HOKKAIDO UNIVERSITY

Title	Secondhand Smoke Exposure During Childhood and Cancer Mortality in Adulthood Among Never Smokers : The Japan Collaborative Cohort Study for Evaluation of Cancer Risk
Author(s)	Teramoto, Masayuki; Iso, Hiroyasu; Wakai, Kenji et al.
Citation	American Journal of Epidemiology, 191(5), 834-842 https://doi.org/10.1093/aje/kwab284
Issue Date	2022-05-01
Doc URL	https://hdl.handle.net/2115/89280
Rights	This is a pre-copyedited, author-produced version of an article accepted for publication in American Journal of Epidemiology following peer review. The version of record Masayuki Teramoto, Hiroyasu Iso, Kenji Wakai, Akiko Tamakoshi, Secondhand Smoke Exposure During Childhood and Cancer Mortality in Adulthood Among Never Smokers: The Japan Collaborative Cohort Study for Evaluation of Cancer Risk, American Journal of Epidemiology, Volume 191, Issue 5, May 2022, Pages 834-842 is available online at: https://doi.org/10.1093/aje/kwab284
Type	journal article
File Information	revised_manuscript_1014_submit.pdf

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

Title

Secondhand Smoke Exposure during Childhood and Cancer Mortality in Adulthood among Never Smokers: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk

Masayuki Teramoto, Hiroyasu Iso, Kenji Wakai, and Akiko Tamakoshi

Correspondence to: Dr. Hiroyasu Iso

Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565–0871, Japan. (e-mail: iso@pbhel.med.osaka-u.ac.jp)

Fax: +81-6-6879-3919

Tel: +81-6-6879-3911

Author affiliations: Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Japan (Masayuki Teramoto and Hiroyasu Iso); Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan (Kenji Wakai); and Department of Preventive Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan (Akiko Tamakoshi).

Funding

This study has been supported by Grants-in-Aid for Scientific Research from the Ministry of Education,

Culture, Sports, Science and Technology of Japan (MEXT) (MonbuKagaku-sho); Grants-in-Aid for Scientific Research on Priority Areas of Cancer; and Grants-in-Aid for Scientific Research on Priority Areas of Cancer Epidemiology from MEXT (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026, 20390156, 26293138), and JSPS KAKENHI No.16H06277. This research was also supported by Grant–in–Aid from the Ministry of Health, Labour and Welfare, Health and Labor Sciences research grants, Japan (Comprehensive Research on Cardiovascular Disease and Life-Style Related Diseases: H20–Junkankitou [Seishuu]–Ippan–013; H23–Junkankitou [Seishuu]–Ippan–005); an Intramural Research Fund (22-4-5) for Cardiovascular Diseases of National Cerebral and Cardiovascular Center; Comprehensive Research on Cardiovascular Diseases and Life-Style Related Diseases (H26-Junkankitou [Seisaku]-Ippan-001) and H29–Junkankitou [Seishuu]–Ippan–003 and 20FA1002.

Conflict of interest: none declared

Running head: Secondhand smoke in childhood and cancer mortality

Abbreviations

CI: confidence interval

DNA: deoxyribonucleic acid

HR: hazard ratio

SHR: subdistribution hazard ratio

Word Count

Abstract: 199 words

Text: 2950 words

Abstract

We examined whether secondhand smoke exposure during childhood was associated with cancer mortality in adulthood among never smokers. In the Japan Collaborative Cohort Study, we analyzed data from 45,722 Japanese lifetime non-smokers who were aged 40–79 years with no history of cancer at the baseline (1988–1990) and completed a lifestyle questionnaire including the number of family members who smoked at home during their childhood (0/1/2/3+ members). The Cox proportional hazards model and competing risk regression were used to calculate the multivariable hazard ratios (HRs) and subdistribution hazard ratios (SHRs) with 95% confidence intervals (CIs) of all and site-specific cancer mortality, according to the number of smoking family members during the participant's childhood after adjusting for potential confounding factors. During the median follow-up of 19.2 years, a total of 2,356 deaths from cancer were documented. Secondhand smoke exposure was positively associated with the risk of mortality from pancreatic cancer in adulthood; the multivariable HR of 3+ smoking family members was 2.32 (95% CI: 1.14, 4.72), compared with 0 members. The associations were not evident for the risks of total or other types of smoking-related cancers. In conclusion, secondhand smoke exposure during childhood was associated with an increased risk of mortality from pancreatic cancer in adulthood.

