Table 2. Workplace Smoking Ban Status (%) According to Basic Characteristics, Using Survey Weights (Before PS Weighting)

Characteristics	Complete smoking ban (weighted n = 8 156 369) %	Partial smoking ban (weighted n = 20 828 196) %	No smoking ban (weighted n = 5 368 676) %
Total	23.7	60.6	15.6
Sex			
Men	19.6	63.9	16.4
Women	29.5	56.0	14.5
Age group			
20–29 years	28.8	57.6	13.6
30–39 years	24.7	58.5	16.8
40–49 years	22.8	64.0	13.3
50–59 years	18.3	63.6	18.2
60–64 years	24.9	56.1	19.0
Employment category			
Regular employee	24.8	62.0	13.2
Others including part-time worker	23.5	60.2	16.3
Extra working hours per month			
0–44	24.9	60.4	14.8
45–79	18.5	68.2	13.3
80 or more	10.7	47.0	42.3
Health checkup within the last year			
No	25.1	43.1	31.8
Yes	23.5	63.5	13.0
Worksite scale (employee number)			
10–29	22.4	48.1	29.4
30–49	29.8	57.8	12.4
50–99	20.5	58.9	20.6
100–299	24.6	73.4	2.0
300–999	21.6	72.6	5.8
1000 or more	26.8	69.0	4.3
Industries			
Forestry, mining and construction	21.2	47.2	31.7
Manufacturing	7.3	76.6	16.1
Electricity, gas, heat supply, water, information and communications	21.5	77.6	0.9
Transport and postal services	3.4	70.0	26.6
Wholesale and retail trade	18.0	69.3	12.7
Finance, insurance, real estate, goods rental and leasing	26.0	63.1	11.0
Scientific research, professional and technical services	27.5	59.3	13.2
Accommodations	10.9	81.3	7.8
Eating and drinking services	13.2	68.4	18.3
Services	31.7	50.0	18.3
Education and learning support	66.3	24.6	9.2
Medical, health care and welfare	60.4	27.2	12.3
Area block			
Hokkaido	1.5	60.2	38.4
Tohoku	8.0	54.1	37.9
Kitakanto	16.5	70.6	12.9
Tokyoken	26.7	64.5	8.8
Chubu/Hokuriku	19.8	60.1	20.1
Chukyoken	15.3	65.2	19.5
Kinki	21.3	58.8	20.0
Chugoku	22.8	69.5	7.7
Shikoku	5.2	84.3	10.6
Kyushu/Okinawa	47.8	38.3	13.9

PS = propensity score. Unweighted numbers were 2066 for complete smoking ban, 7906 for partial smoking ban, and 1118 for no smoking ban.

PS Weighting

Goodness-of-fit indicators to evaluate the appropriateness of PS models are shown in Supplementary Table S2. The logistic models used to estimate the PS yielded a c-statistic between 0.75 and 0.81, suggesting the prediction of exposure status was sound. The number of standardized differences exceeding 0.1 mostly decreased after PS weighting. There were some exceptions: for example, a comparison between complete and partial bans among total subjects (n = 9972 [weighted number: 28 984 565]) showed the following: the mean PS for complete ban employees actually exposed was 0.41 (standard

Table 3. Covariate-Adjusted Prevalence Ratios (95% CI) of Current Smoker and SHS-Related Discomfort/Ill-Health According to Workplace Smoking Ban Status

	Among total subjects			Among nonsmokers		
Smoking ban status	Weighted No of total subjects	Current smoker, %	Prevalence ratio[a] for current smoker (95% CI)	Weighted No of nonsmokers	SHS-related discomfort/ill-health, %	Prevalence ratio[a] for SHS-related discomfort/ill-health (95% CI)
Conventional regression						
Complete smoking ban	8 156 369	25.0	**0.74 (0.66, 0.84)**	6 115 950	12.4	**0.51 (0.42, 0.62)**
Partial smoking ban	20 828 196	36.9	0.94 (0.86, 1.03)	13 137 418	24.3	0.97 (0.83, 1.13)
No smoking ban	5 368 676	43.9	1 (reference)	3 009 716	28.2	1 (reference)
Propensity score weighting						
TET estimations						
Complete smoking ban	7 675 912	25.1	**0.79 (0.73, 0.85)**	12 826 731	15.9	**0.47 (0.40, 0.54)**
vs. partial smoking ban	8 067 850	33.3	1 (reference)	13 038 331	24.3	1 (reference)
Complete smoking ban	7 907 414	25.7	**0.87 (0.77, 0.99)**	5 945 823	12.3	**0.46 (0.38, 0.56)**
vs. no smoking ban	8 125 648	28.2	1 (reference)	5 463 652	28.8	1 (reference)
Partial smoking ban	19 998 123	37.2	**1.19 (1.12, 1.26)**	12 711 970	24.5	0.90 (0.75, 1.07)
vs. no smoking ban	33 257 554	21.4	1 (reference)	18 286 200	24.6	1 (reference)
TEU estimations						
Complete smoking ban	19 857 017	29.5	**0.89 (0.85, 0.93)**	18 498 744	14.9	**0.63 (0.58, 0.69)**
vs. partial smoking ban	20 644 092	36.8	1 (reference)	19 141 079	25.3	1 (reference)
Complete smoking ban	5 301 729	28.7	**0.68 (0.58, 0.78)**	2 972 288	15.4	**0.52 (0.41, 0.67)**
vs. no smoking ban	5 346 614	43.9	1 (reference)	2 995 885	27.8	1 (reference)
Partial smoking ban	5 323 968	39.3	0.97 (0.90, 1.04)	2 901 086	27.7	0.99 (0.86, 1.13)
vs. no smoking ban	5 346 614	43.9	1 (reference)	3 001 486	28.0	1 (reference)

CI = confidence interval; No = number; SHS = secondhand smoke; TET = treatment effect among treated; TEU = treatment effect among untreated. Unweighted numbers of total subjects were 2066 for complete smoking ban, 7906 for partial smoking ban and 1118 for no smoking ban, and those of nonsmokers were 1541, 5142, and 670, respectively. Boldface indicates statistical significance of $P < .05$.

[a]Adjusted for all potential confounders listed in Table 1.

deviation, 0.26) compared with 0.19 (0.18) for partial ban employees. The probability density of the PS is shown in Supplementary Figure S1. After restricting subjects with overlapping PS between the complete and partial ban groups, the remaining baseline population was 9724 (weighted number: 28 326 389) before PS weighting; after PS weighting, a sufficiently decreased number of standardized differences exceeding 0.1 was observed (ie, 2 for TET compared with 20 before PS weighting).

Table 3 shows the results of covariate-adjusted PR using PS weighting (trimming level: baseline). Although differences between the two comparative groups were mostly small (Supplementary Tables S2–S5), large differences were observed in some categories: for example, the weighted number of total subjects differed largely between partial ban (n = 19 998 123) and no ban (n = 33 257 554) workplaces for TET estimation. Covariate-adjustment might be able to adjust these baseline differences. Among total subjects, complete ban employees (PR [95% CI] = 0.87 [0.77, 0.99] for TET, 0.68 [0.58, 0.78] for TEU) were significantly less likely to be current smokers than no ban employees, while partial ban employees (PR [95% CI] = 1.19 [1.12, 1.26] for TET, 0.97 [0.90, 1.04] for TEU) were not. Among nonsmokers, complete ban employees (PR [95% CI] = 0.46 [0.38, 0.56] for TET, 0.52 [0.41, 0.67] for TEU) were significantly less likely to perceive discomfort/ill-health than no ban employees, while partial ban employees (PR [95% CI] = 0.90 [0.75, 1.07] for TET, 0.99 [0.86, 1.13] for TEU) were not.

Results from PS trimmings are shown in Table 4. Among total subjects, complete ban employees (PRs ranged from 0.77–0.83 for TET, and 0.68–0.73 for TEU) were consistently significantly less likely to be current smokers than no ban employees, while partial ban employees showed partially significant PRs for TET (results from 1%, 2%, 4%, and 5% trimmings) and no significance for TEU. Similarly, among nonsmokers in the comparison between partial and no ban employees, differences between TET and TEU were observed: that is, there were some significant associations in TET estimations for perceived SHS-related discomfort/ill-health (23%–25% reduction in trimming 3%–10%), whereas no significant associations were observed in TEU estimations. In the comparison between complete and partial ban employees, consistent significant associations were observed for both outcomes and all target populations (TET, TEU, and ATE; Supplementary Table S6). In addition, the results of "univariate" models did not largely differ (Supplementary Tables S7 and S8).

Discussion

Complete workplace smoking bans were significantly associated with lower prevalence levels of current smoking and perceived SHS-related discomfort/ill-health among nonsmokers compared with partial bans or no ban. In contrast, partial bans were not significantly associated with either outcome compared with no ban. These results were obtained from conventional regressions and confirmed by PS weighting analyses. Furthermore, using several levels of PS trimming, we found interesting differences between TET and TEU in a comparison between partial bans and no ban: that is, there were significant associations in TET estimations (but these results were not robust and showed considerably weaker associations than for complete bans), while no significant associations were observed in TEU estimations. This inconsistency of results between TET and TEU may be partly due to the small sample size of the TEU-targeted

Table 4. Results From PS Weight Trimmings with Covariate-Adjustment. Prevalence Ratios (95%CI) of Current Smoker and SHS-Related Discomfort/Ill-Health According to Workplace Smoking Ban Status

Smoking ban status and targeted estimations	Trimming conditions	Among total subjects: Prevalence ratio for current smoker (95% CI)	Among nonsmokers: Prevalence ratio for SHS-related discomfort/ill-health (95% CI)
Complete smoking ban vs. partial smoking ban			
TET estimations	Baseline[a]	0.79 (0.73, 0.85)	0.47 (0.40, 0.54)
	Trimming 1%[b]	0.81 (0.74, 0.87)	0.46 (0.39, 0.54)
	Trimming 2%[b]	0.81 (0.75, 0.88)	0.51 (0.43, 0.60)
	Trimming 3%[b]	0.83 (0.76, 0.90)	0.54 (0.45, 0.64)
	Trimming 4%[b]	0.83 (0.76, 0.91)	0.57 (0.48, 0.68)
	Trimming 5%[b]	0.83 (0.76, 0.91)	0.55 (0.46, 0.66)
	Trimming 10%[b]	0.83 (0.76, 0.92)	0.60 (0.49, 0.73)
TEU estimations	Baseline[a]	0.89 (0.85, 0.93)	0.63 (0.58, 0.69)
	Trimming 1%[b]	0.89 (0.85, 0.94)	0.60 (0.54, 0.67)
	Trimming 2%[b]	0.88 (0.84, 0.93)	0.61 (0.55, 0.68)
	Trimming 3%[b]	0.87 (0.83, 0.92)	0.63 (0.57, 0.71)
	Trimming 4%[b]	0.85 (0.81, 0.90)	0.63 (0.56, 0.70)
	Trimming 5%[b]	0.85 (0.81, 0.90)	0.60 (0.54, 0.67)
	Trimming 10%[b]	0.85 (0.79, 0.91)	0.62 (0.55, 0.70)
Complete smoking ban vs. no smoking ban			
TET estimations	Baseline[a]	0.87 (0.77, 0.99)	0.46 (0.38, 0.56)
	Trimming 1%[b]	0.84 (0.74, 0.96)	0.45 (0.37, 0.55)
	Trimming 2%[b]	0.83 (0.73, 0.95)	0.45 (0.37, 0.54)
	Trimming 3%[b]	0.84 (0.74, 0.96)	0.48 (0.39, 0.59)
	Trimming 4%[b]	0.85 (0.74, 0.97)	0.46 (0.38, 0.57)
	Trimming 5%[b]	0.84 (0.73, 0.96)	0.46 (0.37, 0.56)
	Trimming 10%[b]	0.77 (0.70, 0.85)	0.39 (0.31, 0.50)
TEU estimations	Baseline[a]	0.68 (0.58, 0.78)	0.52 (0.41, 0.67)
	Trimming 1%[b]	0.73 (0.63, 0.85)	0.57 (0.45, 0.74)
	Trimming 2%[b]	0.69 (0.59, 0.81)	0.55 (0.43, 0.72)
	Trimming 3%[b]	0.71 (0.61, 0.83)	0.59 (0.45, 0.77)
	Trimming 4%[b]	0.73 (0.62, 0.86)	0.55 (0.41, 0.72)
	Trimming 5%[b]	0.68 (0.58, 0.81)	0.52 (0.39, 0.71)
	Trimming 10%[b]	0.68 (0.57, 0.82)	0.42 (0.30, 0.60)
Partial smoking ban vs. no smoking ban			
TET estimations	Baseline[a]	**1.19 (1.12, 1.26)**	0.90 (0.75, 1.07)
	Trimming 1%[b]	**0.92 (0.87, 0.98)**	0.88 (0.74, 1.05)
	Trimming 2%[b]	**0.93 (0.88, 0.99)**	0.87 (0.73, 1.04)
	Trimming 3%[b]	**0.96 (0.90, 1.02)**	**0.76 (0.71, 0.81)**
	Trimming 4%[b]	**0.90 (0.85, 0.94)**	**0.76 (0.70, 0.82)**
	Trimming 5%[b]	**0.92 (0.88, 0.96)**	**0.75 (0.70, 0.81)**
	Trimming 10%[b]	0.97 (0.90, 1.04)	**0.77 (0.72, 0.83)**
TEU estimations	Baseline[a]	0.93 (0.84, 1.03)	0.99 (0.86, 1.13)
	Trimming 1%[b]	0.91 (0.82, 1.01)	1.01 (0.87, 1.17)
	Trimming 2%[b]	0.95 (0.85, 1.06)	0.98 (0.84, 1.15)
	Trimming 3%[b]	0.95 (0.85, 1.06)	0.90 (0.76, 1.06)
	Trimming 4%[b]	0.91 (0.81, 1.03)	0.87 (0.73, 1.03)
	Trimming 5%[b]	0.92 (0.82, 1.04)	0.88 (0.74, 1.06)
	Trimming 10%[b]	0.89 (0.77, 1.04)	0.88 (0.69, 1.13)

