Smoking cessation and COPD mortality among Japanese men and women: The JACC study

Yuanying Li [a], Kazumasa Yamagishi [b], Hiroshi Yatsuya [c], Akiko Tamakoshi [d], Hiroyasu Iso [a,*]

[a] Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

[b] Department of Public Health Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8575, Japan

[c] Department of Public Health and Health Systems, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

[d] Department of Public Health, Aichi Medical University School of Medicine, 21 Aza-Karimata, Oaza-Yazako, Nagakute-cho, Aichi 480-1195, Japan

[*] *Corresponding to:* Hiroyasu Iso, MD, PhD, Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Osaka, Japan, 2-2 Yamataoka, Suita-shi, Osaka 565-0871, Japan.

Phone: +81 6 6879 3911; Fax: +81 6 6879 3919

E-mail address: iso@pbhel.med.osaka-u.ac.jp

Objective. To investigate an effect of smoking cessation on chronic obstructive pulmonary disease (COPD) mortality in Asians.

Method. The data was obtained from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study). A total of 41,465 Japanese men and 52,662 Japanese women aged 40-79 years who had no history of COPD, asthma, other chronic lung diseases, cardiovascular disease or cancer were followed between 1988 and 2008.

Results. During median 18-year of follow-up, there were 285 (251 men and 34 women) documented deaths from COPD. Multivariable-adjusted hazard ratios with 95% confidence intervals of COPD death were 4.46 (2.72-7.29) and 9.26 (4.19-20.5), respectively for current male and female smokers when compared to never smokers. Compared with current smokers, the multivariable HRs for 5-9 years and 10 years or more smoking cessation prior to baseline were 0.44 (0.22-0.87) and 0.36 (0.22-0.58) in men, respectively while the HR for never smokers was 0.30 (0.16-0.57). There were an insufficient number of COPD deaths in women to clarify this association.

Conclusion. Smoking cessation for ten years or more prior to enrollment reverses the excess risk of COPD mortality to a level similar to that observed among never smokers in men.

Keywords: Smoking Cessation; COPD; Mortality; Prospective Study; Epidemiology

Introduction

Chronic obstructive pulmonary disease (COPD) is a long-standing, crippling disease characterized by accelerated decline of lung function. The disease is commonly brought by aging and long-term tobacco smoking(Burrows et al., 1977; Fletcher and Peto, 1977). The latest report from World Health Organization described that COPD is the only major cause of deaths that has increased in recent years and that it is predicted to become the third leading cause of death worldwide by 2030, both are due to the expansion of smoking habit in developing world and increasing life expectancy(WHO report, 2008). Recent updated international guidelines define COPD as a preventable and treatable disease by smoking cessation that convincingly palliates the accelerated lung function decline(Rabe et al., 2007).

Several prospective studies have described lower COPD mortality risks in former smokers compared to continuous smokers(Carstensen et al., 1987; Doll et al., 1980; Doll et al., 2004; Rogot and Murray, 1980). However, they were worksite-based studies in male Caucasians(Carstensen et al., 1987; Doll et al., 2004; Rogot and Murray, 1980), except for one study conducted in women(Doll et al., 1980). Moreover, no studies have addressed whether there may be certain duration of smoking cessation that would significantly reduce risk of COPD mortality to the level similar to never smokers.

The detailed examination of this issue would enable us to formulate more an explicit public health recommendation. Therefore, in this 18-year follow-up cohort study of approximately 95,000 Japanese men and women, we examined risk of COPD mortality associated not only with smoking status but time since quitting smoking.

Methods

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study) was initiated 1988-1990(Kawado et al., 2005; Ohno and Tamakoshi, 2001). Self-administered questionnaires that included items on lifestyles and medical histories of COPD, cancer, cardiovascular disease and other diseases were completed by 110,792 persons(46,465 men and 64,327 women) aged 40-79 years from 45 communities across Japan. Among them, 44,201 men and 55,592 women provided valid responses about smoking status. Those who had quit smoking were asked at what age or what year they stopped in order to calculate the years of smoking cessation. We also excluded 2,736 men and 2,930 women with a reported history of COPD, asthma, other chronic lung diseases, cardiovascular disease or cancer at baseline, leaving 41,465 men and 52,662 women for the present analysis.