Keywords: cancer mortality, parental smoking, passive smoking, secondhand smoke

Active and passive smoking in adulthood have been associated with increased risks of cancer at various sites. According to the Surgeon General's report in 2014, smoking is causally linked to cancers of the oropharynx, larynx, esophagus, lung, stomach, liver, pancreas, kidney, cervix, bladder, colorectum, and acute myeloid leukemia (1). The risks of these smoking-related cancers in adulthood could increase by early exposure to active smoking because younger smokers may be more susceptible to physiologic changes caused by smoking, such as deoxyribonucleic acid (DNA) adduct formation and its longer persistence, although evidence on secondhand smoke is not available (2).

Several prospective cohort studies in Europe and the US have reported the association between secondhand smoke exposure during childhood and the risk of cancer in adulthood. The European Prospective Investigation into Cancer and Nutrition showed that environmental tobacco smoke exposure during childhood could be an independent risk factor for an increased incidence of lung (3), bladder (4), and pancreatic (5) cancer in adulthood. In the Nurses' Health Study, parental smoking when the study participants were living with their parents was associated with an increased risk of pancreatic cancer in adulthood among women, while no association was observed with adult secondhand smoke at home or work (6).

For children, living in households with smokers is the biggest risk factor for secondhand smoke exposure (7). Parental smoking, low socioeconomic status, low educational level, and less negative attitudes toward secondhand smoke have been associated with a child's exposure to secondhand smoke at home (8).

Therefore, building scientific evidence on the adverse effects of familial smoking at home during childhood may lead to protection of children from future risks of cancers.

However, previous studies only targeted western cohorts. Among the Asian population, little is known about the impact of secondhand smoke exposure during childhood on cancer mortality in adulthood, although the proportion of smoking in adulthood is generally high among men in Asian countries (9). Considering limited and conflicting evidence regarding the effect of secondhand smoke during childhood on the future risk of cancer, this study aimed to examine the association between secondhand smoke exposure at home during childhood and risk of mortality from total and major types of smoking-related cancers in adulthood using data from a large long-term cohort study on Japanese men and women.

METHODS

Study population and baseline questionnaire

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study) is a nationwide community-based prospective study that started between 1988 and 1990, enrolling 110,585 subjects (46,395 men and 64,190 women) aged 40–79 years and living in 45 communities across Japan. The methodology of the study has been described elsewhere (10).

Briefly, 110,585 participants were asked to complete self-administered questionnaires, including demographic characteristics, medical histories, and lifestyle. Before completing the questionnaire, the

participants or community representatives provided informed consent to be involved in this epidemiological study, according to the guidelines of the Council for International Organizations of Medical Sciences. Informed consent was obtained from each participant in 36 of the 45 study areas (written consent in 35 areas and oral consent in 1 area). In the remaining nine areas, group consent was obtained from the leader of each area. The JACC study protocol was approved by the ethics committees of Hokkaido University, Nagoya University, and Osaka University.

Secondhand smoke during childhood

We asked the participants, "Did your family member smoke at home when you were an elementary or junior high school student?" with the following three possible responses: "yes," "no," or "cannot remember." The age of elementary or junior high school students in Japan is between 6 and 15 years. For those who responded yes, we further asked, "Which of the family members smoked at home?" ("mother," "father," "brother or sister," "grandfather or grandmother," or "others"). According to their responses to these questions, we calculated the number of smoking family members as 0, 1, 2, or 3+.

Of the 110,585 participants, we excluded 50,101 participants (37,368 men and 12,733 women) who had ever smoked or did not provide their smoking status. A total of 8,725 participants (1,514 men and 7,211 women) living in eight communities were excluded because the questions on secondhand smoke exposure during childhood were excluded in the questionnaire. We did not include 5,403 participants (763 men and

4,640 women) because their answer to the first question was “cannot remember” (271 men and 1,881 women), or they did not provide their history of secondhand smoke exposure during childhood (492 men and 2,759 women). Furthermore, 634 participants (29 men and 605 women) were excluded because of a history of cancer at the time of baseline inquiry. A total of 45,722 participants (6,721 men and 39,001 women) were included in the analyses.