CI = confidence interval; PS = propensity score; SHS = secondhand smoke; TET = treatment effect among treated; TEU = treatment effect among untreated. Boldface indicates statistical significance of $P < .05$.

[a]Subjects used as baseline population were employees who had PS between treated-min and untreated-max scores.

[b]Subjects trimmed from the baseline population.

population compared with the TET, although the point estimates were lower in TEU than in TET. In contrast, consistently significant associations were observed in both TET and TEU in comparisons between complete bans and others, partly confirming results from previous studies[1,30] and yielding novel evidence on partial bans. Although these findings were based on a cross-sectional survey and should be interpreted carefully, several possible interpretations include: (1) partial bans, which had already been implemented at the time of the survey, might be associated with favorable outcomes (ie, low smoking prevalence or low perceived SHS-related discomfort/ill-health) compared with no ban; however, (2) the favorable associations between a smoking ban and outcomes may be stronger in employees with complete bans than those with partial bans; (3) if, in future, partial bans are introduced in workplaces which currently have no ban, they may not have a significant positive effect on outcomes; and (4) if complete bans are introduced in workplaces which

currently have partial bans, they may have a significant positive effect on outcomes: for example, an approximately 40% reduction in perceived SHS-related discomfort/ill-health. (Interpretations of (1) and (2) were based on the TET results, and those of (3) and (4) were based on the TEU results.)

Although causality cannot be inferred from the cross-sectional data, our findings indicated that complete bans, but not partial bans, may improve employees' health. Also there is a high cost attached to constructing the facilities necessary for the implementation of a partial ban, whereas there is no such cost for a complete ban. A high proportion of nonsmokers are harmed by exposure to SHS, and control of concentrations in indoor air poses problems in the management of heating, ventilating, and air-conditioning systems.[1] As, theoretically, there is no worksite where it is impossible to implement a complete smoking ban, our findings may be generalizable for all employees in all Japanese workplaces.

This study had several limitations. First, since we used data from a cross-sectional study, causal inference of the results cannot be established. The cross-sectional data does not support the conclusion that workplace smoking bans lead to lower smoking prevalence, because smokers could have chosen workplaces where smoking is allowed, and likewise nonsmokers could have chosen workplaces with smoking bans. This may lead to overestimation of the association. Second, self-reported smoking status and perceived SHS-related discomfort/ill-health were used, but previous studies showed that self-reported smoking or SHS exposure correlated well with biomarker concentrations.[31–33] The words "discomfort or ill-health" can include a wide range of symptoms or complaints,[1,34] suggesting the need for careful interpretation. Furthermore, the decline in smoking prevalence is partially attributed to the increasing social unacceptability of smoking.[35] As the societal norm has become increasingly antismoking, some smokers may not have answered accurately.[1] If this is true in complete ban settings, it may lead to overestimation. Third, partial bans included smoking-room and/or smoking-corner. Although a smoking-room was different from a smoking-corner, the results did not largely differ if these two were used separately as partial bans (data not shown). Fourth, the visibility of smoking might increase the perceived acceptability of smoking,[36] and thus result in continued smoking. We did not account for the visibility of designated rooms and this might result in a recall bias. However, because smoking in designated rooms might be seen as an inappropriate behavior, especially in small, dark rooms, the visibility in designated rooms might not largely increase the perceived acceptability of smoking.[37,38] Fifth, although survey weights were used to calculate the population estimates, we trimmed nonoverlap regions of the PS and excluded some subjects such as teenagers and adults aged 65 or older. Therefore the estimated result is not completely generalizable to the entire population. Sixth, we could not restrict our sample to those who worked indoors. Because employees who mainly work outdoors or in cars were included in the analysis, their smoking behavior in such situations might not be affected by the workplace smoke-free policy. This may lead to underestimation.

Despite these limitations, this study has the strengths of a large sample size with generalizability. Use of a representative sample to estimate the population impact was another strength. We used two different methods with several additional analyses to assess the association (see also Supplementary Data). Because similar associations were observed in all methods, our findings appear to be robust.

Conclusions

Complete smoking bans, but not partial bans, were associated with lower levels of employee smoking and SHS-related discomfort/ill-health. Findings from PS weighting of TEU suggested that partial workplace bans may not benefit Japanese employees who currently have no ban. Therefore, complete bans may be strongly recommended for future implementation, consistent with the World Health Organization Framework Convention on Tobacco Control, but careful interpretation of the data is necessary because of the cross-sectional study design.

Supplementary Material

Supplementary Data, Figure S1, and Tables S1–S8 can be found online at http://www.ntr.oxfordjournals.org

Funding

This study was supported by the Ministry of Health, Labour and Welfare (grant; Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus [H25-010]).

Declaration of Interests

None declared.

Acknowledgments

We thank Julia Mortimer for her English language editing.

References

1. International Agency for Research on Cancer. *IARC Handbooks of Cancer Prevention Tobacco Control Volume 13: Evaluating the Effectiveness of Smoke-free Policies*. Lyon, France: WHO Press; 2009.
2. Eriksen M, Mackay J, Ross H. *The Tobacco Atlas, Fourth Edition*. Atlanta, GA: American Cancer Society; 2012.
3. U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Smoking: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006.
4. World Health Organization. MPOWER. 2014. www.who.int/tobacco/mpower/en/. Accessed July 14, 2014.
5. Callinan JE, Clarke A, Doherty K, Kelleher C. Legislative smoking bans for reducing secondhand smoke exposure, smoking prevalence and tobacco consumption. *Cochrane Database Syst Rev*. 2010;14(4):CD005992. doi:10.1002/14651858.CD005992.pub2.
6. Asbridge M, Cartwright J. The relationship of home smoking bans to the physical and mental health of smokers. *Nicotine Tob Res*. 2011;13(2):70–77. doi:10.1093/ntr/ntq211.
7. McNabola A, Eyre GJ, Gill LW. Environmental tobacco smoke in designated smoking areas in the hospitality industry: exposure measurements, exposure modelling and policy assessment. *Environ Int*. 2012;44:68–74. doi:10.1016/j.envint.2012.01.012.
8. Katanoda K, Jiang Y, Park S, Lim MK, Qiao YL, Inoue M. Tobacco control challenges in East Asia: proposals for change in the world's largest epidemic region. *Tob Control*. 2014;23(4):359–368. doi:10.1136/tobaccocontrol-2012–050852.
9. Ministry of Health, Labour and Welfare. Workplace Smoke-free Guideline. 2003. www.mhlw.go.jp/houdou/2003/05/h0509-2.html. Accessed June 25, 2013.

10. Tabuchi T, Hoshino T, Hama H, et al. Complete workplace indoor smoking ban and smoking behavior among male workers and female nonsmoking workers' husbands: a pseudo cohort study of Japanese public workers. *Biomed Res Int*. 2014;2014:303917. doi:10.1155/2014/303917.
11. Pion M, Givel MS. Airport smoking rooms don't work. *Tob Control*. 2004;13(suppl 1):i37–40. doi:10.1136/tc.2003.005447.
12. Drope J, Bialous SA, Glantz SA. Tobacco industry efforts to present ventilation as an alternative to smoke-free environments in North America. *Tob Control*. 2004;13(suppl 1):i41–47. doi:10.1136/tc.2003.004101.
13. Murata Y. *Environmental Research in Passive Smoking*. Kyoto, Japan: Sekaishisosha; 2012.
14. Cains T, Cannata S, Poulos R, Ferson MJ, Stewart BW. Designated "no smoking" areas provide from partial to no protection from environmental tobacco smoke. *Tob Control*. 2004;13(1):17–22. doi:10.1136/tc.2003.005488.
15. Ministry of Health, Labour and Welfare. Survey on State of Employees' Health. 2007. www.mhlw.go.jp/toukei/list/49-19.html. Accessed July 9, 2014.
16. Centers for Disease Control (CDC). Discomfort from environmental tobacco smoke among employees at worksites with minimal smoking restrictions—United States, 1988. *MMWR. Morbidity and Mortality Weekly Report*. 1992;41(20):351–354.
17. Ministry of Health, Labour and Welfare. Survey on the Prevention of Industrial Accidents. 2011. www.mhlw.go.jp/toukei/list/h23-46-50.html. Accessed July 11, 2014.
18. Ministry of Internal Affairs and Communications. 2009 Economic Census for Business Frame. 2009. www.stat.go.jp/english/data/e-census/. Accessed July 4, 2014.
19. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol*. 2005;162(3):199–200. doi:10.1093/aje/kwi188.
20. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702–706. doi:10.1093/aje/kwh090.
21. Brookhart MA, Wyss R, Layton JB, Stürmer T. Propensity score methods for confounding control in nonexperimental research. *Circ Cardiovasc Qual Outcomes*. 2013;6(5):604–611. doi:10.1161/CIRCOUTCOMES.113.000359.
22. Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. *BMJ*. 2013;347:f5704. doi:10.1136/bmj.f5704.
23. Hoshino T. *Statistics for Observational Data and Surve Data—Causal Inference, Selection Bias and Data Fusion*. Tokyo, Japan: Iwanami Shoten; 2009.
24. Dugoff EH, Schuler M, Stuart EA. Generalizing observational study results: applying propensity score methods to complex surveys. *Health Serv Res*. 2014;49(1):284–303. doi:10.1111/1475-6773.12090.
25. Cook BL, McGuire TG, Meara E, Zaslavsky AM. Adjusting for health status in non-linear models of health care disparities. *Health Serv Outcomes Res Methodol*. 2009;9(1):1–21. doi:10.1007/s10742-008-0039-6.
26. Lee BK, Ploner A, Zhang Z, Gryfelt G, Wikman A, Reilly M. Constructing a population-based research database from routine maternal screening records: a resource for studying alloimmunization in pregnant women. *PLoS One*. 2011;6(3):e27619. doi:10.1371/journal.pone.0018174.
27. Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol*. 2006;98(3):253–259. doi:10.1111/j.1742-7843.2006.pto_293.x.
28. Austin PC. Assessing balance in measured baseline covariates when using many-to-one matching on the propensity-score. *Pharmacoepidemiol Drug Saf*. 2008;17(12):1218–1225. doi:10.1002/pds.1673.
29. Welch RD, Zalenski RJ, Frederick PD, et al.; National Registry of Myocardial Infarction 2 and 3 Investigators. Prognostic value of a normal or nonspecific initial electrocardiogram in acute myocardial infarction. *JAMA*. 2001;286(16):1977–1984. doi:10.1001/jama.286.16.1977.
30. Fichtenberg CM, Glantz SA. Effect of smoke-free workplaces on smoking behaviour: systematic review. *BMJ*. 2002;325(7357):188.
31. Brunekreef B, Leaderer BP, van Strien R, et al. Using nicotine measurements and parental reports to assess indoor air: the PIAMA birth cohort study. Prevention and Incidence of Asthma and Mite Allergy. *Epidemiology*. 2000;11(3):350–352.
32. Johansson A, Halling A, Hermansson G, Ludvigsson J. Assessment of smoking behaviors in the home and their influence on children's passive smoking: development of a questionnaire. *Ann Epidemiol*. 2005;15(6):453–459. doi:10.1016/j.annepidem.2004.09.012.
33. West R, Zatonski W, Przewozniak K, Jarvis MJ. Can we trust national smoking prevalence figures? Discrepancies between biochemically assessed and self-reported smoking rates in three countries. *Cancer Epidemiol Biomarkers Prev*. 2007;16(4):820–822. doi:10.1158/1055-9965.EPI-06-0679.
34. Lam TH, Janghorbani M, Hedley AJ, Ho SY, McGhee SM, Chan B. Public opinion on smoke-free policies in restaurants and predicted effect on patronage in Hong Kong. *Tob Control*. 2002;11(3):195–200. doi:10.1136/tc.11.3.195.
35. Graham H. Smoking, stigma and social class. *J Soc Policy*. 2012;14(1):88–93. doi:10.1017/S004727941100033X.
36. Alesci NL, Forster JL, Blaine T. Smoking visibility, perceived acceptability, and frequency in various locations among youth and adults. *Prev Med*. 2003;36(3):272–281.
37. Sirichotiratana N, Yogi S, Prutipinyo C. Perception of tourists regarding the smoke-free policy at Suvarnabhumi International Airport, Bangkok, Thailand. *Int J Environ Res Public Health*. 2013;10(9):4012–4026.
38. Pearson AL, Nutsford D, Thomson G. Measuring visual exposure to smoking behaviours: a viewshed analysis of smoking at outdoor bars and cafés across a capital city's downtown area. *BMC Public Health*. 2014;14:300.