Mortality surveillance was conducted systematically by reviewing death certificates. The underlying causes of death according to the *International Classification of Diseases* (ICD-10) were obtained centrally from the Ministry of Health and Welfare. COPD was

defined as ICD-10 codes of J41 to J44 and J47. The present study was approved by the Ethical Committee, Nagoya University and Osaka University.

Statistical Analysis

Participants were followed-up until death or they moved away from the original community to the end of 2008. The follow-up of six and five communities ended at the end of 1999 and 2003, respectively. Median follow-up period was 18 years. Sex-specific, age-adjusted means and proportions of selected COPD risk factors were calculated by general linear model.

Sex-specific, age-adjusted and multivariable-adjusted hazard ratios(HRs) and their 95% confidence intervals(95% CIs) were calculated by Cox proportional hazards models. Duration of smoking cessation was divided to three groups (0-4, 5-9 and ≥10 years before the baseline). Variables included in the multivariable-adjusted model were age at baseline, body mass index, ethanol intake, hours of walking, hours of exercise, education, perceived mental stress, and histories of hypertension and diabetes. Number of cigarettes smoked per day and age of smoking initiation were also included in the smoking cessation analysis.

Sensitivity analyses were conducted separately by excluding early deaths from COPD mortality within the first 5-year of follow-up and by excluding those with self-reported persistent phlegm symptom in an attempt to reduce a reverse causal relationship. Interaction for sex-by-smoking status was tested by using cross-product terms of sex with smoking status. In order to evaluate the specificity of association of smoking status or smoking cessation

duration with COPD mortality, all-cause mortality was also modeled, and the result was compared with that of COPD. This was done by computing a test statistic: $(b_1-b_2)^2/\{[SE(b_1)]^2+[SE(b_2)]^2\}$, where b_1 is the coefficient for the association with COPD, b_2 is the coefficient for all-cause mortality, $SE(b_1)$ and $SE(b_2)$ are the corresponding standard errors for the association with COPD and all-cause mortality, respectively(Allison, 1995).

The proportional hazards assumption was confirmed graphically by examining the parallelness of the ln (-ln) survival curves for smoking status as well as by a model including the interaction term between follow-up time and smoking status. The follow-up time was first treated as a continuous scale and then dichotomized at year 11 (middle value of follow-up) in the model. We found no violation for the proportional hazard assumption.

All analyses were performed by using SAS version 9.1.3 Service Pack 4 (SAS Institute, Cary, North Carolina). Two-tailed probability values of <0.05 were considered statistically significant.

Results

The proportions of current and former smokers were 54% and 25% in men, and 6% and 2% in women, respectively. Majority of male smokers (68%) smoked 20 or more cigarettes per day, but the corresponding proportion in female current smokers were 31%. Compared with never or current smokers, former smokers were older, more educated, and more likely to have hypertension and diabetes mellitus in both men and women (Table 1).

A total of 251 deaths from COPD among 41,465 men and 34 deaths among 52,662 women were documented during the 18-year follow-up. Both former and current smoking were significantly associated with increased COPD mortality for both men and women in models adjusted for age and potential confounding variables (Table 2). The multivariable-adjusted HRs (95% CIs) for former and current smokers compared with never smokers were 2.97 (1.76-5.02) and 4.46 (2.72-7.29) in men and 8.57 (2.75-26.7) and 9.26 (4.19-20.5) in women, respectively (Table 2). There appeared dose-response associations between the number of cigarettes smoked daily and age- and multivariable-adjusted risk of COPD mortality among current smokers in both sexes. Although crude COPD mortality rates were higher in men than in women in any smoking status categories at baseline, associations of both former and current smoking with COPD mortality tended to be stronger in women than in men (*P* for sex-by-smoking status interaction =0.08).