Assessment of confounding variables

Other information on demographic and lifestyle factors, namely age, sex, height, weight, past medical history (e.g., diabetes and hypertension), alcohol drinking status, exercise and walking habits, mental status, educational level, occupation, and eating habits, was derived from a self-administered questionnaire at baseline. Body mass index was calculated as body weight (kg) divided by the square of the height (m^2).

Mortality surveillance

In each community, a systematic review of death certificates, all of which were forwarded to the local public health center, was conducted. It is believed that all cohort deaths were recorded, except for those participants who died after moving from their original community, in which case the participants’ data were censored. The date of moving from the community was verified using population-registration documents. Mortality data were sent centrally to the Ministry of Health and Welfare, and the underlying cause of death was coded for the National Vital Statistics System according to the International Classification of Diseases, 10th

revision (ICD-10). In 35 communities, follow-up was conducted until the end of 2009. However, the study was terminated in 4 areas by the end of 1999, in 4 other areas by the end of 2003, and in 2 areas by the end of 2008. The median follow-up period was 19.2 years. With reference to the Surgeon General's report in 2014, cause-specific mortality of smoking-related cancers by each cancer site was defined using ICD-10 codes: lip, oral cavity, pharynx and larynx (n = 34, C000-C149, C320-C329), nose and nasal cavity (n = 6, C300-C301, C310-C319), esophagus (n = 28, C150-C159), stomach (n = 422, C160-C169), colorectum (n = 233, C180-C189, C199, C209), liver (n = 232, C220-C229), pancreas (n = 232, C250-C259), lung (n = 107, C340-C349), cervix (n = 28, C530-C539), bladder (n = 37, C670-C679), kidney (n = 4, C649-C659), or acute myeloid leukemia (n = 27, C920). If participants died after they had moved from their original community, they were treated as withdrawals from observation when they moved out.

Statistical analysis

Person-years of follow-up were calculated from the date of the baseline questionnaire to the date of death or emigration from the community or the end of 2009 (or 1999, 2003, 2008), whichever occurred first. Age-adjusted mean values and prevalence of risk factors for cancer were presented among the categories of the number of smoking family members at home during childhood. Generalized linear models were used to perform trend tests across groups. The sex- and age-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of cancer mortality according to the number of family members who smoked at home during childhood were calculated using the Cox proportional hazards model after adjustment for potential

confounding factors. Competing risk regression models were employed to estimate subdistribution hazard ratios (SHRs) and 95% CIs, with other causes of death as competing risk events to minimize the potential impacts of competing risk bias on the association between secondhand smoke exposure in childhood and smoking-related cancer mortality (11). The potential confounding factors were age (continuous), sex (women or men), body mass index (sex-specific quintile), secondhand smoke status in adulthood at home (never, sometimes, 1–4 days per week, or almost every day) and outside of home (never, sometimes, 1–4 days per week, or almost every day), alcohol consumption (never drinker, ex-drinker, or current drinker of 0.1–45.9 g or ≥ 46.0 g ethanol per day), hours of exercise (almost never, 1–4 h, or ≥ 5 h per week), hours of walking (almost never, 0.5 h, or > 0.5 h per day), perceived mental stress (low, moderate, or high), educational level (≤ 18 years or ≥ 19 years of age on completion of education), employment status (unemployed or employed), and frequency of vegetable and fruit intake (quintile). Furthermore, additional potential confounders were selected for specific cancers: a history of diabetes (yes or no) for pancreatic cancer, red meat, and processed meat intake (quintile) for stomach and colorectal cancers.

To eliminate confounding due to adult secondhand smoke exposure, we performed sensitivity analyses by excluding all participants who reported the adult secondhand smoke exposure at home or outside of home.

SAS version 9.4 (SAS, Inc., Cary, NC) was used for all statistical analyses. All statistical tests were two sided, and P values <0.05 were considered statistically significant.

RESULTS

Age-adjusted baseline characteristics of the participants according to the number of smoking family members during childhood are presented in Table 1. The proportions for the number of smoking family members were 27.4% for none, 56.3% for 1, 14.3% for 2, and 2.0% for 3+ members. Most participants were female (85.3%). Compared with those who had no smoking family members during childhood, those who reported 3+ smoking family members were more likely to have higher proportions of adult secondhand smoke exposure at home and outside of home, higher body mass index, a history of diabetes, higher mental stress, were less educated, and less often ate vegetables. They were also more likely to be current drinkers and unemployed.