J Epidemiol 2016;26(1):14-21
doi:10.2188/jea.JE20140183

Original Article

Tobacco Price Increase and Smoking Cessation in Japan, a Developed Country With Affordable Tobacco: A National Population-Based Observational Study

Takahiro Tabuchi[1], Masakazu Nakamura[2], Tomio Nakayama[1], Isao Miyashiro[1], Jun-ichiro Mori[3], and Hideaki Tsukuma[1]

[1]Center for Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
[2]Department of Health Promotion and Prevention, Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka, Japan
[3]Center for Medical Education, Shinshu University School of Medicine, Matsumoto, Nagano, Japan

Received September 25, 2014; accepted May 25, 2015; released online August 15, 2015

ABSTRACT

Background: Longitudinal assessment of the impact of tobacco price on smoking cessation is scarce. Our objective was to investigate the effect of a price increase in October 2010 on cessation rates according to gender, age, socioeconomic status, and level of tobacco dependence in Japan.

Methods: We used longitudinal data linkage of two nationally representative studies and followed 2702 smokers for assessment of their cessation status. The odds ratios (ORs) for cessation were calculated using logistic regression. To estimate the impact of the 2010 tobacco price increase on cessation, data from 2007 were used as a reference category.

Results: Overall cessation rates significantly increased from 2007 to 2010, from 3.7% to 10.7% for men and from 9.9% to 16.3% for women. Cessation rates were 9.3% for men who smoked 1–10 cigarettes per day, 2.7% for men who smoked 11–20 cigarettes per day, and 2.0% for men who smoked more than 20 cigarettes per day in 2007. These rates increased to 15.5%, 10.0%, and 8.0%, respectively, in 2010. The impact was stronger among subjects who smoked more than 11 cigarettes per day than those who smoked 1–10 cigarettes per day in both sexes: ORs for 2010 were 4.04 for those smoking 11–20 cigarettes per day, 4.26 for those smoking more than 20 cigarettes per day, and 1.80 for those smoking 1–10 cigarettes per day in the main model in men. There were no obvious differences in the relationship between tobacco price increase and smoking cessation across age and household expenditure groups.

Conclusions: The tobacco price increase in Japan had a significant impact on smoking cessation in both sexes, especially among heavy smokers, with no clear difference in effect by socio-demographic status.

Key words: tobacco price increase; smoking cessation; Japan; linkage study

INTRODUCTION

Assessment of the impact of tobacco price increases on changes in smoking behaviors in different social groups is a priority in health policy research.[1,2] Tobacco taxation (generally accompanying a price increase for tobacco products) has been considered the best practice for reducing population tobacco use and inherent smoking inequality.[3,4] From a population health perspective,[5] a population-based intervention, such as a countrywide tobacco price increase, is expected to affect not the only the affluent population but also high-risk and vulnerable populations. Previous studies have shown that tobacco price increases reduce tobacco use and smoking inequality because they have a stronger influence on the poor and the young than the affluent and the old in developed countries, such as the United States, Scotland, and Australia.[4] However, mixed results were also reported for differences in age, gender, and education.[2,6] Moreover, a high rate of tobacco dependence has been shown to strongly predict low rates of smoking behavior change, including smoking cessation.[7]

Since the tobacco tax was established in Japan in 1998, the tobacco tax/price has been increased three times (July 1, 2003; July 1, 2006; and October 1, 2010). Therefore, the price of a pack of 20 of the most popular brand of cigarette in Japan, Mild Seven, increased from 250 yen to 270 yen (8% increase)

Address for correspondence. Takahiro Tabuchi, MD, PhD, Center for Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, 3-3 Nakamichi 1-chome, Higashinari-ku, Osaka 537-8511, Japan (e-mail: tabuchitak@gmail.com).

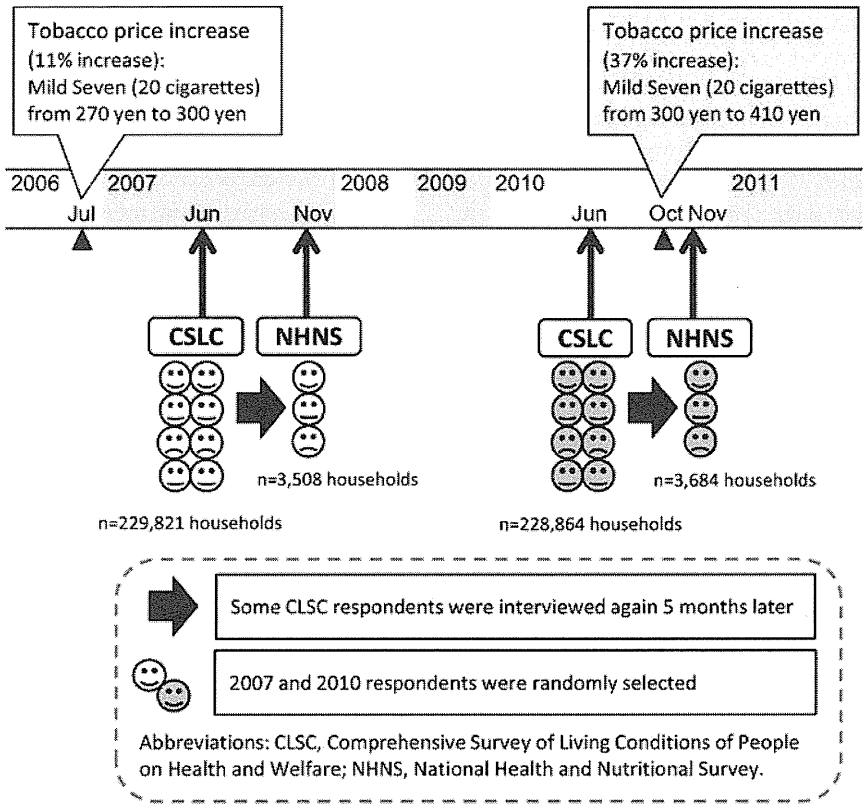

Figure. Time frame around the study.

in 2003, to 300 yen (11% increase) in 2006, and to 410 yen (37% increase) in 2010.[8] The tobacco industry has also increased the price for its own benefit. Partly as a result of these price increases, adult smoking prevalence in Japan has declined: the proportion of current smokers has decreased from 48% in 2001 to 33% in 2010 among men, and from 14% in 2001 to 10% in 2010 among women.[9] However, according to the affordability index, the price of tobacco was considered to be very low in Japan in 2009.[10] Of all developed countries surveyed, cigarettes were most affordable in Japan in 2009 (people only had to work for 11.5 minutes to earn the price of a pack of 20 cigarettes).[10] Even after the 2010 price increase, this figure was expected to be around 16 minutes, whereas in other developed countries, such as Australia, Canada, and the Netherlands, it was 30 minutes in 2009.[10] Because the affordability of tobacco in Japan may create special conditions for smokers, the impact of a tobacco price increase on smoking behavior and smoking inequality should be specifically assessed. Very few longitudinal studies have examined the effect of tobacco price on rates of smoking cessation,[4,11,12] and the present paper is the first to use linkage data (ie, used as longitudinal data) to explore this effect in Japan.

Our objective was to investigate the impact of tobacco price increases on rates of smoking cessation according to and adjusted for different variables, such as gender, age, socioeconomic status and level of tobacco dependence, in Japan, a developed country with affordable tobacco.[10]

METHODS

Data

We used linkage data from the 2007 and 2010 versions of the Comprehensive Survey of Living Conditions of People on Health and Welfare (CSLC) and the National Health and Nutritional Survey (NHNS), which were conducted by the Japanese Ministry of Health, Labour and Welfare (MHLW). The CSLC collects information on health-related factors, such as smoking behaviors, every 3 years in the first week of June, while the NHNS collects information on smoking behaviors annually in November (on a weekday). Out of 940 000 inhabited census tracts (the sampling unit for national census in 2005), 5440 were randomly sampled across Japan in 2007 (5510 in 2010, independently from 2007) for the collection of CSLC data from all household members within each census tract. Of the tracts selected for CLSC, 300 were randomly selected for the NHNS; therefore, some CLSC respondents were interviewed again 5 months later in the NHNS (Figure).

Data were available for 229 821 (response rate: 79.9%) households in 2007 and 228 864 (79.1%) households in 2010 for the CSLC[9] and 3508 (66.5%) households in 2007 and

3684 (68.8%) in 2010 for the NHNS.[13,14] Linkage data within each year from subjects who responded to both surveys with smoking information and who were aged 20–79 years at baseline were analyzed. Of 11 088 non-institutionalized eligible subjects (2639 men and 2995 women in 2007; 2598 men and 2856 women in 2010), 2702 were current smokers at baseline in the present study (1080 men and 355 women in 2007 and 961 men and 306 women in 2010). Data were used with permission from MHLW. Analyses of national survey data are exempt from ethical review according to the Epidemiological Research Guidelines.

Smoking

First, individuals from the 2007 and 2010 CSLC were categorized as current smokers or non-current smokers at baseline. In the CSLC, smoking habits were assessed based on the following four categories: (a) "I don't smoke"; (b) "I smoke every day"; (c) "I smoke occasionally but not every day"; and (d) "I have stopped smoking for more than 1 month". We categorized (b) and (c) as current smokers (as of June). The NHNS divided subjects into "ever smokers" and "never smokers" and asked, "Do you now smoke cigarettes every day, some days, or not at all (stopped smoking more than 1 month)?" We categorized ever smokers who reported smoking "every day" or "some days" as current smokers (as of November).

Current smoker prevalence was defined as the rate of current smokers among study subjects (considering June or November timing of outcome assessment as subgroups). Smoking cessation was identified by smokers in June (CSLC) who were no longer smokers in November (NHNS). The smoking cessation rate was calculated as the percentage of current smokers (as of June) who did not smoke at the time of the NHNS (as of November): that is, the percentage of "non-current smokers" in the NHNS among current smokers in the CSLC.