Compared with current smokers, former smokers at baseline were associated with lower COPD mortality in men but only when cessation duration was five years or more before the baseline (Table 3). Men who had quit smoking more than 10 years before baseline had COPD mortality risk close to never smokers. Quitters for less than five years did not experience the lowering of mortality risk compared to current continuous smokers. The finding did not change materially even after excluding COPD deaths that occurred within five years from the baseline or individuals who reported persistent phlegm symptom at baseline (HRs: 95% CIs were 1.19 0.80-1.79 and 1.11: 0.71-1.72, respectively). There were too few death cases in

female former smokers (n=4) at each smoking cessation group to yield meaningful results.

The associations of smoking status (P=0.005 in men, P<0.001 in women) and smoking cessation duration (P<0.001 in men) with COPD mortality were stronger than those with all-cause mortality (Supplemental tables 1 and 2).

Discussion

We observed the excess risk of COPD mortality among current and former smokers of both sexes in this large prospective cohort study of Japanese. Our finding is consistent with the results from previous prospective studies, including US veterans cohort(Rogot and Murray, 1980), British doctors' cohort(Doll et al., 1980; Doll et al., 2004), Swedish registers' cohort(Carstensen et al., 1987), Copenhagen registers' cohort(Lange et al., 1992), and Washington white registers' cohort(Tockman and Comstock, 1989).

Our study also revealed that the duration of smoking cessation was inversely associated with COPD mortality in men, and the excess risk that would have been observed if they had continuous smoking could be reduced after long-term (≥10 years) cessation before the baseline similar to the level observed in never smokers.

A few studies have evaluated the duration of quitting smoking associated with COPD mortality and morbidity(Lokke et al., 2006; Rogot and Murray, 1980). Our finding that accounted for other smoking-related variables, which previous studies did not address, was similar to that of a 25-year follow-up study in a general population of both sexes(Lokke et al.,

2006). That study showed a dose-response relationship between the duration of smoking cessation and cumulative incidence of COPD, and the odds ratio for stage 2 or more COPD in ex-smokers who had quit 25 years or more at the end of follow-up compared to continuous smokers was similar to that in never smokers(Lokke et al., 2006). Another 16-year observation in the US veterans described that crude COPD mortality rate fell to approximately one fifth of continuous smokers if subjects had quit smoking 20 years or more at the end of follow-up(Rogot and Murray, 1980).

It is noteworthy that both former and current smokers were more strongly associated with COPD mortality in women than in men, especially in female heavy smokers who currently smoked 20 or more cigarettes per day. The interaction for sex-by-smoking status was found to be of borderline significance (P=0.08) in the multivariable model. Similarly, Copenhagen City Heart Study(Lange et al., 1992) and British doctors' cohort study(Doll et al., 1980; Doll et al., 2004) also presented that the COPD mortality ratio associated with smoking in female was higher than that in male, however the number of female deaths from COPD was too small in both studies to confirm the gender difference. The higher age-adjusted relative risks for COPD hospitalization in female smokers compared the risk in male smokers was also observed in Danish longitudinal population study (P=0.08 for the interaction for sex by pack-years categories). Previous prospective studies demonstrated that at comparable levels of smoking exposure, women expressed a faster decline in lung function (FEV_1)(Prescott et al., 1997; Xu et al., 1994). A possible explanation for the faster deterioration is that women

have smaller airways and lung volume than dose men, which results in higher exposure in per volume of lung tissues with each cigarette. In addition, estrogen and related compounds have been reported to increase smoking-induced lung damage possibly through up-regulating the expression of cytochrome P450 enzymes in lungs(Benowitz et al., 2006). Cytochrome P450 enzymes facilitate to transform some harmless substances in cigarette smoke into toxic chemicals, for example benzo[*a*]pyrene into benzo[*a*]pyrene-7,8-diol (Ben-Zaken Cohen et al., 2007). A family study of early-onset COPD probands found no differences in lung function between their female and male first-degree relatives. However, smoking female first-degree relatives, women showed significantly lower lung function than smoking male first-degree relatives ,which implied a genetic predisposition for smoking-induced lung damage in women(Silverman et al., 2000). In the current study, the misclassification of smoking status as never smoking in women was smaller than that in men, which may contribute to the stronger association between smoking and mortality in women. In addition, the finding might have been observed by chance due to small number of women who died from COPD.