During the median follow-up of 19.2 years, a total of 2,356 (478 men and 1,878 women) deaths from cancers were documented. Table 2 shows the multivariable HRs and SHRs of cancer mortality according to the number of smoking family members during childhood. The results shown in Table 2 are limited to cancer sites with at least 100 observed cases. In age- and sex-adjusted analyses, no association was observed between secondhand smoke during childhood and the risks of mortality from all or smoking-related cancers in adulthood. The excess risk of mortality from pancreatic cancer associated with 3+ smoking family members was statistically significant. After adjustment for additional potential confounding factors, the association did not change; the multivariable HRs of pancreatic cancer mortality were 2.32 (95% CI: 1.14, 4.72) among 3+ smoking family members. Such an association was not evident for other cancer sites. In the competing risk regression models, a similar association with pancreatic cancer mortality was observed; the

multivariable SHRs of pancreatic cancer mortality were 2.25 (95% CI: 1.10, 4.60) among 3+ smoking family members, compared with no members.

Because the number of cases among 3+ smoking family members was small in liver, lung, and colorectal cancers, we collapsed the categories of 2 and 3+ smoking family members. None of the multivariable HRs and SHRs did not reach statistical significance.

Compared to no smoking family member, any smoking family member (1+ smoking family members) during childhood was associated with an increased risk of mortality from pancreatic cancer, although the association did not reach statistical significance.

In the sensitivity analyses, the exclusion of all participants who reported the adult secondhand smoke exposure at home or outside of home did not change the results materially (Web Table 1).

DISCUSSION

In this large prospective study of Japanese male and female lifetime non-smokers aged 40 to 79 years with a median follow-up of 19.2 years, we observed that smoking of 3＋ family members during childhood was associated with approximately double the risk of mortality from pancreatic cancer in adulthood, compared with 0 family member. The result did not alter materially after the exclusion of participants with adult secondhand smoke exposure. In the JACC study, Lin et al. previously reported that the presence of a smoker

among family members in childhood was not associated with an increased risk of pancreatic cancer mortality in adulthood (RR: 1.21; 95% CI: 0.87, 1.68) among lifetime non-smoking women (12). However, they adjusted only for age, BMI, and history of diabetes, but not for passive smoking status in adulthood. We conducted more comprehensive analyses, adjusting for multiple potential confounding factors and examined the association between the number of smoking family members in childhood among lifetime non-smoking men and women. To the best of our knowledge, this is the first study to report the positive association of secondhand smoke estimated by the number of smoking family members during childhood and pancreatic cancer in adulthood among Asian populations. We did not observe any significant associations of the risk of mortality from total or other smoking-related cancers. A potential explanation for the lack of association could be attributed to the relatively small number of cases in this mostly lifetime non-smoking women.

Our findings on the suggestive effects of childhood secondhand smoke exposure on the future risks of pancreatic cancer are consistent with findings from previous studies in Western countries. In the European Prospective Investigation into Cancer and Nutrition cohort of 112,430 European lifetime non-smokers, daily exposure to secondhand smoke during childhood was associated with an increased risk of pancreatic cancer in adulthood, compared with non-exposure; multivariable HRs were 2.09 (95% CI: 1.14, 3.84) (13). However, such an association was not evident for the risk of total and other types of smoking-related cancers. In the Nurses' Health Study of 86,673 women, a history of parental smoking exposure significantly

increased the risk of pancreatic cancer incidence in adulthood; multivariable relative risks of developing pancreatic cancer among individuals exposed to parental smoking were 1.41 (95% CI: 1.03, 1.91), compared with non-exposure (6).

An underlying mechanism of the associations between secondhand smoke exposure in childhood and the risk of pancreatic cancer in adulthood can be due to a chronic pancreatic inflammatory process with fibrosis induced by secondhand smoke exposure found in an animal study (14). Another potential mechanism of pancreatic carcinogenesis can be explained by DNA adducts caused by smoke carcinogens, such as nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and its major metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (15). A previous animal experiment showed that the DNA adducts in the pancreas increased when rats were given water containing 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (16). Once DNA adducts are formed, they can be removed by DNA repair enzymes in the body, and the DNA returns to normal. However, if the DNA is seriously damaged and repair is insufficient, DNA adducts can persist and result in miscoding during DNA replication and the development of cancer (17).

