1 Passive smoking and chronic obstructive pulmonary disease mortality: findings from the Japan

2 collaborative cohort study

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Abstract

Objectives: To elucidate the association between passive smoking at home and chronic obstructive pulmonary disease (COPD) mortality via a large-scale nationwide cohort study in Japan.

Methods: Never smokers (n=34,604) aged 40–79 years at baseline (1988–1990; 4,884 men, 29,720 women) were included in the analysis. Passive smoking at home was measured based on self-reported frequency of weekly exposure to passive smoking at home. An inverse probability of treatment weighted competing risk model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for COPD mortality.

Results: During a median follow-up of 16.4 years, 33 participants (10 men, 23 women) died of COPD. The HR for participants exposed to passive smoking at home ≤4 days per week or those who had almost daily exposure to passive smoking at home had a significantly increased risk of COPD mortality (HR: 2.40, 95% CI: 1.39–4.15; HR: 2.88, 95% CI: 1.68–4.93, respectively).

Conclusions: The present findings suggest that avoiding passive smoking at home may be beneficial for preventing death due to COPD among never smokers.

Key words: Prevention, Secondhand smoke, Carcinogens

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a chronic abnormal inflammatory response and an accelerated decline in lung function (Vestbo et al. 2012). COPD is estimated to become the third most common cause of death by 2020 (Murray and Lopez 1997). Active smoking is the major risk factor for COPD (Eisner et al. 2010), although approximately one quarter of diagnosed COPD cases in Japan (25.0%) (Fukuchi et al. 2004), the US (24.9%) (Behrendt 2005), and the UK (29.5%) (Shahab et al. 2006) occur in non-smokers. Several studies have examined this phenomenon, including two cross-sectional studies (Hagstad et al. 2014; Yin et al. 2007), one case-control study (Sezer et al. 2006), and one cohort study (He et al. 2012). Two of these studies reported that passive smoking at home was significantly associated with an increased prevalence of COPD (Sezer et al. 2006; Yin et al. 2007). However, only one cohort study has investigated the association between exposure to passive smoking at home and death due to COPD among non-smokers, reporting no statistically significant association (adjusted relative risk: 1.67, 95% CI: 0.49–5.78) (He et al. 2012). Thus, additional prospective evidence regarding the association between passive smoking at home and COPD mortality among non-smokers is needed. Therefore, the current study aimed to determine whether passive smoking at home is associated with COPD mortality via a large-scale nationwide cohort study among Japanese never smokers who were 40–79 years old.

Materials and Methods

Study population

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) was established in 1988–1990 and has been described in detail elsewhere (Tamakoshi et al. 2013). In brief, 110,585 apparently healthy individuals (46,395 men and 64,190 women; 40–79 years old) were enrolled from 45 areas throughout Japan. Participants were generally recruited at the time of their health check-up and were evaluated using a self-administered questionnaire, with a response rate of 83%. The design of the present study was approved by the Ethical Board of Nagoya University School of Medicine.

Data collection

Information regarding exposure to passive smoking at home was obtained by asking the following question: "In the past, were you exposed to tobacco smoke at home?" Participants who answered "yes" to this question were also asked to report the frequency of this passive exposure as "sometimes", "1–2 days/week", "3–4 days/week", or "almost every day". Owing to the low number of participants who responded "sometimes", "1–2 days/week" or "3–4 days/week", we categorized the frequencies into three groups: none, ≤4 days per week, and almost every day. We only evaluated never smokers (n = 60,484; 9,027 men and 51,457 women). We excluded 13,406 potential participants who lived in five areas, as the questionnaires for those areas did not include the question regarding passive smoking at home. We also

1 excluded 12,474 additional participants with missing data regarding passive smoking at home. Therefore,

2 the present study analyzed data from 34,604 individuals (4,884 men and 29,720 women) who had never

3 smoked.