Variables

Variables related to smoking behaviors (identified from the CSLC) were used to identify the characteristics of the baseline study subjects and to control for their possible confounding effects (if they met the requirements for confounding). In line with previous studies,[15,16] we used age, household expenditure, housing tenure (home-owner or not), employment status (working or not), marital status (married, never married, or widowed/divorced), self-rated health (poor or not), number of cigarettes smoked per day (1–10, 11–20, or >20), and number of other household smokers (0 or ≥1) (see supplementary methods in eMaterial). The number of cigarettes smoked per day was regarded as a proxy indicator for tobacco dependence.[17,18] The cutoffs of 10 and 20 cigarettes were used because the CSLC questionnaire had categories of 1–10, 11–20, 21–30, and ≥31 cigarettes, and we modified the category on the basis of its distribution.

Statistical analysis

As the tobacco price increase occurred during the period between the CSLC (June) and the NHNS (November) in 2010, we had a unique opportunity to analyze the effect of the increase. Statistical analyses were conducted separately for men and women, because there are large gender differences in smoking behaviors in most Asian countries, including Japan.[19] Basic characteristics and smoking cessation rates were tabulated according to the above-mentioned variables. Fisher's exact test was used to compare the differences in subject characteristics and cessation rates between 2007 and 2010.

Univariate logistic regression among a pooled sample of participants in 2007 and 2010 (separately for men and women) was applied to calculate crude odds ratios (ORs) with 95% confidence intervals (CIs) for smoking cessation. Multivariate logistic regression was used to calculate adjusted ORs. To estimate the impact of the October 2010 tobacco price increase on smoking cessation, cessation status in 2007 was used as a reference category (ie, 2007 versus 2010), because there was no price increase during the 5 months of follow-up from June to November in 2007.

In addition to sex separation, stratified analyses were implemented to estimate whether the association between tobacco price increase and smoking cessation rates varied according to age, socioeconomic status, or tobacco dependence. We used household expenditure as a socioeconomic variable in the stratified analysis, because expenditure is an analog of income (ie, a representative socioeconomic factor) in Japan.[20] Subjects with a missing value for cigarettes smoked per day were excluded from the regression analyses, while a missing value category on expenditure was used as a dummy variable because of the high frequency of missing expenditure values. In addition, to confirm the interaction effect between tobacco price and personal factors, such as age, we also conducted multivariate analyses using interaction terms. We modified the interaction term according to the results of the stratified analyses, generating a new dichotomized category; for example, cigarettes smoked per day of 11 or more (ie, both "11–20" and ">20") were scored as 1 for the "2010/Cigarettes per day of 11 or more" category and as 0 for the remaining three combination categories (eg, "2007/Cigarettes per day of 1–10").

Probability values for statistical tests were two tailed, and $P < 0.05$ was regarded as statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

The prevalence of current smoking in June 2007 and 2010 among all subjects (including smokers and non-smokers) is shown in eTable 1. The overall prevalence of current smoking in June significantly decreased from 2007 to 2010 for men (40.9% to 37.0%) but not for women, although prevalence

Table 1. Basic characteristics of current smokers in June, comparison between 2007 and 2010 (baseline)

Characteristics	Men			Women		
	2007 $n = 1080$	2010 $n = 961$	P for difference[a]	2007 $n = 355$	2010 $n = 306$	P for difference[a]
Cigarettes per day			0.009			0.257
1–10	205 (19.0)	219 (22.8)		121 (34.1)	125 (40.9)	
11–20	523 (48.4)	490 (51.0)		186 (52.4)	150 (49.0)	
>20	348 (32.2)	249 (25.9)		45 (12.7)	29 (9.5)	
Missing	4 (0.4)	3 (0.3)		3 (0.9)	2 (0.7)	
Other household smoker(s)			0.509			0.813
None	733 (67.9)	639 (66.5)		147 (41.4)	130 (42.5)	
One or more	347 (32.1)	322 (33.5)		208 (58.6)	176 (57.5)	
Household expenditure			0.369			0.434
1st (lowest) tertile	335 (31.0)	293 (30.5)		115 (32.4)	98 (32.0)	
2nd tertile	338 (31.3)	316 (32.9)		104 (29.3)	99 (32.4)	
3rd (highest) tertile	338 (31.3)	307 (32.0)		108 (30.4)	94 (30.7)	
Missing	69 (6.4)	45 (4.7)		28 (7.9)	15 (4.9)	
Age group, years			0.230			0.727
20–39	378 (35.0)	317 (33.0)		149 (42.0)	122 (39.9)	
40–59	459 (42.5)	397 (41.3)		151 (42.5)	130 (42.5)	
60–79	243 (22.5)	247 (25.7)		55 (15.5)	54 (17.7)	
Home owner			0.165			0.678
No	226 (20.9)	226 (23.5)		118 (33.2)	97 (31.7)	
Yes	854 (79.1)	735 (76.5)		237 (66.8)	209 (68.3)	
Employment status			0.621			0.662
Working	926 (85.7)	811 (84.4)		239 (67.3)	197 (64.4)	
Not working	142 (13.2)	136 (14.2)		113 (31.8)	107 (35.0)	
Missing	12 (1.1)	14 (1.5)		3 (0.9)	2 (0.7)	
Marital status			0.174			0.967
Married	834 (77.2)	710 (73.9)		226 (63.7)	198 (64.7)	
Never married	191 (17.7)	201 (20.9)		69 (19.4)	57 (18.6)	
Widowed/Divorced	55 (5.1)	50 (5.2)		60 (16.9)	51 (16.7)	
Poor self-rated health			0.354			0.466
No	914 (84.6)	826 (86.0)		281 (79.2)	254 (83.0)	
Yes	129 (11.9)	97 (10.1)		62 (17.5)	44 (14.4)	
Missing	37 (3.4)	38 (4.0)		12 (3.4)	8 (2.6)	

[a]P for difference was calculated by Fisher's exact test.

decreased by approximately 10% in both sexes from 2007 to 2010.

Basic characteristics of current smokers in June, comparing 2007 with 2010, are shown in Table 1. A statistically significant difference in the distribution between 2007 and 2010 was observed only in "cigarettes smoked per day" in men. All other variables were not significantly different between 2007 and 2010. Based on these results, we treated "cigarettes smoked per day" as a confounding factor for men in subsequent multivariate analyses.

Rates of smoking cessation among smokers after 5 months of follow-up, according to basic characteristics, are shown in Table 2. Overall cessation rates significantly differed between 2007 and 2010 (3.7% to 10.7% for men and 9.9% to 16.3% for women). Smoking cessation rates were 9.3% for men who smoked 1–10 cigarettes per day, 2.7% for men who smoked 11–20 cigarettes per day, and 2.0% for men who smoked more than 20 cigarettes per day in 2007; these rates increased to 15.5%, 10.0%, and 8.0%, respectively, in 2010. A statistically significant difference in cessation rates between 2007 and 2010 was observed in the following groups: those who smoked 11–20 cigarettes per day, the highest household expenditure tertile, non-home-owners, and married participants of both sexes; and men who smoked more than 20 cigarettes per day, did not live with other household smokers, who lived with one or more household smokers, all age groups, home-owners, who were working, and who did not have poor self-rated health.

Table 3 shows logistic regression results for 2010 compared with 2007 for smoking cessation rates according to baseline stratification. The cigarettes smoked per day-adjusted model (ie, the crude model in the cigarettes smoked per day stratification) was considered an appropriate model (main model) to account for confounding in men, while the unadjusted crude model was used in women. For men, significant ORs for cessation for the period of June to November 2010 were observed in all stratifications except for 1–10 cigarettes smoked per day and did not change materially after additional adjustment for age group (adjustments for other variables also did not significantly change the results; data not shown). The ORs for cessation were stronger among men than among women (ORs of 3.01 [95% CI, 2.06–4.39]

Table 2. Smoking cessation rates (during 5 months of follow-up) and increase (absolute value) in 2010 compared with 2007 among smokers according to baseline characteristics

Characteristics	Smoking cessation rates (%) among smokers							
	Men				Women			
	2007 %	2010 %	Increase % point	*P* for difference[a]	2007 %	2010 %	Increase % point	*P* for difference[a]
Overall population	3.7	10.7	7.0	<0.001	9.9	16.3	6.5	0.014
Cigarettes per day								
1–10	9.3	15.5	6.3	0.057	18.2	22.4	4.2	0.432
11–20	2.7	10.0	7.3	<0.001	5.9	13.3	7.4	0.023
>20	2.0	8.0	6.0	0.001	2.2	3.5	1.2	Not applicable
Other household smoker(s)								
None	4.1	11.3	7.2	<0.001	12.2	18.5	6.2	0.180
One or more	2.9	9.6	6.8	0.000	8.2	14.8	6.6	0.051
Household expenditure								
1st (lowest) tertile	3.0	12.0	9.0	<0.001	11.3	12.2	0.9	0.835
2nd tertile	3.0	8.5	5.6	0.002	5.8	13.1	7.4	0.092
3rd (highest) tertile	4.7	12.4	7.7	0.001	10.2	24.5	14.3	0.008
Age group, years								
20–39	3.7	10.1	6.4	0.001	9.4	16.4	7.0	0.098
40–59	2.8	9.8	7.0	<0.001	8.6	13.9	5.2	0.184
60–79	5.4	13.0	7.6	0.005	14.6	22.2	7.7	0.332
Home owner								
No	2.7	9.7	7.1	0.003	5.9	14.4	8.5	0.041
Yes	4.0	11.0	7.0	<0.001	11.8	17.2	5.4	0.107
Employment status								
Working	3.1	10.7	7.6	<0.001	8.4	13.2	4.8	0.118
Not working	7.0	11.0	4.0	0.297	13.3	22.4	9.2	0.081
Marital status								
Married	3.1	11.6	8.4	<0.001	11.1	19.7	8.6	0.015
Never married	5.8	8.5	2.7	0.332	8.7	14.0	5.3	0.401
Widowed/Divorced	5.5	8.0	2.6	0.706	6.7	5.9	−0.8	Not applicable
Poor self-rated health								
No	3.7	10.4	6.7	<0.001	11.0	16.9	5.9	0.080
Yes	3.1	9.3	6.2	0.060	4.8	13.6	8.8	0.158

[a]*P* for difference was calculated by Fisher's exact test.
Note: Some increases do not match the results using these figures due to rounding up.

for men and 1.80 [95% CI, 1.13–2.87] for women in the main model). The ORs for cessation were higher among subjects of both sexes who smoked 11–20 or more than 20 cigarettes per day than among those smoked 1–10 cigarettes per day (eg, ORs of 4.04 [95% CI, 2.20–7.42] for 11–20 cigarettes smoked per day, 4.26 [95% CI, 1.77–10.23] for more than 20 cigarettes smoked per day, and 1.80 [95% CI, 0.99–3.27] for 1–10 cigarettes smoked per day in the main model in men). There were no obvious differences in the relationships between the stratified gradation of household expenditure tertiles or age groups and the impact of the tobacco price increase on smoking cessation for either sex (eg, the OR for cessation was highest in the lowest expenditure tertile than in the highest expenditure tertile in men, while the inverse was true in women). In additional models using an interaction term, the interaction term "2010/Cigarettes smoked per day of 11 or more" category showed a significant OR of 2.32 (95% CI, 1.06–5.05) in men. No other interaction terms were significant in either sex (data not shown).