The strength of the present study is its prospective study design that eliminates the recall bias of exposure assessment. Furthermore, since the Japanese smoking prevalence rate was relatively high during the

participants' childhood, the present study had a sufficient number of smoking family members (n = 894, for 3+ smoking family members) to find the association.

This study, however, has several limitations. First, misclassification due to the recall of secondhand smoke exposure during childhood can be a potential problem. However, in the present study, the proportion of participants who reported one or more family members to have smoked at home during their childhood was approximately 70%. This result was almost consistent with the Japanese smoking prevalence from the 1950s to the 1960s (18). Additionally, a previous study examined the validity of offspring-reported parental smoking status during the offspring's childhood (19). The result showed that adults reported their parent's smoking status during their childhood quite accurately; the sensitivity for the offspring's correct report of the parent's smoking status during childhood (0–10 years) was 0.82 (95% CI: 0.81, 0.84) and specificity was 0.95 (95% CI: 0.95, 0.96). Therefore, the effect of misclassification in the present study can be limited. Second, we used mortality data, not incident data, which may lead to misclassification in the diagnosis of cancer sites. However, the widespread use of computed tomography scans or magnetic resonance imaging in local Japanese hospitals since the 1980s has probably made a death certificate diagnosis of cancer sufficiently accurate (20).

Third, we used the self-reported number of smoking family members during childhood as a proxy for exposure to secondhand smoke in childhood; therefore, the duration and intensity of secondhand smoke in childhood were not measured, resulting in nondifferential misclassification. Forth, these findings could be due to chance, since they were based on the small number of cases, and counter-intuitive with the previous

report on a rapid decrease in pancreatic cancer risk among adult former smokers (5). Finally, despite our efforts to adjust for potential confounding factors, we cannot rule out the effects of unmeasured factors or residual confounding, such as prenatal smoke exposure, behavioral change over time, and quantity of individual and passive smoking in adulthood.

In conclusion, secondhand smoke exposure during childhood can be an independent risk factor for pancreatic cancer regardless of the conventional risk factors and lifestyle during adulthood, while the association is not evident for the risk of mortality from total or other types of smoking-related cancers. As previously reported, interventions to achieve smoking cessation among parents for the sake of the children may be recommended (21). The present study reinforces the importance of such interventions because smoking cessation among parents not only benefits their health but also benefits their children in the long run.

Acknowledgments

We thank all staff members involved in this study for their valuable help in conducting the baseline survey and follow-up.

References

1. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014. Available at: https://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/index.htm (Accessed: 18 March 2021).

2. Wiencke JK, Thurston SW, Kelsey KT, et al. Early age at smoking initiation and tobacco carcinogen DNA damage in the lung. J Natl Cancer Inst. 1999;91(7):614‐619. doi: 10.1093/jnci/91.7.614

3. Vineis P, Airoldi L, Veglia F, et al. Environmental tobacco smoke and risk of respiratory cancer and chronic obstructive pulmonary disease in former smokers and never smokers in the EPIC prospective study. BMJ. 2005;330(7486):277. doi: 10.1136/bmj.38327.648472.82

4. Bjerregaard BK, Raaschou-Nielsen O, Sørensen M, et al. Tobacco smoke and bladder cancer--in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2006;119(10):2412‐2416. doi: 10.1002/ijc.22169

5. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2010;126(10):2394‐2403. doi: 10.1002/ijc.24907

6. Bao Y, Giovannucci E, Fuchs CS, et al. Passive smoking and pancreatic cancer in women: a prospective cohort study. Cancer Epidemiol Biomarkers Prev. 2009;18(8):2292-2296. doi: 10.1158/1055-9965.EPI-09-0352

7. Sims M, Tomkins S, Judge K, et al. Trends in and predictors of second-hand smoke exposure indexed by cotinine in children in England from 1996 to 2006. Addiction. 2010;105(3):543-553. doi: 10.1111/j.1360-0443.2009.02805.x

8. Orton S, Jones LL, Cooper S, et al. Predictors of children's secondhand smoke exposure at home: a systematic review and narrative synthesis of the evidence. PLoS One 2014;9:(11)e112690. doi: 10.1371/journal.pone.0112690