4

5 *Follow-up*

6 Dates and causes of death were confirmed using death certificates and were coded according to the 10th

7 revision of the International Classification of Disease. The primary outcome for the present study was

8 death due to COPD (J41–44 or J47).

9

10 *Statistical analysis*

11 The baseline characteristics of the study participants according to exposure to passive smoking at home

12 were compared using analysis of covariance or χ^2 test as appropriate. Multivariable hazard ratios (HRs)

13 and confidence intervals (CIs) for COPD mortality were calculated using a Cox proportional hazards

14 model. We attempted to care a small number of outcomes by using an inverse probability of treatment

15 weighted (IPTW) method based on generalized propensity scores (Robins et al. 2000). This approach is a

16 statistical alternative to implementing propensity score matching to balance for confounders in

17 non-randomized studies. To develop the generalized propensity score, we conducted a multinomial

18 logistic regression analysis using variables for all demographic information (Imbens 2008), such as age (a

continuous variable), sex, study area (as a dummy variable), body mass index (BMI; <18.5 kg/m^2, 18.5–24.9 kg/m^2, ≥25.0 kg/m^2, or unknown), educational level (junior high school, high school, college diploma, or unknown), alcohol consumption (never, former, current alcohol drinker, or unknown), walking time (≤1 h/day, >1 h/day, or unknown), and a history of tuberculosis (yes or other) (Table 1). We included variables such as study area in the model because the smoking rate and cause of death differ by geographic region in Japan (Ministry of Health 2015a; Tamakoshi et al. 2013). The C-statistic of the model was 0.677. To assess covariate balance, we showed propensity score overlap with kernel density plots (Supplementary Figure 1). We then conducted an IPTW Cox proportional hazards model with robust variance (Sugihara 2010). Furthermore, we implemented a competing risk model (So et al.) in which we treated death from cancer (C00-97, D00-09), cardiovascular diseases (I00-99), and respiratory diseases other than COPD (J00-39, 45, 46, 60-99) as a competing risk because they have been reported to be associated with passive smoking (Cao et al. 2015; Gibbs et al. 2016; Lv et al. 2015). Trend p-values were calculated to assess the associations between the categories of passive smoking at home (0, none; 1, <4 days per week; 2, almost every day) and the risk of COPD mortality. An alpha level of 0.05 was considered to be statistically significant. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) and JMP software (version 12.2.0; SAS Institute Inc., Cary, NC, USA).

1 Results

2 The mean participant age at baseline was 56.7 ± 10.0 years (men: 56.5 ± 10.3 years, women: 56.7 ± 10.0
3 years). Table 1 shows the participants' baseline characteristics according to their exposure to passive
4 smoking at home. Compared to the participants who had not been exposed to passive smoking at home,
5 participants with almost daily exposure to passive smoking at home tended to be younger, female, better
6 educated, daily walkers, not be alcohol drinkers, and to have non-normal BMI. The difference among
7 those three exposures of passive smoking at home was reduced after weighting (Supplementary Table 1).

8 During the median follow-up of 16.4 (maximum, 22.0) years, 33 participants (10 men and 23
9 women) died as a consequence of COPD, 6,372 participants moved away from the study area, 9,227
10 participants died from cancer, 8,330 participants died from cardiovascular diseases, 3,150 participants
11 died from respiratory diseases other than COPD, and 6,274 participants died from other causes. Table 2
12 shows the HRs for COPD mortality that were associated with passive smoking at home. Compared to the
13 participants who were not exposed to passive smoking at home, participants who were exposed to passive
14 smoking at home ≤4 days per week and those who were exposed to passive smoking at home almost daily
15 had a significantly increased risk of COPD mortality (HR: 1.98; 95% CI: 1.07–3.88; HR: 2.27; 95% CI:
16 1.27–4.03, respectively), but there was no dose-response relationship (P = 0.09). In the competing risk
17 analysis, participants who had ≤4 days per week exposure and almost daily exposure to passive smoking
18 at home had a significantly increased risk of COPD mortality (HR: 2.40; 95% CI: 1.39–4.15; HR: 2.88;

1 95% CI: 1.68–4.93, respectively) with a dose-response relationship (P < 0.001).