Potential effects of smoking cessation on pulmonary pathology have been reported. Macroscopic signs of chronic bronchitis (edema, erythema and mucus) disappeared totally after 6 months' smoking cessation(Skold et al., 1992). In addition, after smoking cessation, the number of macrophages in bronchoalveolar lavage fluid(Skold et al., 1992), blood neutrophils and lymphocytes(Jensen et al., 1998) was largely reversed, and those in

bronchoalveolar lavage fluid normalized at 6, 9, 15 months, respectively(Skold et al., 1996). These data indicated that the inflammatory changes are reversible rapidly after smoking cessation. However, in the present study, quitters for less than five years did not experience the lowering of COPD mortality risk compared to current continuous smokers. One possible explanation is that the sample in the present study included people who already had preclinical but irreversible emphysema. Indeed, a recent study in Japan showed that only 9.4% of cases with airflow limitation reported a previous diagnosis of COPD(Fukuchi et al., 2004). Even among early stage COPD patient, it takes 11-years or more for sustained quitters to experience the same rate of FEV_1 decline as never smokers(Anthonisen et al., 2002).

We could not clarify the association between the duration of smoking cessation and COPD mortality in women due to the small number of deaths in former smokers. However, one previous intervention study demonstrated that women experienced larger improvements in lung function with smoking cessation than men ($\triangle FEV_1$ change: 3.7% vs. 1.6%)(Connett et al., 2003). The effect of smoking cessation on COPD incidence and mortality in women warrants further investigation.

Since persons who quit smoking years prior to the enrollment were more likely to be unhealthy or had some respiratory symptoms, we conducted analyses by excluding the early deaths of COPD within 5-year of follow-up or those who had persistent phlegm at baseline. This exclusion, however, did not alter our results essentially.

Some limitations in the present study merit discussion. COPD develops in a long-term

process and is often undiagnosed(Fukuchi et al., 2004; Mannino et al., 2000). Therefore, the duration of smoking cessation to reduce mortality from COPD (≥10 year before baseline) might be longer than that to reduce the incidence of COPD. Smoking information was assessed only at baseline and was not updated throughout the entire study period in the present study. However, the examination of about one-third of the present sample with 5-year follow-up data indeed showed that the percentage of current smokers had decreased(Kawado et al., 2005) by 5.6 point for men, 0.4 point for women in the present study sample. This suggests that the beneficial effect for smoking cessation may be underestimated, especially for men.

Our study takes advantages of a long observation period, a large population-based samples and the availability of information about potential confounding factors for COPD. We have found that smoking status and smoking cessation duration were more strongly associated with COPD than with all-cause mortality.

Overall, the present study suggests that women may be more susceptible to smoking cigarettes for COPD mortality, and that longer time of smoking cessation was associated with progressively decreased COPD mortality in men. We conclude that smokers should be encouraged to stop smoking as early as possible for the prevention of COPD.

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manuscript.

Conflict of interest: The authors declare that there are no conflicts of interest.

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Table 1. Sex-specific, age-adjusted means and proportions according to smoking status at baseline, Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), 1988-2008.

	Men					Women				
				Cigarettes smoked* (no./day)					Cigarettes smoked* (no./day)	
	Never smokers	Former smokers	Current smokers	1–19	≥20	Never smokers	Former smokers	Current smokers	1–19	≥20
No. at risk	8,613	10,394	22,458	7,174	14,973	48,914	853	2,895	1,932	848
Age (years)	56.6	60.0	55.9	59.0	54.4	57.1	60.0	56.0	56.7	54.2
Body mass index (kg/m^2)	23.0	22.9	22.4	22.0	22.6	22.9	23.3	22.8	22.7	23.2
History of hypertension (%)	19.1	26.0	17.8	21.4	16.0	21.6	27.4	22.2	23.2	20.2
History of diabetes (%)	5.7	8.4	6.2	6.7	6.1	3.5	6.8	5.0	4.8	4.5
Ethanol intake (g/day)	18.2	22.5	27.4	24.4	28.9	1.2	4.7	6.9	5.5	10.5
Walk half an hour or more/day (%)	69.3	68.2	69.8	71.1	69.3	71.9	64.5	69.3	70.8	66.2
Exercise 5 hours or more/week (%)	7.2	8.3	6.6	8.0	5.9	4.5	4.3	4.0	4.3	3.2
High perceived mental stress (%)	22.4	21.8	23.9	19.7	25.9	20.0	24.1	26.2	24.1	30.7
College or higher education (%)	18.3	20.2	15.9	15.2	16.3	10.1	12.5	8.5	9.1	7.5

* Information on number of cigarettes smoked per day among current smokers was missing for 311 men and for 115 women.