9. GBD 2015 Tobacco Collaborators. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the Global Burden of Disease Study 2015. Lancet. 2017;389(10082):1885-1906. doi: 10.1016/S0140-6736(17)30819-X

10. Tamakoshi A, Ozasa K, Fujino Y, et al. Cohort profile of the Japan Collaborative Cohort Study at final follow-up. J Epidemiol. 2013;23(3):227-232. doi: 10.2188/jea.je20120161

11. Fine JP and Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496-509. doi: 10.1080/01621459.1999.10474144

12. Lin Y, Yagyu K, Ueda J, et al. Active and passive smoking and risk of death from pancreatic cancer: findings from the Japan Collaborative Cohort Study. *Pancreatology*. 2013;13(3):279-284. doi:10.1016/j.pan.2013.03.015

13. Chuang SC, Gallo V, Michaud D, et al. Exposure to environmental tobacco smoke in childhood and incidence of cancer in adulthood in never smokers in the European Prospective Investigation into Cancer and Nutrition. Cancer Causes Control. 2011;22(3):487–494. doi: 10.1007/s10552-010-9723-2

14. Wittel UA, Pandey KK, Andrianifahanana M, et al. Chronic pancreatic inflammation induced by environmental tobacco smoke inhalation in rats. Am J Gastroenterol. 2006;101(1):148–159. doi: 10.1111/j.1572-0241.2006.00405.x

15. Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer [published correction appears in Nat Rev Cancer. 2004 Jan;4(1):84]. Nat Rev Cancer. 2003;3(10):733–744. doi: 10.1038/nrc1190

16. Balbo S, Johnson CS, Kovi RC, et al. Carcinogenicity and DNA adduct formation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and enantiomers of its metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in F-344 rats. Carcinogenesis. 2014;35(12):2798-2806. doi: 10.1093/carcin/bgu204

17. Ma B, Stepanov I, Hecht SS. Recent studies on DNA adducts resulting from human exposure to tobacco smoke. Toxics. 2019;7(1):16. doi: 10.3390/toxics7010016

18. Funatogawa I, Funatogawa T, Yano E. Trends in smoking and lung cancer mortality in Japan, by birth cohort, 1949-2010. Bull World Health Organ. 2013;91(5):332–340. doi: 10.2471/BLT.12.108092

19. Coultas DB, Peake GT, Samet JM. Questionnaire assessment of lifetime and recent exposure to environmental tobacco smoke. Am J Epidemiol. 1989;130(2):338–347. doi: 10.1093/oxfordjournals.aje.a115340

20. Mieno MN, Tanaka N, Arai T, et al. Accuracy of death certificates and assessment of factors for misclassification of underlying cause of death. J Epidemiol. 2016;26(4):191-198. doi: 10.2188/jea.JE20150010

21. Rosen LJ, Noach MB, Winickoff JP, et al. Parental smoking cessation to protect young children: a systemic review and meta-analysis. Pediatrics. 2012;129(1):141-152. doi: 10.1542/peds.2010-3209

Table1. Age-adjusted Baseline Characteristics of Participants According to the Number of Smoking Family Members During Childhood, Japan, 1988-1990

Characteristic[a]	No. of smoking family members								*P* for trend
	0 (n = 12539)		1 (n = 25743)		2 (n = 6546)		3＋ (n = 894)		
	No.	%	No.	%	No.	%	No.	%	
Age, y	58.0		56.6		56.5		58.4		0.23
Male	2033	16.2	3792	14.7	797	12.2	99	11.1	<0.001
Body mass index[b]	23.0		23.0		23.1		23.3		0.005
Secondhand smoke at home≥1day/week	3649	42.3	9907	52.9	2669	57.0	395	62.3	<0.001
Secondhand smoke outside of home ≥1day/week	1675	18.0	3841	19.4	1059	21.1	174	27.9	<0.001
Current drinker	2422	21.8	5199	22.2	1403	23.6	178	22.4	0.49
High mental stress	2073	20.2	4582	20.9	1332	22.0	182	22.6	0.05
College or higher education	1266	11.8	2653	11.6	672	11.6	68	9.2	0.03
Unemployed	2084	17.8	3876	18.5	1026	18.8	158	17.3	0.71
Walking>30min/day	7652	71.8	15503	71.3	4064	71.7	526	68.8	0.09
Exercise≥1h/week	2883	25.0	5735	24.8	1521	24.8	199	23.3	0.28
History of diabetes mellitus	456	3.7	940	4.0	260	4.4	41	4.6	0.17
Vegetable intake, times/week	15.5		15.2		14.9		14.6		<0.001
Fruits intake, times/week	8.1		8.3		8.3		8.2		0.39
Number of cases by cancer sites									
All cancers	674	5.4	1323	5.1	304	4.6	55	6.2	

