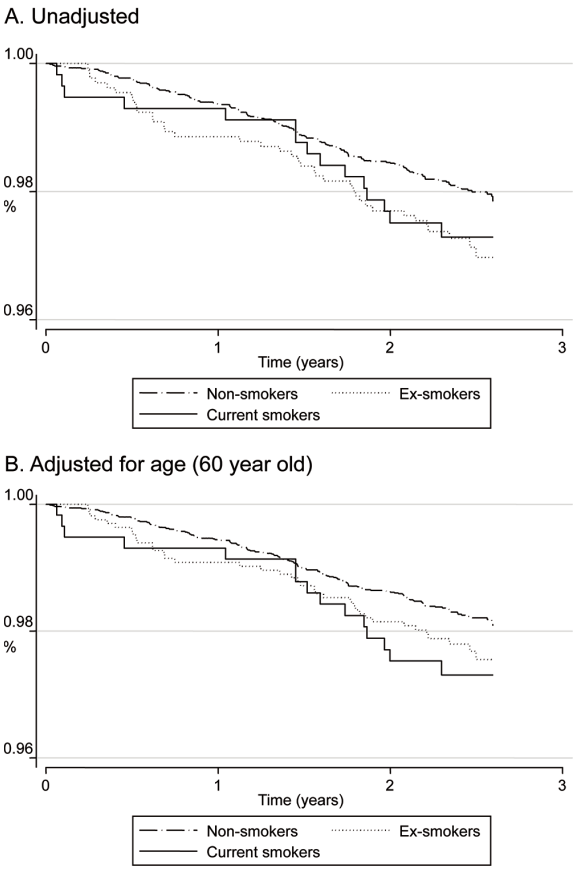

Fig. 2 Kaplan-Meier smoke-related survival estimates for smoking status.
A. Unadjusted
B. Adjusted for age (60 year old) and sex

was about the same risk as non-diabetes population[19]. Risk of death from smoking is higher than benefit from lipid lowering agent.

About 14% of our diabetes population was ex-smoker. The mortality rate of ex-smoker was as high as the mortality rate of current smoker were 1.52 (1.19-1.95) and 1.55 (1.10-2.19) times higher than non-smoker. However, ex-smoker patients were in high-risk population such as elder, longer duration of diabetes, with high prevalence of hypertension and diabetic complication. Our findings are reflecting that higher motivation in quit smoking in elder and diabetes patients with complication. Crude death rate may be confounded by these important risk factors. After adjustment for all covariates, death rate of ex-smoker was lower than current smoker and equal to non-smokers. In general, population, ex-smokers are at lower risk for total mortality compared with continuing smokers[5,20,21]. The authors showed the same benefit in our diabetes population. The time required for the risk for total mortality among quitters to reach the level of never smokers differs among studies, ranging from 6 to 10 years in one study[22] to 10 or more years in other studies[20,23]. All-cause mortality risks were higher for recent quitters (1-9 years) than for those who quit earlier (≥10 years), compared with subjects who have never smoked[24]. However, we cannot demonstrate the same time response effect of quit smoking.

In order to reduce mortality related to smoking, smoking cessation program must be introduced to all smoking patients. Intensive smoking cessation program including a strong physician message, group sessions by using behavior modification, nicotine gum and maintenance program with stressed coping skills, was a higher rate of quit smoking[21]. Intensive smoking cessation program also decreases all cause-mortality. Thus, we may need to develop our intensive program for Thai diabetes patients.

Conclusion

The authors demonstrated current diabetic smoker had a higher mortality rate than diabetic non-smokers by 74%. Diabetic patients who quit smoking had a mortality rate the same as non-smokers.

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Potential conflicts of interest

None.

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การสูบบุหรี่และการเสียชีวิตในผู้ป่วยเบาหวานไทย: โครงการลงทะเบียนผู้ป่วยโรคเบาหวานในประเทศไทย

ธงชัย ประฏิภาณวัตร, เพชร รอดอารีย์, ธัญญา เชฏฐากุล, พงศ์อมร บุญนาค, ฉัตรประอร งามอุโฆษ, ยุพิน เบ็ญจสุรัตน์วงศ์, รัตนา ลีลาวัฒนา, ณัฐพงศ์ โฆษชุณหนันท์, ณัฐเชษฐ์ เปล่งวิทยา, ชัยชาญ ดีโรจนวงศ์, สมพงษ์ สุวรรณวลัยกร, สิริเนตร กฤติยาวงศ์, สิริมา มงคลสัมฤทธิ์, จุฬาลักษณ์ โกมลตรี, กลุ่มงาน TDR

วัตถุประสงค์: *เพื่อศึกษาผลของการสูบบุหรี่และการหยุดสูบบุหรี่ที่มีต่ออัตราการการเสียชีวิตของผู้ป่วยโรคเบาหวานที่ติดตามรักษาที่คลินิกโรคเบาหวานในโรงพยาบาลมหาวิทยาลัยและโรงพยาบาลระดับทุติยภูมิในประเทศไทย*

วัสดุและวิธีการ: *การศึกษานี้เป็นการติดตามผู้ป่วยที่อยู่ในโครงการลงทะเบียนผู้ป่วยโรคเบาหวานในประเทศไทย ระหว่างเดือนเมษายน พ.ศ. 2546 ถึง กุมภาพันธ์ พ.ศ. 2549 จากคลินิกโรคเบาหวานในโรงพยาบาลมหาวิทยาลัย และโรงพยาบาลระดับทุติยภูมิในประเทศไทย จำนวน 10 แห่งในกรุงเทพฯ และเมืองใหญ่ ๆ ทั้ง 4 ภาค ของประเทศไทย*

ผลการศึกษา: *เมื่อแบ่งตามสถานะของการสูบบุหรี่ออกเป็น 3 กลุ่ม กลุ่มสูบบุหรี่ (current smoker) 7,487 ราย กลุ่มที่ไม่เคยสูบบุหรี่ (non-smoker) 1,315 ราย และกลุ่มที่เคยสูบบุหรี่แต่หยุดสูบแล้ว (ex-smoke) 568 ราย เมื่อยังไม่คำนึงถึงปัจจัยอื่น กลุ่มที่เคยสูบบุหรี่แต่หยุดสูบแล้ว และกลุ่มสูบบุหรี่ มีอัตราการเสียชีวิตมากกว่าผู้ที่ไม่เคยสูบบุหรี่ ถึงร้อยละ 52 และ 55 แต่เมื่อปรับตามปัจจัยเสี่ยงต่าง ๆ ที่มีผลต่ออัตราการเสียชีวิต พบว่ากลุ่มที่สูบบุหรี่ยังคงมีอัตราการเสียชีวิตมากกว่ากลุ่มที่ไม่สูบบุหรี่ถึงร้อยละ 74 แต่กลุ่มที่หยุดสูบบุหรี่แล้ว มีอัตราการเสียชีวิตไม่แตกต่างจากกลุ่มที่ไม่เคยสูบบุหรี่*

สรุป: *การสูบบุหรี่เพิ่มอัตราการเสียชีวิตถึงร้อยละ 74 การหยุดสูบบุหรี่ทำให้อัตราการเสียชีวิตลดลงมาเท่ากับผู้ที่ไม่สูบบุหรี่*