Table 3. Incidence rate ratios for SPC incidence according to drinking, smoking and the interactions, 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)
Never drinker (reference)	11,364 (40.9)	593	1 (reference)	206	1 (reference)	311	1 (reference)
Ever drinker	16,398 (59.1)	1,191	0.88 (0.73–1.08)	496	0.85 (0.62–1.17)	852	0.92 (0.69–1.22)
Never smoker (reference)	11,446 (41.2)	492	1 (reference)	189	1 (reference)	226	1 (reference)
Ever smoker	16,316 (58.8)	1,292	**1.21 (1.01–1.46)**	513	0.95 (0.69–1.31)	937	**1.51 (1.17–1.94)**
Ever drinker and ever smoker (interaction term)	12,458 (44.9)	1,029	**1.33 (1.05–1.68)**	436	**1.97 (1.33–2.92)**	774	**1.50 (1.08–2.09)**
Never drinker (reference)	11,364 (40.9)	593	1 (reference)	206	1 (reference)	311	1 (reference)
Current drinker	13,259 (47.8)	936	0.89 (0.72–1.10)	379	0.87 (0.62–1.23)	673	1.00 (0.74–1.35)
Never smoker (reference)	11,446 (41.2)	492	1 (reference)	189	1 (reference)	226	1 (reference)
Current smoker	9,299 (33.5)	774	1.23 (0.99–1.53)	316	0.88 (0.60–1.29)	587	**1.49 (1.11–2.00)**
Current drinker and current smoker (interaction term)	6,464 (23.3)	557	**1.38 (1.05–1.81)**	247	**2.31 (1.45–3.68)**	441	**1.58 (1.09–2.28)**
Never drinker (reference)	11,364 (40.9)	593	1 (reference)	206	1 (reference)	311	1 (reference)
Heavy drinker	1,870 (6.7)	182	**1.81 (1.00–3.28)**	92	**2.62 (1.14–6.04)**	147	**2.35 (1.08–5.10)**
Never smoker (reference)	11,446 (41.2)	492	1 (reference)	189	1 (reference)	226	1 (reference)
Heavy smoker	3,208 (11.6)	305	1.46 (0.98–2.16)	124	0.88 (0.40–1.92)	244	**1.77 (1.04–2.98)**
Heavy drinker and heavy smoker (interaction term)	696 (2.5)	84	1.20 (0.60–2.39)	42	1.89 (0.64–5.58)	72	1.21 (0.50–2.92)

[1]Adjusted for age groups and calendar periods at first cancer diagnosis, sex, stage, first cancer site, follow-up interval, drinking, smoking and interaction term.
SPC = subsequent primary cancer; No. = patients number; IRR = incidence rate ratio; CI = confidence interval.
Bold = statistical significance of $p < 0.05$.

SPCs than those of neither related cancer sites, even after adjustment for individual alcohol and tobacco use at first cancer diagnosis (Supporting Information Tables S2–S3). From an etiological point of view, patients with cancer of these sites were considered to have high alcohol and/or tobacco consumption before the cancer diagnosis. Because the data at the time of diagnosis could only capture a partial aspect of time-dependent drinking and smoking behaviors, our categorization might underestimate the potential long-term effect of alcohol and tobacco use. For example, former heavy use over the course of a lifetime could not be adjusted for. To determine an individual risk for SPCs, appropriate assessment of lifetime consumption of alcohol and tobacco might be necessary, especially for cancer survivors of alcohol- and tobacco-related sites.

There are several limitations of this study. First, because self-reported alcohol and tobacco consumption can be unreliable due to the changeable nature of drinking and smoking habits or underreporting: *i.e.*, we did not consider behavioral changes after the initial diagnosis of cancer,[2,30] the analyses may produce a conservative result. Furthermore, there were differences in drinking and smoking patterns between joint categories: *e.g.*, the proportion of heavy drinkers was higher among ever-drinker/ever-smoker (13.7%) than among ever-drinker/never-smoker (4.2%). Such differences were not adjusted for in the analyses using joint categories and

Table 4. SIRs, EARs and Poisson regression results for specific SPC according to joint behaviors (ever-drinker/ever-smoker *vs.* never-drinker/never-smoker)