Smoking-related cancer[c]	417	3.3	857	3.3	193	2.9	34	3.8
Lip, oral cavity, pharyngeal and laryngeal cancer	10	0.1	20	0.1	4	0.1	0	0.0
Nose and nasal cavity cancer	0	0.0	3	0.0	2	0.0	1	0.1
Esophagus cancer	3	0.0	20	0.1	4	0.1	1	0.1
Stomach Cancer	125	1.0	244	0.9	43	0.7	10	1.1
Colorectal Cancer	63	0.5	138	0.5	28	0.4	4	0.4
Liver Cancer	67	0.5	124	0.5	37	0.6	4	0.4
Pancreatic Cancer	56	0.4	139	0.5	28	0.4	9	1.0
Lung Cancer	76	0.6	132	0.5	35	0.5	3	0.3
Kidney Cancer	2	0.0	2	0.0	0	0.0	0	0.0
Bladder Cancer	8	0.1	20	0.1	8	0.1	1	0.1
Acute Myeloid Leukemia	7	0.1	15	0.1	4	0.1	1	0.1
Cervical Cancer	9	0.1	16	0.1	2	0.0	1	0.1

[a] Data are age-adjusted mean for continuous variables and age-adjusted percentages for categorical variables.

[b] Weight (kg)/height (m)^2.

[c] Smoking-related cancer sites included lip, oral cavity, pharynx and larynx (C000-C149, C320-C329), nose and nasal cavity (C300-C301, C310-C319), esophagus (C150-C159), stomach (C160-C169), colorectum (C180-C189, C199, C209), liver (C220-C229), pancreas (C250-C259), lung (C340-C349), cervix (C530-C539), bladder (C670-C679), kidney (C649-C659), and acute myeloid leukemia (C920).

Table 2. Multivariable HRs and SHRs for Mortality from Cancers According to the Number of Smoking Family Members during Childhood, Japan, 1988-1990

No. of smoking family members	No. of cases	HR [a]	95% CI	Multivariable HR [b]	95% CI	Multivariable SHR [b]	95% CI
All cancers							
0	674	1.00	Referent	1.00	Referent	1.00	Referent
1	1323	1.03	0.94-1.13	1.03	0.94-1.13	1.04	0.94-1.14
2	304	0.94	0.82-1.08	0.94	0.82-1.08	0.95	0.83-1.10
3 +	55	1.20	0.91-1.59	1.21	0.92-1.59	1.18	0.89-1.56
P for trend		0.93		0.85		0.85	
0 vs 1+		1.02	0.93-1.11	1.03	0.94-1.12	1.03	0.94-1.13
Smoking-related cancer [c]							
0	417	1.00	Referent	1.00	Referent	1.00	Referent
1	857	1.09	0.97-1.23	1.10	0.97-1.23	1.10	0.97-1.23
2	193	0.98	0.83-1.17	0.98	0.82-1.17	0.99	0.83-1.18
3 +	34	1.20	0.84-1.70	1.20	0.84-1.70	1.15	0.81-1.64
P for trend		0.56		0.59		0.60	
0 vs 1+		1.07	0.96-1.20	1.08	0.96-1.21	1.08	0.96-1.21
Non-smoking-related cancer [d]							
0	257	1.00	Referent	1.00	Referent	1.00	Referent
1	466	0.93	0.80-1.08	0.95	0.81-1.11	0.94	0.81-1.10
2	111	0.88	0.70-1.10	0.89	0.71-1.12	0.90	0.72-1.13
3 +	21	1.21	0.78-1.89	1.24	0.79-1.94	1.20	0.77-1.88
P for trend		0.52		0.67		0.66	
0 vs 1+		0.93	0.80-1.07	0.95	0.81-1.10	0.94	0.81-1.09
Pancreatic cancer							
0	56	1.00	Referent	1.00	Referent	1.00	Referent
1	139	1.31	0.96-1.79	1.30[f]	0.95-1.77	1.33[f]	0.97-1.83
2	28	1.04	0.66-1.64	1.04[f]	0.66-1.64	1.06[f]	0.66-1.68
3 +	9	2.30	1.14-4.65	2.32[f]	1.14-4.72	2.25[f]	1.10-4.60
P for trend		0.14		0.13		0.14	
0 vs 1+		1.29	0.95-1.74	1.32	0.97-1.79	1.31	0.96-1.78
Liver cancer							
0	67	1.00	Referent	1.00	Referent	1.00	Referent
1	124	0.98	0.72-1.31	1.00	0.74-1.36	1.00	0.73-1.36
2	41	1.14	0.77-1.68	1.12[e]	0.75-1.66	1.11[e]	0.74-1.66