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Table 2. Sex-specific, age- and multivariable-adjusted hazard ratios and 95% confidence intervals of mortality from COPD according to smoking status, Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), 1988-2008.

	Never smokers	Former smokers	Current smokers	Cigarettes smoked (no./day)	
				1–19	≥20
Men					
No. at risk	8,613	10,394	22,458	7,174	14,973
No. of person-years	138,752	157,215	346,870	106,398	235,693
No. of death	18	68	165	53	111
Crude death rate*	13	43	48	50	47
Age-adjusted HR	1.0	2.76 (1.64-4.64)	4.84 (2.97-7.88)	3.57 (2.09-6.09)	6.06 (3.67-10.0)
Multivariable HR†	1.0	2.97 (1.76-5.02)	4.46 (2.72-7.29)	3.27 (1.91-5.60)	5.60 (3.38-9.29)
Women					
No. at risk	48,914	853	2,895	1,932	848
No. of person-years	796,017	12,463	44,454	29,454	13,099
No. of death	20	4	10	6	4
Crude death rate*	3	32	22	20	31
Age-adjusted HR	1.0	8.82 (3.01-25.9)	10.1 (4.71-21.6)	8.35 (3.35-20.8)	19.3 (6.58-56.4)
Multivariable HR†	1.0	8.57 (2.75-26.7)	9.26 (4.19-20.5)	7.54 (2.95-19.3)	18.3 (5.96-56.3)

*: Mortality rate was expressed as rate per 100,000 person-years.

†: Multivariable adjustment: age (continuouse), body mass index (sex-specific quintiles), ethanol intake (never, former, current intake of 1–22, 23–45, 46–68, and ≥69 g per day), hours of walking (<0.5, 0.5, 0.6–0.9, and ≥1.0 hour per day), hours of exercise (<1, 1–2, 3–4, and ≥5 hours per week), education (<10, 10–12, 13–15, and ≥16 years), perceived mental

stress (low, medium, and high), and histories of hypertension and diabetes.

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Table 3. Sex-specific, age- and multivariable-adjusted hazard ratios and 95% confidence intervals of mortality from COPD according to years since quitting, Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), 1988-2008.

	Current smokers	No. of years since quitting smoking before the baseline*			Never smokers
		0-4	5-9	≥10	
Men					
No. at risk	22,458	2,599	2,360	4,964	8,613
No. of person-years	346,870	39,582	35,889	74,612	138,752
No. of death	165	32	9	20	18
Crude death rate**	48	81	25	27	13
Age-adjusted HR	1.0	1.24 (0.85-1.82)	0.41 (0.21-0.80)	0.30 (0.19-0.48)	0.21 (0.13-0.34)
Multivariable HR†	1.0	1.23 (0.83-1.81)	0.44 (0.22-0.87)	0.36 (0.22-0.58)	0.30 (0.16-0.57)
Women					
No. at risk	2,895	251	184	315	48,914
No. of person-years	44,454	3,758	2,657	4,510	796,017
No. of death	10	0	2	2	20
Crude death rate**	22	0	75	44	3
Age-adjusted HR	1.0	----------1.00 (0.31-3.18)----------			0.10 (0.05-0.21)

*: Information on number of years since quitting smoking was missing for 471 men and for 103 women.

**: Mortality rate was expressed as rate per 100,000 person-years.

†: Multivariable adjustment: variables included in multivariable model in table 2 plus number of cigarettes smoked per day (<20, 20–29, and ≥30) and age of smoking initiation

(<20, 20–24, 25–29, and ≥30 years).

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