DISCUSSION

The tobacco price increase in Japan, which was implemented in October 2010, was found to be associated with significantly increased cessation rates in 2010 compared with rates in 2007. Our findings support the notion that tobacco price increase is one of the best practices for advancing tobacco control.[2] The tobacco price increase was estimated to increase absolute smoking cessation rates by 7.0% for men and 6.5% for women during 5 months in 2010 compared with the same time period in 2007. Since there are no local-level price variations and the regulated elevated tobacco price was applied concurrently at the time of tobacco taxation and industrial price increase within Japan under the Tobacco Business Law[21] (ie, with no time-delay of the market price increase overall Japan), all subjects were assumed to be affected by the price increase in 2010. Although the tax was increase on October 1, 2010, at least 1 month before the survey in November 2010, the intervention may have had an impact prior to its

Table 3. Crude and adjusted odds ratios for year 2010 (versus 2007) for smoking cessation among smokers

Stratification variable	OR (95% CI)	
	Men	Women
	2010 (ref = 2007)	2010 (ref = 2007)
Total	*n* = 2034	*n* = 656
Crude	3.12 (2.14, 4.55)	1.80 (1.13, 2.87)[a]
Cigarettes per day-adjusted	3.01 (2.06, 4.39)[a]	1.68 (1.04, 2.70)
Age and cigarettes per day-adjusted	3.09 (2.12, 4.50)	1.78 (1.12, 2.85)
1–10 cigarettes per day	*n* = 424	*n* = 246
Crude	1.80 (0.99, 3.27)[a]	1.30 (0.70, 2.43)[a]
Age-adjusted	1.84 (1.01, 3.35)	1.29 (0.69, 2.41)
11–20 cigarettes per day	*n* = 1013	*n* = 336
Crude	4.04 (2.20, 7.42)[a]	2.45 (1.13, 5.29)[a]
Age-adjusted	3.93 (2.14, 7.23)	2.40 (1.11, 5.19)
>20 cigarettes per day	*n* = 597	*n* = 74
Crude	4.26 (1.77, 10.23)[a]	1.57 (0.09, 26.15)[a]
Age-adjusted	4.15 (1.72, 10.00)	NC
Household expenditure, lowest	*n* = 628	*n* = 212
Crude	4.41 (2.14, 9.07)	1.00 (0.43, 2.35)[a]
Cigarettes per day-adjusted	4.52 (2.19, 9.35)[a]	NC
Age and cigarettes per day-adjusted	4.50 (2.18, 9.31)	NC
Household expenditure, middle	*n* = 650	*n* = 201
Crude	3.07 (1.46, 6.45)	2.47 (0.90, 6.79)[a]
Cigarettes per day-adjusted	2.92 (1.38, 6.17)[a]	2.82 (1.00, 7.94)
Age and cigarettes per day-adjusted	2.94 (1.39, 6.22)	2.84 (1.01, 8.03)
Household expenditure, highest	*n* = 642	*n* = 201
Crude	2.84 (1.55, 5.20)	2.83 (1.29, 6.18)[a]
Cigarettes per day-adjusted	2.69 (1.45, 4.99)[a]	NC
Age and cigarettes per day-adjusted	2.67 (1.43, 4.97)	NC
Age group, 20–39 years	*n* = 691	*n* = 267
Crude	2.94 (1.54, 5.62)	1.94 (0.92, 4.11)[a]
Cigarettes per day-adjusted	2.64 (1.37, 5.08)[a]	NC
Age group, 40–59 years	*n* = 856	*n* = 280
Crude	3.74 (1.97, 7.11)	1.69 (0.80, 3.61)[a]
Cigarettes per day-adjusted	3.55 (1.86, 6.76)[a]	NC
Age group, 60–79 years	*n* = 487	*n* = 109
Crude	2.60 (1.33, 5.08)	1.68 (0.63, 4.50)[a]
Cigarettes per day-adjusted	2.77 (1.41, 5.47)[a]	1.65 (0.60, 4.51)

CI, confidence interval; NC, not converged; OR, odds ratio; ref, reference category.
[a]Models that were considered as main models accounting for confounding.

implementation in practice (eg, via anticipation effects).[22] In fact, according to a survey of cessation intention among smokers in August–September 2010 (ie, immediately before the tax increase),[23] 53% of smokers intended to quit because of the tax increase (1 or 2 months after the survey), and 72% of cessation-intending smokers reported that they intended to quit by the day of the tax increase. Therefore, cessation during June to November in 2010 was evaluated as a total effect of the tobacco price increase compared with 2007. Because there were no major smoking restrictions or other tobacco control measures between 2007 and 2010 (except medication for nicotine dependence using varenicline and nicotine patches, which started to be sold in 2008) in Japan,[21] we considered 2007 to be a reasonable reference category.

The ORs for smoking cessation after implementation of the price increase were higher among men than among women. Although women showed higher absolute cessation rates than men in both 2007 and 2010, tobacco price increase may have a more powerful effect on smoking cessation in men than in women. This is possibly because men have relatively less disposable money than women,[24] women are more health conscious than men,[25] and women may have more occasions to stop smoking, such as during a pregnancy, than men.[26] Because no other major tobacco control policies were implemented between 2007 and 2010 in Japan,[21] the price increase appears likely to have been the cause of the increased cessation rates.

Generally, tobacco dependence inhibits smoking cessation.[7] However, the effect of tobacco dependence on the association between tobacco price increase and smoking cessation was previously unknown.[4] In the current study, the price increase showed higher ORs for smoking cessation among those who smoked more heavily, although we did not focus on women who smoke more than 20 cigarettes per day, because they showed wide variance due to the small number of outcomes ($n = 2$) in the category. The additional analyses using interaction terms confirmed our interpretation of the results using stratification analyses, although the non-significance of the interaction terms in women did not mean that there was no interaction; this lack of an interaction effect might be due in part to the small sample size. When the number of cigarettes smoked per day was interpreted as a proxy of tobacco dependence, the analysis yielded a surprising tendency toward cessation among heavier smokers, in contrast to the expectation that tobacco dependence inhibits smoking cessation.[7,12] This result may be because the increase in tobacco price has a greater impact on those who smoke more heavily. Further, smokers who were likely to be sensitive to tobacco price increases and who were likely to have stopped smoking might have continued to smoke, as tobacco remains affordable in Japan despite the price increases.[10]

Policy implication

The Health Japan 21 (second version), a health promotion strategy in Japan, prioritized the reduction of smoking prevalence and health inequality, including smoking inequality.[27] The strategy's primary target for smoking prevalence was 12% among adults by 2022. In 2010, NHNS showed a large reduction in smoking prevalence in Japan due to the 2010 tobacco price increase, but the 2011 NHNS (which enrolled an independent sample from the 2010 survey) reported an increased smoking prevalence compared with 2010 (from 19.5% to 20.1% for adults of both sexes).[14] Among smokers who quit, only a small proportion succeed long-term[28]; this relapse might be due in part to the low tobacco price in Japan, even after the price increase in 2010. A previous study in California revealed that the impact of a price increase only lasted for 4 months after the tobacco price was raised by 95 cents in 1998.[29] Further intensive tobacco price increases will be required in Japan to promote continued smoking cessation.

Previous studies found that tobacco price increases promoted smoking cessation more among the poor and the

young than among the affluent and the old.[1,2,4] However, our findings in the present study did not support these associations, with increased cessation rates observed in all groups. The early years of public health interventions, such as health information campaigns, are often damaging in terms of health equity.[5] According to the inverse equity hypothesis,[30] affluent sections of society preferentially benefit from, or exploit, such interventions, leading to an initial increase in inequalities (the "early stage"). Deprived sections of society only begin to catch up once affluent sections of society have extracted the maximum possible benefit (the "late stage"). Having the cheapest tobacco price of all developed countries may keep Japan in the "early stage" of the tobacco price control intervention, delaying progression to the "late stage" phase of reducing health inequality. From a health inequality perspective, further tobacco price increases are necessary in Japan.

Limitations

There are several limitations to the study. First, smoking variables were self-reported, without biomarker validation; however, the reliability of self-reported smoking behavior was generally high.[31] Second, we could not separate the effect of other tobacco control measures from those of the tobacco price increase. However, the weight of this effect may be small, because the only other major tobacco control measures in Japan between 2007 and 2010 were the use of varenicline and the introduction of nicotine patches in 2008.[21] Third, the estimated association may be biased by unmeasured factors, which may contribute to the heterogeneity in findings of the present study and other tobacco price research, including industry activity to reduce price for consumers, opportunities for tax avoidance, smuggling, economic inflation, and product substitution due to wide price ranges.[3,4] However, the influence of the former four factors might be low in Japan, because the tobacco industry did not reduce the tobacco price; it is difficult to avoid tax across national borders because Japan is an island country; smuggling into Japan is rare, although smuggling from Japan is a problem[32]; and, although it is important to account for the effects of inflation when multiple years of data are employed,[4] changes in the rate of the inflation in Japan were very small between 2007 and 2010.[33] An increased share of low-price tobacco products was observed in Japan after 2010 according to tobacco industry reports[34]: For example, a popular cheap brand, "Echo", increased its share of the market by 0.5% in 2011 compared with 2010. Therefore, the impact of product substitution is expected, although the magnitude may not be large. Fourth, the longitudinal approach is ideally suited to the study of change in smoking behaviors over time. However, longitudinal studies generally include fewer subjects than other methods, so a high percentage of the subjects will be lost to follow up.[13] If those lost to follow-up differ in important respects from those who continue to be studied, the results may be compromised.[35]

Conclusion

We found that the 2010 tobacco price increase had a significant impact on smoking cessation among both sexes in Japan, especially those who smoked a large number of cigarettes. There were no obvious differences in the relationship between tobacco price increase and smoking cessation according to socio-demographic status, such as age or household expenditure. These findings suggest that there is an urgent need for additional tobacco price increases to reduce tobacco use and smoking inequality in Japan.

ONLINE ONLY MATERIALS

eTable 1. Number (prevalence) of current smokers at June according to basic characteristics of total subjects.
eMaterial 1. Supplemental methods, results, reference.
eMaterial 2. Abstract and main text in Japanese.

ACKNOWLEDGEMENTS

This work was supported by the Ministry of Health, Labour and Welfare (Grant; Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus (H25-010)). We thank Dr. A. Oshima for valuable comments. We also thank Dr. J. Mortimer for her English language editing.

Conflicts of interest: Dr. Nakamura received a Medical Education grant from Pfizer Japan, Inc., for the smoking cessation training program development and dissemination project (J-STOP) as a member of Japan Medical-Dental Association for Tobacco Control.

REFERENCES

1. Hill S, Amos A, Clifford D, Platt S. Impact of tobacco control interventions on socioeconomic inequalities in smoking: review of the evidence. Tob Control. 2014;23(e2):e89–97.
2. Thomas S, Fayter D, Misso K, Ogilvie D, Petticrew M, Sowden A, et al. Population tobacco control interventions and their effects on social inequalities in smoking: systematic review. Tob Control. 2008;17:230–7.
3. Wilson LM, Avila Tang E, Chander G, Hutton HE, Odelola OA, Elf JL, et al. Impact of tobacco control interventions on smoking initiation, cessation, and prevalence: a systematic review. J Environ Public Health. 2012;2012:961724.
4. International Agency for Research on Cancer. IARC Handbooks of Cancer Prevention Tobacco Control Volume 14: Effectiveness of Tax and Price Policies for Tobacco Control. Lyon, France; 2011.
5. Frohlich KL, Potvin L. Transcending the known in public health practice: the inequality paradox: the population approach and vulnerable populations. Am J Public Health. 2008;98:216–21.
6. Amos A, Greaves L, Nichter M, Bloch M. Women and tobacco: a call for including gender in tobacco control research, policy and practice. Tob Control. 2012;21:236–43.
7. Vangeli E, Stapleton J, Smit ES, Borland R, West R. Predictors