2

3 Discussion

4 In this large cohort study, we found that exposure to passive smoking at home significantly increased the

5 risk of COPD mortality, compared to individuals without exposure to passive smoking at home, among

6 Japanese never smokers.

7 Potential pathways by which passive smoking might lead to COPD mortality are not fully

8 established. One possibility is that despite low levels of passive smoking, exposure increases levels of

9 elastin degradation products such as isodesmosine (Slowik et al. 2011); these products are chemotactic for

10 neutrophils and macrophages in the lung (Houghton et al. 2006; Senior et al. 1980) and cause an

11 inflammatory state, resulting in lung degradation (Hogg et al. 2004). Furthermore, experimental studies

12 have demonstrated that the acute detrimental effects of passive smoking on the respiratory system are

13 similar to those of active smoking (Flouris et al. 2009; Slowik et al. 2011). Thus, passive smoking can

14 increase the levels of proinflammatory cytokines (including interleukin-4, interleukin-5, interleukin-6,

15 tumor necrosis factor-α, and interferon-γ), as well as serum and urine levels of cotinine. Moreover, a

16 review article reported the presence of several candidate genes for COPD susceptibility and COPD

17 pathophysiology which influence the development of chronic airflow obstruction in response to smoking

18 (Silverman 2006). All of these factors can negatively affect lung function, which indicates the biological

plausibility of passive smoking as a causal factor for COPD mortality.

To our knowledge, this is the first cohort study to report a statistically significant association between passive smoking at home and COPD mortality among never smokers. This association is consistent with the findings of three previous studies, which included a Chinese cross-sectional study (Yin et al. 2007) and a Turkish case-control study (Sezer et al. 2006). There was an association between self-reported exposure to passive smoking at home and the prevalence of COPD (adjusted odds ratio: 1.60, 95% CI: 1.23–2.10 for high-level exposure, equivalent to 40 h/week for >5 years) among 20,430 Chinese men and women who were >50 years old (Yin et al. 2007) and among 74 cases and 74 controls that were selected from among Turkish housewives (adjusted odds ratio: 4.96, 95% CI: 1.65–14.86 for >30 years of exposure) (Sezer et al. 2006). In contrast, a cohort study with a 17-year follow-up evaluated the relationship between passive smoking and death due to COPD among 910 Chinese individuals (439 men and 471 women) who never smoked, but there was no statistically significant association between passive smoking and COPD mortality (adjusted relative risk: 1.67, 95% CI: 0.49–5.78) (He et al. 2012). However, the results of both previous studies were highly imprecise. Furthermore, the confidence intervals around the estimated measures of association in those were similar; thus, the results were not mutually inconsistent.

The smoking rate in Japan is one of the highest among developed countries (Schultz 1998). For example, the prevalence of smoking in 1990 was 53.1% for men and 9.7% for women (Ministry of Health

1993), compared to that in the present cohort of 53.1% and 5.5%, respectively. Although the prevalence of smoking has gradually decreased in Japan (34.1% for men and 9.0% for women in 2012) (Ministry of Health 2012), the smoking rate remains high, thus non-smokers are frequently exposed to passive smoking. For the country of Japan, the present findings reemphasize the importance of implementing an effective smoking cessation campaign, including public education to reduce passive smoking exposure in the home; such a campaign should be based on the World Health Organization's Framework Convention on Tobacco Control (World Health Organization 2014).