	Never-drinker/never-smoker				Ever-drinker/ever-smoker				Poisson regression[3]
Site of SPC	No. SPC	Person-years at risk	SIRs (95% CI)	EARs	No. SPC	Person-years at risk	SIRs (95% CI)	EARs	Adjusted IRRs[4] (95% CI)
Mouth/pharynx[12]	7	42,205.6	1.73 (0.69–3.56)	2.9	60	53,460.7	**4.38 (3.34–5.63)**	46.3	2.38 (0.83–6.83)
Esophagus[12]	2	42,925.8	0.42 (0.05–1.51)	−2.8	115	54,621.9	**4.52 (3.73–5.42)**	89.5	**17.42 (3.91–77.65)**
Stomach[2]	48	37,513.1	1.30 (0.96–1.73)	11.2	189	44,344.8	**1.78 (1.54–2.06)**	83.1	1.39 (0.90–2.15)
Colorectum[1]	48	39,632.0	1.26 (0.93–1.67)	9.9	116	51,286.2	**1.39 (1.14–1.66)**	32.2	1.17 (0.73–1.85)
Liver[12]	33	41,783.3	1.22 (0.84–1.71)	5.9	118	52,694.6	**1.33 (1.10–1.59)**	29.1	1.47 (0.86–2.51)
Gallbladder	13	42,916.9	1.27 (0.68–2.17)	2.7	11	56,908.5	0.65 (0.32–1.16)	−6.0	**0.24 (0.08–0.67)**
Pancreas[2]	13	42,835.2	1.06 (0.57–1.82)	0.8	34	56,516.8	1.33 (0.92–1.86)	8.4	1.84 (0.80–4.21)
Larynx[12]	2	43,024.4	2.22 (0.27–8.03)	1.1	21	52,002.4	**3.13 (1.94–4.79)**	14.3	2.54 (0.37–17.28)
Lung[2]	31	40,613.8	0.97 (0.66–1.37)	−1.1	205	51,295.7	**1.89 (1.64–2.17)**	96.8	**3.13 (1.95–5.02)**
Breast (female)[1]	35	24,634.3	**1.66 (1.16–2.31)**	13.9	7	5,545.0	1.50 (0.60–3.09)	2.3	1.04 (0.46–2.37)
Uterus	15	37,825.2	1.24 (0.69–2.05)	2.9	6	55,546.2	2.43 (0.89–5.29)	3.5	2.32 (0.89–6.07)
Ovary	9	42,529.7	1.43 (0.65–2.72)	2.7	1	57,066.1	0.76 (0.02–4.23)	−0.3	NA
Prostate	6	42,659.8	2.70 (0.99–5.87)	3.8	69	54,003.5	**2.12 (1.65–2.68)**	36.4	0.78 (0.34–1.80)
Kidney/urinary tract/bladder[2]	16	42,041.0	**1.81 (1.04–2.94)**	7.2	68	53,324.4	**2.14 (1.66–2.72)**	36.3	1.18 (0.58–2.41)
Thyroid	15	41,183.2	**3.64 (2.04–6.00)**	10.9	5	56,430.5	1.64 (0.53–3.82)	1.9	**0.27 (0.07–0.96)**
Blood	24	41,124.8	**1.97 (1.26–2.93)**	11.8	35	54,695.1	1.30 (0.91–1.81)	8.1	0.82 (0.42–1.61)
Other	14	41,719.5	1.09 (0.60–1.83)	1.2	27	54,957.2	1.03 (0.68–1.50)	0.9	0.85 (0.35–2.09)

[1]Alcohol-related cancer sites.
[2]Tobacco-related cancer sites.
[3]Results for ever-drinker/ever-smoker vs. never-drinker/never-smoker (reference).
[4]Adjusted for age groups and calendar periods at first cancer diagnosis, sex, stage, alcohol-related first cancer site, follow-up interval and the joint category.
SIR = standardized incidence ratio; EAR = excess absolute risk; SPC = subsequent primary cancer; IRR = incidence rate ratio; CI = confidence interval; No. = patients number; NA = not applicable.
Bold = statistical significance of $p < 0.05$.

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interaction terms. Because the examination of combinations of and interactions between drinking and smoking was limited in the current study, further investigation is required in the future.[23] Second, drinking and smoking may be associated not only with each other, but also with other risk-taking behaviors such as use of other addictive substances, unhealthy diet and little physical exercise.[23] This may lead to an overestimation of the results. Third, because the statistical methods used in the study censored patients at the time of death, competing risks such as death from other diseases were considered in the analyses.[5] However, bias due to competing risks was not completely eliminated: *i.e.*, there might be underreporting of subsequent cancers related to competing risks from comorbidity conditions and shortened life expectancies.[5] Fourth, although we used all, alcohol-related and tobacco-related cancer sites, other categorizations such as both-alcohol-and-tobacco-related sites might be also appropriate for evaluating the joint effect of alcohol and tobacco use. We may need to consider this approach in a separate analysis. Fifth, all cancer survivors may undergo more intense screening efforts after the initial cancer diagnosis. Screening bias of this nature may have resulted in overestimates of second primary cancers among these cancer survivors.[28] Last, although the large sample size is a strength of this study, this is an institution-based cohort. Despite these limitations, this study may have a strength: because a randomized trial to assign people to drink alcohol is not feasible as well as those to make people smoke tobacco, we have to base our best judgment on observational data such as that collected in this study.[7,14]

In conclusion, because the joint effect of alcohol and tobacco use on subsequent cancer incidence had been clearly evident in the general population and cancer patients of limited sites such as upper aerodigestive tract and breast,[6,8–10,23,28] our research only additionally confirmed the evidence among comprehensive cancer survivors. However, these two modifiable lifestyle factors remain highly prevalent

even in cancer patients who are often hospitalized and in contact with medical professionals; thus our findings will reinforce the necessity for medical facilities to provide support for patients to adapt their lifestyles.

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