of attempts to stop smoking and their success in adult general population samples: a systematic review. Addiction. 2011;106: 2110–21.
8. Ito Y, Nakamura M. The effect of increasing tobacco tax on tobacco sales in Japan. Nihon Koshu Eisei Zasshi. 2013;60: 613–8 (in Japanese).
9. Ministry of Health, Labour and Welfare. Comprehensive survey of living condition of people on health and welfare. Tokyo; 2014 [cited 2014 May 9]. Available from: http://www.mhlw.go.jp/toukei/list/20-21.html.
10. Eriksen M, Mackay J, Ross H. The Tobacco Atlas, Fourth Edition. Atlanta, USA: American Cancer Society; 2012.
11. Ross H, Blecher E, Yan L, Hyland A. Do cigarette prices motivate smokers to quit? New evidence from the ITC survey. Addiction. 2011;106:609–19.
12. Dunlop SM, Perez D, Cotter T. Australian smokers' and recent quitters' responses to the increasing price of cigarettes in the context of a tobacco tax increase. Addiction. 2011;106:1687–95.
13. Nishi N, Nakade M, Sarukura N, Nozue M, Tsubota M, Miyoshi M, et al. Response rate and the related factors of National Health and Nutritional Survey. Kosei no Shihyo. 2012;59:10–5 (in Japanese).
14. Ministry of Health, Labour and Welfare. National Health and Nutritional Survey Tokyo 2014 [cited 2014 May 9]. Available from: http://www.mhlw.go.jp/bunya/kenkou/kenkou_eiyou_chousa.html.
15. Fukuda Y, Nakamura K, Takano T. Socioeconomic pattern of smoking in Japan: income inequality and gender and age differences. Ann Epidemiol. 2005;15:365–72.
16. Fukuda Y, Nakao H, Imai H. Different income information as an indicator for health inequality among Japanese adults. J Epidemiol. 2007;17:93–9.
17. Durkin SJ, Biener L, Wakefield MA. Effects of different types of antismoking ads on reducing disparities in smoking cessation among socioeconomic subgroups. Am J Public Health. 2009; 99:2217–23.
18. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. 1991;86: 1119–27.
19. International Agency for Research on Cancer. A review of human carcinogens. Part E: Personal habits and indoor combustions. Lyon, France; 2012.
20. Fukuda Y, Hiyoshi A. Associations of household expenditure and marital status with cardiovascular risk factors in Japanese adults: analysis of nationally representative surveys. J Epidemiol. 2013;23:21–7.
21. Katanoda K, Jiang Y, Park S, Lim MK, Qiao YL, Inoue M. Tobacco control challenges in East Asia: proposals for change in the world's largest epidemic region. Tob Control. 2014;23: 359–68.
22. Abadie A, Diamond A, Hainmueller J. Synthetic control methods for comparative case studies: estimating the effect of California's tobacco control program. J Am Stat Assoc. 2010; 105:493–505.
23. Pfizer Japan Inc. Internet survey for Japanese smokers before tobacco tax increase in 2010. 2010 [cited 2014 16 September]. Available from: http://www.pfizer.co.jp/pfizer/company/press/2010/2010_09_16.html.
24. Softbrain field co. ltd. Spending money in husband and wife Tokyo 2012 [cited 2013 10 December]. Available from: http://www.sbfield.co.jp/news/2012/06/29_130000.html.
25. Eguchi E, Iso H, Tanabe N, Wada Y, Yatsuya H, Kikuchi S, et al. Healthy lifestyle behaviours and cardiovascular mortality among Japanese men and women: the Japan collaborative cohort study. Eur Heart J. 2012;33:467–77.
26. Kaneko A, Kaneita Y, Yokoyama E, Miyake T, Harano S, Suzuki K, et al. Smoking trends before, during, and after pregnancy among women and their spouses. Pediatr Int. 2008; 50:367–75.
27. Ministry of Health, Labour and Welfare. Health Japan 21 (Second) 2012 [cited 2012 6 Aug]. Available from: http://www.mhlw.go.jp/bunya/kenkou/kenkounippon21.html.
28. Stapleton J. Cigarette smoking prevalence, cessation and relapse. Stat Methods Med Res. 1998;7:187–203.
29. Reed MB, Anderson CM, Vaughn JW, Burns DM. The effect of cigarette price increases on smoking cessation in California. Prev Sci. 2008;9:47–54.
30. Victora CG, Vaughan JP, Barros FC, Silva AC, Tomasi E. Explaining trends in inequities: evidence from Brazilian child health studies. Lancet. 2000;356:1093–8.
31. Caraballo RS, Giovino GA, Pechacek TF, Mowery PD. Factors associated with discrepancies between self-reports on cigarette smoking and measured serum cotinine levels among persons aged 17 years or older: Third National Health and Nutrition Examination Survey, 1988–1994. Am J Epidemiol. 2001;153: 807–14.
32. Wen CP, Peterson RA, Cheng TY, Tsai SP, Eriksen MP, Chen T. Paradoxical increase in cigarette smuggling after the market opening in Taiwan. Tob Control. 2006;15:160–5.
33. OECD. OECD Data Lab Paris 2013 [cited 2013 15 Nov]. Available from: http://www.oecd.org/statistics/datalab/.
34. Tobacco Institute of Japan. Cigarette statistics in Japan Tokyo 2013 [cited 2013 15 Nov]. Available from: http://www.tioj.or.jp/data/index.html.
35. International Agency for Research on Cancer. IARC Handbooks of Cancer Prevention Tobacco Control Volume 13: Evaluating the Effectiveness of Smoke-free Policies. Lyon, France; 2009.

IJC
International Journal of Cancer

Joint and independent effect of alcohol and tobacco use on the risk of subsequent cancer incidence among cancer survivors: A cohort study using cancer registries

Takahiro Tabuchi[1], Koken Ozaki[2], Akiko Ioka[1] and Isao Miyashiro[1]

[1] Center for Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, 3-3, Nakamichi 1-Chome, Higashinari-Ku, Osaka 537-8511, Japan

[2] Graduate School of Business Sciences, University of Tsukuba, 3-29-1, Otsuka, Bunkyo-Ku, Tokyo 112-0012, Japan

Drinking alcohol and smoking tobacco are major modifiable risk factors for cancer. However, little is known about whether these modifiable factors of cancer survivors are associated with subsequent primary cancer (SPC) incidence, regardless of the first cancer sites. 27,762 eligible cancer survivors diagnosed between 1985 and 2007 were investigated for SPC until the end of 2008, using hospital-based and population-based cancer registries. The association between drinking, smoking and combined drinking and smoking (interaction) at the time of the first cancer diagnosis and incidence of SPCs (*i.e.*, all SPCs, alcohol-related, smoking-related and specific SPCs) was estimated by Poisson regression. Compared with never-drinker/never-smoker, the categories ever-drinker/ever-smoker, current-drinker/current-smoker and heavy-drinker/heavy-smoker had 43–108%, 51–126% and 167–299% higher risk for all, alcohol-related and tobacco-related SPCs, respectively. The interaction of drinking and smoking had significantly high incidence rate ratios (IRRs) for SPCs among ever-drinker/ever-smoker and current-drinker/current-smoker, although ever drinking did not show a significant risk. Ever-drinker/ever-smoker had also significantly higher IRRs for esophageal and lung SPCs than never-drinker/never-smoker. Among comprehensive cancer survivors, ever and current drinkers only had a SPC risk when combined with smoking, while ever and current smokers had a SPC risk regardless of drinking status. Heavy drinking and heavy smoking were considered to be independent additive SPC risk factors. To reduce SPC incidence, it may be necessary (*i*) to reduce or stop alcohol use, (*ii*) to stop tobacco smoking and (*iii*) dual users, especially heavy users, should be treated as a high-risk population for behavioral-change intervention.

Epidemiology

Drinking alcohol and smoking tobacco are widespread, representative, modifiable lifestyle factors. Of 834,000 deaths from non-communicable diseases in 2007 in Japan, drinking alcohol and smoking tobacco accounted for 31,000 and 129,000 deaths, respectively.[1] There is a large potential health gain if these risk factors are jointly controlled.[2] This may be true not only for the general population but also cancer survivors.

In recent years, the number of second or further subsequent primary cancers (SPCs) has been growing, partly due to prolonged survival times for cancer patients: 5–15% of cancer survivors develop a SPC.[3,4] Curtis *et al.* reported that approximately 35% of all excess risk for SPCs may be attributable to behavioral factors, such as drinking and smoking, which underscores the importance of these modifiable risk factors, especially in patients with tobacco-related and alcohol-related cancers.[5,6] For example, in a meta-analysis of early stage non-small-cell lung cancer, Parsons *et al.* reported a relative risk of 4.3 (95% confidence interval [CI] 1.1–17.0) of SPCs in patients who continued to smoke.[7] Patients with head and neck cancers with heavy alcohol intake at diagnosis showed a relative risk of 2.1 (1.4–3.3) for SPCs among non-daily drinkers.[8] However, population-based cancer registries do not usually collect data on lifestyle factors and previous studies which used the joint category of alcohol and tobacco consumption have only focused on SPC after a diagnosis of head, neck or breast cancer.[6,9–11] Thus, little is known about whether the modifiable factors of drinking and smoking are associated with SPC incidence among cancer survivors, regardless of the first cancer site. Our objective was,

Key words: drinking alcohol, smoking tobacco, subsequent primary cancer, cancer survivors, Japan

Abbreviations: CIs: confidence intervals; EAR: excess absolute risk; IRR: incidence rate ratio; OCR: Osaka Cancer Registry; OMCC: Osaka Medical Center for Cancer and Cardiovascular Diseases; SIR: standardized incidence ratio; SPC: subsequent primary cancer.

Additional Supporting Information may be found in the online version of this article.

Grant sponsor: Japan Cancer Society "Relay for Life" [H26]

DOI: 10.1002/ijc.29575

History: Received 6 Jan 2015; Accepted 15 Apr 2015; Online 21 Apr 2015

Correspondence to: Takahiro Tabuchi, Center for Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, 3-3, Nakamichi 1-chome, Higashinari-ku, Osaka 537-8511, Japan, Tel.: +81-6-6972-1181, E-mail: tabuchitak@gmail.com

What's new?
Drinking alcohol and smoking tobacco increase one's risk of cancer. But how much do they influence the risk of developing a subsequent cancer at a different site? In this paper, the authors calculate the risk for patients who had ever been or were currently drinkers or smokers. Not surprisingly, smoking increased the chance of getting a second cancer regardless of alcohol habits; drinking some alcohol increased the risk only when combined with smoking. Heavy drinking and heavy smoking, however, both increased the risk of a later cancer.

therefore, to estimate the risk for SPC incidence according to joint and independent alcohol and tobacco use at first cancer diagnosis among comprehensive cancer survivors. This will provide insights into preventive measures for clinical oncologists and other health professionals.[12]

Methods

Data

Data were gathered through record linkage between a hospital-based cancer registry and the Osaka Cancer Registry (OCR).[13] Study subjects were all eligible patients initially diagnosed with a first cancer, excluding *in situ* carcinomas and benign intracranial tumors, at the Osaka Medical Center for Cancer and Cardiovascular Diseases (OMCC), between 1985 and 2007 who had survived for at least 3 months. Patients who developed synchronous SPC within 3 months were excluded and eligibility was restricted to subjects living in Osaka and aged 20–79 years at the time of diagnosis. Subjects were identified from the hospital-based cancer registry, which has collected information on diagnosis, clinical stage and lifestyle factors including alcohol and tobacco use, since 1963. OMCC medical records or resident offices were used for follow-up (up to 10 years), which was 99% complete. Subjects' files and OCR files were collated to obtain other information on SPC incidence, by means of a semi-automated record linkage which comprised patients' surname, given name, birth-year and birth-month.[14] The study was approved by the OMCC institutional review board.

Alcohol and Tobacco Use

Information on alcohol and tobacco consumption was collected through an integrated common questionnaire across all departments at the time of first cancer diagnosis. To collect smoking and drinking status, we also used data from clinical, medical and nursing records. Consumption of common alcoholic beverages (Japanese sake, beer, whisky and others) was determined in terms of a *go*, this is standard measure in Japan and contains 23 g of ethanol. A *go* was calculated from the equivalent measure of 180 mL of Japanese sake (rice wine), which was converted by the average number of various drinks per day.[15] The following definitions were used. Never drinkers were those who had never drunk regularly. Ever drinkers were those who drank alcohol regularly either before or at diagnosis and were categorized as current or former drinkers. Current drinkers were those who drank alcohol almost every day or occasionally at diagnosis. Former drinkers were those who stopped drinking before diagnosis. Among current drinkers, heavy drinkers were those who drank more than 2 *go* per day.[16] Never smokers were those who had never smoked regularly. Ever smokers were those who had smoked tobacco regularly either before or at diagnosis and were categorized as current and former smokers. Current smokers were those who smoked cigarettes regularly at diagnosis. Former smokers were those who stopped smoking before diagnosis. Among current smokers, heavy smokers were those who smoked more than 20 cigarettes per day.[17]

Four combinations of dichotomized alcohol and tobacco use were used as joint categories, with never drinker and never smoker as the common reference category. (*i*) ever drinker and never smoker, never drinker and ever smoker, or ever drinker and ever smoker; (*ii*) current drinker and current smoker; (*iii*) heavy drinker and heavy smoker and (*iv*) non-heavy ever drinker and non-heavy ever smoker.