The strengths of the present study include its prospective cohort design, long follow-up period, and inclusion of participants from throughout Japan. However, the present study also includes some limitations that warrant consideration. First, a meta-analysis reported patients with COPD were more likely to die due to lung cancer (Wang et al. 2012). Therefore, as COPD and lung cancer share cigarette smoking as a common risk factor, some misclassification of the outcome might occur, leading to an underestimation of deaths due to COPD (Caramori et al. 2011). To avoid this bias, we conducted a competing risk analysis. Second, data regarding passive smoking was obtained via self-report, thus there may have been inaccurate reports of exposure to passive smoking (Kim et al. 2013). Third, the information on passive smoking and potential confounders was collected only at baseline and was not updated during the study period. Since we could not consider the time-dependent nature of the characteristics of the study participants, our results might have included some information and residual

confounding bias. Particularly, as the proportion of active smokers and passive smokers is gradually decreasing in Japan (Ministry of Health 2015b), there may have been an overestimation of passive smoking. Fourth, there are potential confounders, such as history of asthma (Silva et al. 2004), history of respiratory infection in infancy (van der Zalm et al. 2009), and exposure to air pollution (e.g. traffic-related air pollution (Schikowski et al. 2005), for which information was not obtained. To clarify the magnitude of the effect of passive smoking exposure on COPD mortality, further epidemiologic studies are needed that collect comprehensive baseline information regarding potential confounders. Fifth, due to the relatively low number of deaths from COPD, the risk estimate might not be precise. Further epidemiologic studies with a larger sample size or a pooled analysis of multiple cohort studies would help to clarify the present results.

In conclusion, this nationwide cohort study provides the first evidence that passive smoking at home increases the risk of COPD mortality among Japanese never smokers who were 40–79 years old. Thus, reducing exposure to passive smoking at home may help prevent COPD mortality among never smokers.

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Table 1. Baseline participant characteristics according to exposure to passive smoking at home in Japan, 1988–1990

Characteristic	Category	Exposure to passive smoke at home			P-value
		None (n = 14,359)	≤4 days per week (n = 5,519)	Almost every day (n = 14,726)	
Age, years		57.6 ± 10.5	56.3 ± 9.7	55.9 ± 9.5	<0.001
Sex, male		3,098 (21.6)	886 (16.1)	900 (6.1)	<0.001
Body mass index, kg/m^2	<18.5	888 (6.2)	289 (5.2)	805 (5.5)	<0.001
	18.5–24.9	9,901 (69.0)	3,751 (68.0)	9,937 (67.5)	
	≥25.0	2,863 (19.9)	1,272 (23.0)	3,525 (23.9)	
	Unknown	707(4.9)	207 (3.8)	459 (3.1)	
College education	Yes	9,719 (67.7)	3,661 (66.3)	10,445 (71.0)	<0.001
	No	3,879 (27.0)	1,607 (29.1)	3,608 (24.5)	
	Unknown	761 (5.3)	251 (4.5)	663 (4.5)	
Alcohol consumption	Current	4,197 (44.3)	1,588 (28.8)	3,682 (25.0)	<0.001
	Former	253 (1.8)	107 (1.9)	189 (1.3)	
	Never	9,638 (67.1)	3,684 (66.8)	10,543 (71.6)	
	Unknown	271 (1.9)	140 (2.5)	312 (2.1)	
Daily walking time, h/day	>1	6,111 (39.7)	2,811 (46.0)	7,479 (45.9)	<0.001
	≤1	7,765 (54.1)	2,811 (50.9)	7479 (50.8)	
	Unknown	483 (3.4)	172 (3.1)	482 (3.3)	
History of tuberculosis	Yes	690 (4.8)	217 (3.9)	686 (4.7)	<0.001

Values are expressed as mean ± standard deviation or number (%). P-values were calculated using analysis of covariance or χ^2 test as appropriate.