3 +							
P for trend		0.60		0.63		0.66	
0 vs 1+		1.01	0.76-1.34	1.03	0.77-1.38	1.02	0.76-1.38
Lung cancer							
0	76	1.00	Referent	1.00	Referent	1.00	Referent
1	132	0.91	0.68-1.20	0.91	0.68-1.21	0.90	0.67-1.20
2 3 +	38	0.91 [e]	0.62-1.34	0.92 [e]	0.62-1.37	0.92 [e]	0.62-1.37
P for trend		0.56		0.60		0.60	
0 vs 1+		0.91	0.69-1.19	0.91	0.69-1.20	0.90	0.68-1.19
Stomach cancer							
0	125	1.00	Referent	1.00	Referent	1.00	Referent
1	244	1.05	0.85-1.31	1.03 [g]	0.83-1.29	1.02 [g]	0.82-1.28
2	43	0.75	0.53-1.06	0.74 [g]	0.52-1.05	0.74 [g]	0.52-1.05
3 +	10	1.20	0.63-2.29	1.15 [g]	0.60-2.20	1.09 [g]	0.57-2.09
P for trend		0.49		0.40		0.36	
0 vs 1+		1.00	0.81-1.23	0.98	0.79-1.22	0.97	0.79-1.21
Colorectal cancer							
0	63	1.00	Referent	1.00	Referent	1.00	Referent
1	138	1.16	0.86-1.56	1.15 [g]	0.85-1.56	1.14 [g]	0.84-1.54
2 3 +	32	0.92	0.60-1.41	0.93 [e, g]	0.60-1.43	0.93 [g]	0.60-1.44
P for trend		0.95		0.94		0.94	
0 vs 1+		1.11	0.83-1.48	1.10	0.82-1.48	1.10	0.82-1.47

HR, hazard ratio; SHR, subdistribution hazard ratio; CI, confidence interval.

[a] Adjusted for age and sex.

[b] Multivariable HR and SHR: adjusted for age (continuous), sex, body mass index (sex-specific quintile), secondhand smoke status in adulthood at home (never, sometimes, 1–4 days per week, or almost every day) and outside of home (never, sometimes, 1–4 days per week, or almost every day), alcohol consumption (never drinker, ex-drinker, or current drinker of 0.1–45.9 g or ≥ 46.0 g ethanol per day), hours of exercise (almost never, 1–4 h, or ≥ 5 h per week), hours of walking (almost never, 0.5 h, or > 0.5 h per day), perceived mental stress (low, moderate, or high), educational level (≤ 18 years or ≥ 19 years of age on completion of education), employment status (unemployed or employed), and frequency of vegetable and fruit intake (quintile).

[c] Smoking-related cancer sites included lip, oral cavity, pharynx and larynx (C000-C149, C320-C329), nose and nasal cavity (C300-C301, C310-C319), esophagus (C150-C159), stomach (C160-C169), colorectum (C180-C189, C199, C209), liver (C220-C229), pancreas (C250-C259), lung (C340-C349), cervix (C530-C539), bladder (C670-C679), kidney (C649-C659), and acute myeloid leukemia (C920).

[d] Non-smoking–related cancer sites included all the other sites not stated above.

[e] Multivariable HR and SHR of 0 vs 2+ smoking family members. We collapsed the categories of 2 and 3+ smoking family members when less than 5 participants are included in the 3+ smoking family member category.

[f] HR and SHR were further adjusted for self-reported diabetes status.

[g] HR and SHR were further adjusted for red meat and processed meat intake.