SPC definitions

Metachronous SPC was defined as that diagnosed between 3 months and 10 years after the first cancer diagnosis.[14,18] The incidence of four SPC groups (*i.e.*, all, alcohol-related, tobacco-related and specific SPCs) was investigated up to the end of 2008 for a maximum of 10 years after the first cancer diagnosis. Each cancer was categorized into 16 selected major groups and the others according to ICD-10, corresponding to the specific SPC sites.[4] Alcohol-related cancer sites comprised the mouth/pharynx, esophagus, colorectum, liver, larynx and breast.[19,20] Tobacco-related cancer sites were the mouth/pharynx, esophagus, stomach, liver, pancreas, larynx, lung and kidney / urinary tract/bladder.[21] More details on SPC definitions are available in the Supporting Information or elsewhere.[4,14]

Statistical analyses

Person-years at risk were calculated as the time from 3 months after the first cancer diagnosis until: December 31, 2008; date of SPC diagnosis; date of death; or 10 years after first cancer diagnosis, whichever came first.[4] The expected number was calculated according to stratified person-years with all, alcohol-related, smoking-related and site-specific cancer incidence rates among Osaka residents (from OCR) stratified for sex, age (5-year) and calendar period (5-year). The observed number of SPCs was compared with the

expected number, according to drinking and smoking behaviors, sex, age group, calendar period, clinical stage, first cancer site and follow-up interval. A standardized incidence ratio (SIR) was then obtained by dividing the observed number of SPCs by the expected number. Another indicator is the excess absolute risk (EAR), which is the absolute number of excess cancer cases, obtained by subtracting the expected number from the observed number of SPCs. The EAR may be of interest for clinical and public health purposes. The SIR and EAR are used to estimate the risk of a cancer patient developing a SPC compared to the incidence of cancer among the general population. The statistical significance and 95% CIs for the SIRs were tested assuming Poisson distribution.

We used Poisson regression analysis to estimate the incidence rate ratio (IRR) and 95% CIs for SPC in cancer survivors according to their joint and independent alcohol and tobacco use. These ratios were adjusted for potential confounding factors: sex, age at first cancer diagnosis, stage, calendar period, follow-up interval and first cancer site, using the expected level of cancer incidence in the general population as an offset.[5,22] To account for the interaction effect between drinking and smoking in an additional analysis, one interaction term was used in each model, given by the product of the two exposure variables (*i.e.,* ever-drinker/ever-smoker, current-drinker/current-smoker and heavy-drinker/heavy-smoker).[23] For example, score 1 for the "ever-drinker/ever-smoker" category and score 0 for the remaining categories (*i.e.,* "never-drinker/never-smoker," "ever-drinker/never-smoker" and "never-drinker/ever-smoker").

Probability values for statistical tests were two-tailed and $p < 0.05$ was regarded as statistically significant. Results with wide CIs should be interpreted cautiously. All statistical analyses were performed using the SAS statistical package version 9.2 (SAS Institute, Cary, NC) with macro programming.[24]

Results

After excluding study subjects with a missing value for alcohol and tobacco use ($n = 3{,}182$), 27,762 remained. Distribution of first cancer sites is shown in Supporting Information. During follow-up (median follow-up duration: 4.4 years, mean: 5.1 years), SPCs were found in 1,784 subjects (6.4%) as second cancer, 110 (0.4%) as third cancer and 10 (0.04%) as fourth cancer. Alcohol-related and tobacco-related SPCs were found in 702 (2.5%) and 1,163 (4.2%), respectively, as second to fourth primary cancer (Table 1). Table 2 shows adjusted IRRs for SPCs according to drinking and smoking behaviors from the Poisson regression analyses (SIRs and EARs in Supporting Information Table S1).

Independent effect

After adjustment for smoking (adjusted model), heavy drinkers had 39%, 104% and 65% higher risk for all, alcohol-related and tobacco-related SPCs, respectively, than never drinkers, although light drinkers did not show significantly higher risk. Former drinkers showed higher risk of SPCs than never drinkers. After adjustment for drinking, former and current smokers had significantly higher risk of SPCs than never smokers in a dose-dependent manner.

Supporting Information Tables S2 and S3 show adjusted IRRs for SPCs according to patient characteristics in independent and joint models. Younger, female and recently diagnosed patients had significantly elevated risk for all and tobacco-related SPCs, but not for alcohol-related SPCs. First cancer sites of both alcohol- and tobacco-related cancer showed a 36–56% higher risk for SPCs than neither alcohol- nor tobacco-related sites.

Joint effect of alcohol and tobacco use

Compared to never-drinker/never-smoker, the joint category of ever-drinker/ever-smoker had 43%, 60% and 108% higher risk for all, alcohol-related and tobacco-related SPCs, respectively. Never-drinker/ever-smoker showed significantly higher risk for all and tobacco-related SPCs than never-drinker/never-smoker, while ever-drinker/never-smoker showed lower risk, although this was not significant.

Compared to never-drinker/never-smoker, current-drinker/current-smoker had 52%, 77% and 136% higher risk for all, alcohol-related and tobacco-related SPCs, respectively, while heavy-drinker/heavy-smoker had 217%, 334% and 402% higher risk, respectively. Non-heavy ever-drinker/never-smoker had 13%, 12% and 15% less risk, respectively, than never-drinker/never-smoker, although these were not significant. Never-drinker/ever-smoker, never-drinker/current-smoker, never-drinker/heavy-smoker had significantly higher risk for all and tobacco-related SPCs, although they did not show risk for alcohol-related SPCs. Heavy-drinker/never-smoker showed significantly higher risk for all, alcohol-related and tobacco-related SPCs than never-drinker/never-smoker, although other drinker and never smokers categories showed negative values.

Interaction between drinking and smoking

Table 3 shows adjusted IRRs for SPCs according to dichotomized drinking and smoking and the interaction term. The interaction term of drinking and smoking showed significantly high IRRs for SPCs among ever-drinker/ever-smoker and current-drinker/current-smoker, although ever drinking did not show significant risk. In addition, ever smoking showed significant risk for all and tobacco-related SPCs, although not for alcohol-related SPC. Thus, ever drinking only showed risk for SPCs in combination with smoking, while ever smoking had risk for all and tobacco-related SPCs, regardless of drinking status. In terms of alcohol-related SPCs, combined drinking and smoking showed significant risk. Current drinking and current smoking showed similar results to ever drinking and ever smoking. Among heavy users, the interaction terms did not show significant IRRs, although they had positive values, especially for alcohol-related SPC: 1.89. Heavy smoking showed significantly high

Table 1. SIRs and EARs for SPC incidence among cancer survivors according to joint drinking and smoking behaviors, age group and calendar period at first cancer diagnosis, sex, stage, first cancer site and follow-up interval

		All SPCs				Alcohol-related SPCs				Tobacco-related SPCs			
Characteristics	No. of cancer survivors (%)	No. of all SPC	Person-years at risk	SIRs (95% CI)	EARs	No. of the SPC	Person-years at risk	SIRs (95% CI)	EARs	No. of the SPC	Person-years at risk	SIRs (95% CI)	EARs
Joint behaviors at first cancer diagnosis													
Never drinker and never smoker	7,506 (27.0)	330	42,314.6	**1.21 (1.08–1.34)**	56.3	129	42,766.5	1.13 (0.94–1.34)	14.4	148	42,895.6	1.07 (0.90–1.25)	9.3
Ever drinker and never smoker	3,940 (14.2)	162	21,330.2	1.01 (0.86–1.18)	1.7	60	21,577.4	0.93 (0.71–1.20)	−4.4	78	21,567.9	0.82 (0.65–1.03)	−16.9
Never drinker and ever smoker	3,858 (13.9)	263	16,871.3	**1.29 (1.14–1.45)**	58.6	77	17,247.4	1.02 (0.80–1.27)	1.2	163	17,096.9	**1.19 (1.02–1.39)**	26.1
Ever drinker and ever smoker	12,458 (44.9)	1,029	54,866.0	**1.58 (1.48–1.67)**	375.9	436	56,098.2	**1.78 (1.62–1.96)**	191.4	774	55,572.5	**1.70 (1.59–1.83)**	319.6
Age groups at first cancer diagnosis													
20–49 years	5,315 (19.1)	123	32,767.2	**1.59 (1.32–1.90)**	45.8	44	32,938.5	1.19 (0.86–1.59)	6.9	60	32,973.2	**1.99 (1.52–2.56)**	29.8
50–64 years	12,233 (44.1)	738	61,028.1	**1.51 (1.41–1.63)**	250.7	345	61,996.2	**1.64 (1.47–1.82)**	134.5	468	61,834.2	**1.52 (1.39–1.67)**	160.6
65–79 years	10,214 (36.8)	923	41,586.9	**1.27 (1.19–1.35)**	195.9	313	42,754.9	**1.24 (1.11–1.39)**	61.1	635	42,325.5	**1.30 (1.20–1.41)**	147.7
Sex													
Male	15,412 (55.5)	1,288	66,564.8	**1.40 (1.32–1.47)**	364.7	506	68,153.7	**1.50 (1.37–1.64)**	168.5	932	67,461.3	**1.41 (1.32–1.51)**	272.5
Female	12,350 (44.5)	496	68,817.3	**1.35 (1.23–1.47)**	127.7	196	69,535.9	**1.21 (1.05–1.39)**	34.1	231	69,671.7	**1.40 (1.22–1.59)**	65.6
Stage of first cancer													
Localized/regional	21,837 (78.7)	1,609	117,890.4	**1.42 (1.35–1.49)**	477.2	638	1,20,030.3	**1.46 (1.34–1.57)**	199.7	1,040	119,506.2	**1.44 (1.36–1.53)**	318.7
Distant/unknown	5,925 (21.3)	175	17,491.7	1.10 (0.94–1.27)	15.2	64	17,659.3	1.05 (0.81–1.34)	2.9	123	17,626.8	1.19 (0.99–1.42)	19.4
Period at first cancer diagnosis													
1985–1992	8,598 (31.0)	599	49,201.5	**1.26 (1.16–1.37)**	124.9	248	49,970.7	**1.36 (1.19–1.54)**	65.3	397	49,843.2	**1.27 (1.15–1.40)**	83.8
1993–2000	9,116 (32.8)	741	54,706.4	**1.40 (1.30–1.51)**	212.4	296	55,786.3	**1.44 (1.28–1.61)**	89.7	492	55,493.7	**1.47 (1.34–1.60)**	156.4
2001–2007	10,048 (36.2)	444	31,474.3	**1.54 (1.40–1.69)**	155.2	158	31,932.5	**1.43 (1.22–1.67)**	47.5	274	31,796.0	**1.56 (1.38–1.75)**	97.9
Follow-up interval													
3 months to 5 years	NA	1,123	87,577.7	**1.40 (1.32–1.48)**	320.7	437	88,580.7	**1.41 (1.28–1.54)**	126.1	741	88,261.7	**1.44 (1.34–1.55)**	227.4
5 years to 10 years	NA	661	47,804.5	**1.35 (1.25–1.46)**	171.7	265	49,108.9	**1.41 (1.24–1.59)**	76.5	422	48,871.2	**1.36 (1.23–1.49)**	110.7
First cancer site													
Neither alcohol nor tobacco–related sites	6,159 (22.2)	334	31,560.1	**1.28 (1.15–1.42)**	72.8	122	31,964.1	**1.22 (1.01–1.46)**	22.1	206	31,934.8	**1.30 (1.12–1.49)**	47.0

Table 1. SIRs and EARs for SPC incidence among cancer survivors according to joint drinking and smoking behaviors, age group and calendar period at first cancer diagnosis, sex, stage, first cancer site and follow-up interval (Continued)

		All SPCs				Alcohol-related SPCs				Tobacco-related SPCs			
Characteristics	No. of cancer survivors (%)	No. of all SPC	Person-years at risk	SIRs (95% CI)	EARs	No. of the SPC	Person-years at risk	SIRs (95% CI)	EARs	No. of the SPC	Person-years at risk	SIRs (95% CI)	EARs
Only tobacco–related sites	6,088 (21.9)	307	38,943.4	**1.25 (1.12–1.40)**	62.1	112	39,467.1	1.08 (0.89–1.30)	8.1	188	39,315.0	**1.44 (1.24–1.66)**	57.3
Only alcohol–related sites	10,052 (36.2)	602	43,025.3	**1.18 (1.09–1.28)**	93.8	250	43,754.6	**1.32 (1.16–1.49)**	60.3	348	43,755.3	1.01 (0.91–1.13)	4.6
Both alcohol and tobacco–related sites	5,463 (19.7)	541	21,853.4	**1.95 (1.79–2.12)**	263.8	218	22,503.8	**2.06 (1.80–2.35)**	112.2	421	22,127.9	**2.20 (1.99–2.42)**	229.2
Total cancer survivors	27,762 (100.0)	1,784	135,382.2	**1.38 (1.32–1.45)**	492.5	702	137,689.6	**1.41 (1.30–1.51)**	202.6	1,163	137,132.9	**1.41 (1.33–1.49)**	338.1

SIR = standardized incidence ratio; EAR = excess absolute risk; SPC = subsequent primary cancer; No. = patients number; CI = confidence interval; NA= not applicable.
Bold = statistical significance of $p < 0.05$.