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Table 2. Hazard ratios of chronic obstructive pulmonary disease mortality according to exposure to passive smoking at home using a Cox proportional hazards model in Japan, 1988–1990

	Exposure to passive smoking at home			
Category	None	≤4 days per week	Almost every day	P for trend
Person-years	237,456	94,700	236,188	
Number of cases	11	7	15	
HR (95% CI)[a]	ref	1.95 (0.75–5.03)	2.41 (1.08–5.37)*	0.03
HR (95% CI)[b]	ref	2.38 (0.89–6.35)	2.86 (1.23–6.68)*	0.09
HR (95% CI)[c]	ref	2.40 (1.39–4.15)*	2.88 (1.68–4.93)*	<0.001

HR: hazard ratio, CI: confidence interval; ref, reference. *p<0.05

[a]adjusted for age and sex

[b]inverse propensity of treatment weighted model with robust variance.

[c]inverse propensity of treatment weighted competing risk model with robust variance.

P for trend was calculated across the categories of exposure to passive smoking at home.

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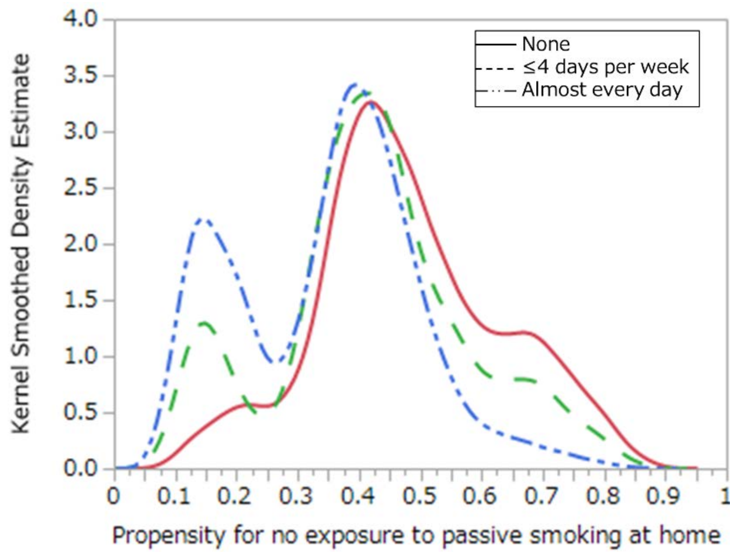
1 A. Unadjusted estimates



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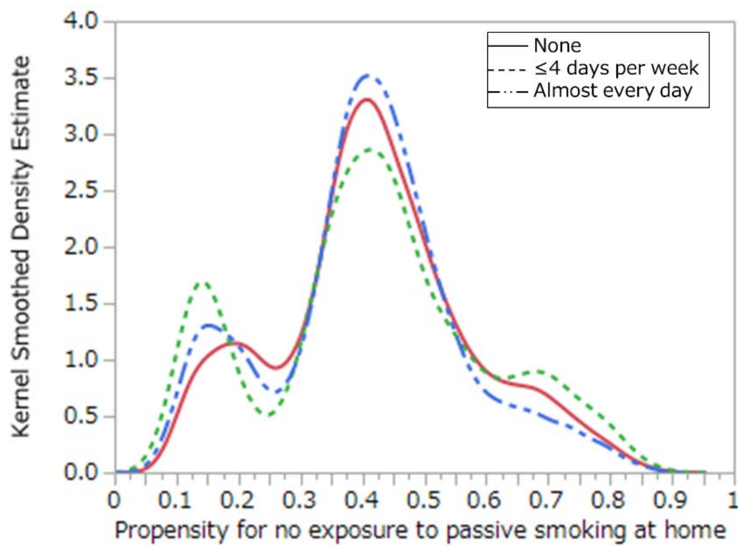
3 B. Adjusted estimates



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5 **Supplementary Figure 1. Kernel smoothed density estimate of propensity for no exposure**

6 **to passive smoking at home in Japan, 1988–1990**

7 Kernel smoothed density estimates show improved overlap of propensity for no exposure to

8 passive smoking after inverse probability of treatment weighting.