IRRs for tobacco-related SPCs, as did heavy drinking for all three types of SPC.

Specific SPCs

Table 4 shows SIRs, EARs and Poisson regression results for specific SPCs according to joint category (ever-drinker/ever-smoker *vs.* never-drinker/never-smoker). While never-drinker/never-smoker had significantly high SIRs for breast (female), kidney/urinary-tract/bladder, thyroid and blood SPCs, ever-drinker/ever-smoker had significantly high SIRs for oral/pharyngeal, esophageal, stomach, colorectal, liver, laryngeal, lung, prostate and kidney/urinary-tract/bladder SPCs. EARs in esophageal, stomach and lung SPCs were higher than 50. Ever-drinker/ever-smoker had significantly elevated IRRs for esophageal and lung SPCs, compared with never-drinker/never-smoker, although ever-drinker/ever-smoker had lower IRRs for gallbladder and thyroid SPCs compared with never-drinker/never-smoker. Similarly, current-drinker/current-smoker showed higher IRRs for esophageal, stomach and lung SPCs than never-drinker/never-smoker, while heavy-drinker/heavy-smoker showed higher IRRs for mouth/pharynx, esophagus, stomach and lung SPCs although EARs were relatively small among heavy-drinker/heavy-smoker (Supporting Information Tables S4–S5).

Discussion

To our knowledge, this is the first study to assess the risk of combined alcohol and tobacco consumption for SPC incidence among comprehensive cancer survivors.[14,25] Compared with the never-drinker/never-smoker group, the groups ever-drinker/ever-smoker, current-drinker/current-smoker and heavy-drinker/heavy-smoker had 43–108%, 51–126% and 167–299% higher risk for all, alcohol-related and tobacco-related SPCs, respectively. Never-drinker/ever-smoker showed higher risk for all and tobacco-related SPCs than never-drinker/never-smoker, while ever-drinker/never-smoker did not show a risk, and IRR estimates were higher in ever-drinker/ever-smoker than those in never-drinker/ever-smoker. According to a counterfactual interpretation, drinking might increase SPC risk when the subjects smoke, while non-heavy drinking might not increase the risk when they did not smoke. This interpretation was confirmed by the analyses using the interaction terms of drinking and smoking. The results suggest that ever and current drinkers only had SPC risk when drinking was combined with smoking, while ever and current smokers had SPC risk regardless of drinking status. Heavy drinking and heavy smoking had independent risk, particularly for tobacco-related SPC. Because the interaction term between heavy drinking and heavy smoking was not significant, heavy drinking and heavy smoking were considered to be independent additive risk factors for SPCs, especially for tobacco-related SPCs. Furthermore, non-heavy drinker/never smoker showed a lower risk for SPCs than never-drinker/never-smoker, consistent with J-shaped risk of alcohol consumption for cancer mortality in Japanese

Table 2. Incidence rate ratios for SPC incidence according to drinking, smoking and joint behaviors, Poisson regression analyses

Drinking and smoking behaviors at first cancer diagnosis	No. of cancer survivors (%)	All SPCs		Alcohol-related SPCs		Tobacco-related SPCs	
		No. of all SPC	Adjusted IRRs[1] (95% CI)	No. of the SPC	Adjusted IRRs[1] (95% CI)	No. of the SPC	Adjusted IRRs[1] (95% CI)
Alcohol drinking							
Never drinker (reference)	11,364 (40.9)	593	1 (reference)	206	1 (reference)	311	1 (reference)
Former drinker	3,139 (11.3)	255	**1.25 (1.06–1.47)**	117	**1.77 (1.37–2.28)**	179	**1.43 (1.17–1.76)**
Current light drinker	9,642 (34.7)	677	0.99 (0.88–1.12)	262	1.15 (0.93–1.41)	471	1.12 (0.95–1.31)
Current heavy drinker	1,870 (6.7)	182	**1.39 (1.15–1.67)**	92	**2.04 (1.55–2.70)**	147	**1.65 (1.33–2.05)**
Current drinker (unknown amount)	1,747 (6.3)	77	1.03 (0.81–1.31)	25	0.98 (0.64–1.49)	55	**1.37 (1.02–1.83)**
Tobacco smoking							
Never smoker (reference)	11,446 (41.2)	492	1 (reference)	189	1 (reference)	226	1 (reference)
Former smoker	7,017 (25.3)	518	**1.21 (1.03–1.41)**	197	1.15 (0.90–1.47)	350	**1.50 (1.22–1.84)**
Current light smoker	5,925 (21.3)	460	**1.49 (1.28–1.73)**	189	**1.53 (1.21–1.94)**	334	**2.03 (1.67–2.47)**
Current heavy smoker	3,208 (11.6)	305	**1.80 (1.51–2.14)**	124	**1.65 (1.25–2.19)**	244	**2.59 (2.08–3.23)**
Current smoker (unknown amount)	166 (0.6)	9	1.17 (0.60–2.28)	3	1.05 (0.33–3.31)	9	**2.24 (1.14–4.40)**
Joint categories of drinking and smoking							
Never-drinker/ never-smoker (reference)	7,506 (27.0)	330	1 (reference)	129	1 (reference)	148	1 (reference)
Ever-drinker/never-smoker	3,940 (14.2)	162	0.88 (0.73–1.08)	60	0.85 (0.62–1.17)	78	0.92 (0.69–1.22)
Never-drinker/ever-smoker	3,858 (13.9)	263	**1.21 (1.01–1.46)**	77	0.95 (0.69–1.31)	163	**1.51 (1.17–1.94)**
Ever-drinker/ever-smoker	12,458 (44.9)	1,029	**1.43 (1.21–1.69)**	436	**1.60 (1.22–2.09)**	774	**2.08 (1.65–2.62)**
Never-drinker/ never-smoker (reference)	7,506 (27.0)	330	1 (reference)	129	1 (reference)	148	1 (reference)
Current-drinker/ never-smoker	3,340 (12.0)	138	0.89 (0.72–1.10)	51	0.87 (0.62–1.23)	71	1.00 (0.74–1.35)
Never-drinker/current-smoker	2,288 (8.2)	151	**1.23 (1.00–1.53)**	41	0.88 (0.60–1.29)	90	**1.49 (1.11–2.00)**
Current-drinker/ current-smoker	6,464 (23.3)	557	**1.52 (1.26–1.83)**	247	**1.77 (1.30–2.39)**	441	**2.36 (1.82–3.04)**
Never–drinker/ never-smoker (reference)	7,506 (27.0)	330	1 (reference)	129	1 (reference)	148	1 (reference)
Heavy-drinker/ never-smoker[2]	166 (0.6)	13	**1.81 (1.00–3.28)**	7	**2.62 (1.14–6.04)**	8	**2.35 (1.08–5.10)**
	636 (2.3)	42	1.46 (0.98–2.16)	9	0.88 (0.40–1.92)	26	**1.77 (1.04–2.98)**

Table 2. Incidence rate ratios for SPC incidence according to drinking, smoking and joint behaviors, Poisson regression analyses (Continued)

Drinking and smoking behaviors at first cancer diagnosis	No. of cancer survivors (%)	All SPCs		Alcohol-related SPCs		Tobacco-related SPCs	
		No. of all SPC	Adjusted IRRs[1] (95% CI)	No. of the SPC	Adjusted IRRs[1] (95% CI)	No. of the SPC	Adjusted IRRs[1] (95% CI)
Never-drinker/ heavy-smoker[2]							
Heavy-drinker/ heavy-smoke[2]	696 (2.5)	84	**3.17 (2.19–4.61)**	42	**4.34 (2.36–7.96)**	72	**5.02 (3.11–8.12)**
Never-drinker/ never-smoker (reference)	7,506 (27.0)	330	1 (reference)	129	1 (reference)	148	1 (reference)
Non-heavy ever drinker/never-smoker[2]	2,945 (10.6)	127	0.87 (0.70–1.07)	46	0.88 (0.62–1.26)	59	0.85 (0.62–1.17)
Never-drinker/non-heavy ever-smoker[2]	3,170 (11.4)	215	**1.22 (1.00–1.48)**	67	1.11 (0.80–1.55)	131	**1.50 (1.14–1.97)**
Non-heavy ever-drinker/Non-heavy ever-smoker[2]	8,031 (28.9)	635	**1.31 (1.09–1.57)**	260	**1.62 (1.21–2.17)**	453	**1.82 (1.42–2.35)**

[1]Adjusted for age groups and calendar periods at first cancer diagnosis, sex, stage, first cancer site, follow-up interval and drinking and smoking (each other).
[2]When heavy categories were used, subjects with missing amount were excluded.
SPC = subsequent primary cancer; No. = patients number; IRR = incidence rate ratio; CI = confidence interval.
Bold = statistical significance of $p < 0.05$.

cohort.[26] However, we should not recommend non-drinkers to drink lightly on the basis of the results of this study, since it was not an intervention and additionally because drinking alcohol was certainly defined as a carcinogen (Group 1) by the International Agency for Research on Cancer, and safe levels of alcohol consumption for preventing carcinogenesis have not been defined to date.[27] Thus, to reduce SPCs incidence among cancer survivors, it may be necessary (*i*) to reduce or stop alcohol use, (*ii*) to stop smoking tobacco and (*iii*) dual users (especially heavy users) should be treated as a high-risk population for behavioral-change intervention in the future.

In the independent model (without interaction term), heavy and former drinkers had significantly higher risk for SPCs than never drinkers, regardless of first cancer sites, after adjustments for covariates including smoking, while light drinkers did not. In contrast, all tobacco smokers showed higher risk for SPCs than never smokers, regardless of the smoking intensity, after adjustments for alcohol drinking and others. These findings confirm previous evidence and add a novel aspect about the risk of alcohol and tobacco use for SPCs, because the risk of alcohol consumption and smoking intensity had not been evaluated in previous studies of comprehensive cancer patients,[14,25] and, furthermore, there were no data for the interaction between drinking and smoking on SPCs, even in previous studies for breast and, head and neck SPCs.[8–11,28] In our previous study, which focused on smoking,[14] ex-smokers showed 20–30% less risk for SPCs than current smokers. The results suggested that smoking cessation may decrease the risk for SPCs, although this suggestion was based on the counterfactual interpretation from an observational study. In the current study, heavy drinkers showed higher risk for SPCs, especially for alcohol-related SPCs, than never drinkers. We also assume they show a higher risk than light drinkers, then, the comparative results of "light drinker *versus* heavy drinker" are analogous to the above-mentioned results from smoking categories in a previous study.[14] Thus, the findings of the current study also suggest that reducing alcohol use may decrease the risk for SPCs among cancer survivors. However, we should interpret this finding carefully, because this is an observational study with possible unmeasured confounding. Furthermore, the risk for drinkers did not appear in a complete dose-dependent manner: *i.e.*, current light drinkers showed less risk for SPCs than former drinkers. Many abstainers might stop drinking because of their alcohol-related health problem such as alcohol-related cirrhosis or genetic predisposition like aldehyde-dehydrogenase-2 deficiency.[29] Characteristics that were not measured in the study, such as comorbidity and genetics, might differ between current heavy, light, former and never drinkers.

The SPC risk might differ according to first cancer sites (Supporting Information Table S6), although the small sample size made the statistics unstable. According to the combined categories of first cancer sites, cancer survivors of both alcohol- and tobacco-related first cancer site (*i.e.*, mouth/pharynx, esophagus, liver and larynx) showed higher risk for