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The Combined Effects of Alcohol Consumption and Smoking on Cancer Risk by Exposure Level: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Alcohol consumption is a major risk factor for cancer, and when combined with smoking, the risk increases. Nevertheless, few studies have comprehensively evaluated the combined effects of alcohol consumption and smoking on the risk of various cancer types. Therefore, to assess these effects, we conducted a systematic review and meta-analysis.
Methods: We performed a systematic search of five literature databases, focusing on cohort and case-control studies. Considering exposure levels, we quantified the combined effects of alcohol consumption and smoking on cancer risk and assessed multiplicative interaction effects.
Results: Of 4,452 studies identified, 24 (4 cohort studies and 20 case-control studies) were included in the meta-analysis. We detected interaction effect of light alcohol and moderate smoking on head and neck cancer risk (relative risk [RR], 4.26; 95% confidence interval [CI], 2.50–7.26; I^2 = 65%). A synergistic interaction was observed in heavy alcohol and heavy smoking group (RR, 35.24; 95% CI, 23.17–53.58; I^2 = 69%). In more detailed cancer types, the interaction effect of heavy alcohol and heavy smoking was noticeable on oral (RR, 36.42; 95% CI, 24.62–53.87; I^2 = 46%) and laryngeal (RR, 38.75; 95% CI, 19.25–78.01; I^2 = 69%) cancer risk.
Conclusion: Our study provided a comprehensive summary of the combined effects of alcohol consumption and smoking on cancers. As their consumption increased, the synergy effect became more pronounced, and the synergy effect was evident especially for head and neck cancer. These findings provide additional evidence for the combined effect of alcohol and smoking in alcohol guidelines for cancer prevention.

Keywords: Systematic Review; Meta-Analysis; Alcohol Drinking; Smoking; Neoplasms

INTRODUCTION

As a risk factor for various diseases, particularly cancer, alcohol consumption is a public health problem. The 2019 Global Burden of Disease Study reported that 4.3% of deaths

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Disclosure

The authors have no potential conflicts of interest of disclose.

Author Contributions

Conceptualization: Jun S, Park H[1]. Data curation: Jun S, Park H[2], Kim UJ. Formal analysis: Jun S. Investigation: Jun S, Park H[2], Kim UJ. Methodology: Lee HA, Park B, Lee SY, Park H. Software: Jun S, Lee HA. Validation: Lee HA, Park B, Lee SY, Jee SH. Visualization: Jun S, Park H[2]. Writing - Jun S. Writing - review & editing: Park H[2], Kim UJ, Lee HA, Park B, Lee SY, Jee SH, Park H[1]. Supervision: Park H[1].

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and 3.7% of disability-adjusted life years (DALYs) are attributable to alcohol.[1] Alcohol consumption is associated with cancer risk, as stated previously, and the International Agency for Research on Cancer (IARC) has classified alcohol as a Group 1 carcinogen.[2] According to a study on the global burden of cancer, alcohol accounted for 5.2% of all cancer DALYs in 2019 (7.4% in males, 2.3% in females).[3] Additionally, an estimated 741,300 new cancer cases (95% confidence interval [CI], 558,500–951,200) in 2020 were attributable to alcohol consumption.[4] Alcohol consumption is a major risk factor for a wide range of cancers, including oral, pharyngeal, laryngeal, esophageal, liver, pancreatic, colorectal, and breast cancers.[5]

Smoking is also classified as a Group 1 carcinogen by the IARC and is known to be a major risk factor for various cancer.[6] Studies have investigated alcohol consumption and cancer risk, considering smoking as a major confounding factor, but alcohol consumption and smoking may interact. Alcohol poses a greater risk to smokers, and several studies have reported interaction effects for specific cancers. Esophageal cancer risk increased nearly two-fold in smokers consuming alcohol,[7] and the risk of oral cancer was significantly elevated by alcohol consumption and smoking (odds ratio [OR], 5.37; 95% CI, 3.54–8.14).[8] In a multi-country study using the individual-level pooled data, the combined OR of alcohol and tobacco for head and neck cancer was 5.73 (95% CI, 3.62–9.06), which was found to be statistically significant in terms of multiplicative interaction.[9]

However, most studies have assessed alcohol consumption and smoking on an individual basis, with few comprehensively evaluated both risk factors for cancer together. Accordingly, in this study, we analyzed the risk posed by simultaneous exposure to alcohol and smoking, focusing on alcohol-related carcinomas.[10] We conducted a comprehensive meta-analysis of recent cohort and case-control studies investigating the associations of alcohol consumption and smoking with cancer risk. We quantitatively analyzed cancer risk according to the levels of alcohol consumption and smoking.

METHODS

Search strategy and eligibility criteria

This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. The focus questions were constructed using the Population, Intervention/Exposure, Comparison, Outcomes (PICO) search strategy: P, general population; I, alcohol consumption and smoking levels; C, no consumption; O, cancer.[11] Cancers of interest included alcohol-related cancers (oral cavity and pharyngeal, laryngeal, esophageal, liver, pancreatic, lung, stomach, colorectal, prostate, and female breast cancers).[10] The Embase, Cochrane Library, PubMed, Scopus, and Web of Science databases were systematically searched for original articles published up to December 2021. The keywords used were 'alcohol,' 'alcohol drinking,' 'smoking,' 'tobacco,' 'synergy,' 'interaction,' 'neoplasm,' and 'carcinoma.' Furthermore, we searched the reference sections of articles for additional relevant studies.

The following exclusion criteria were applied: study designs other than cohort or case-control; languages other than English or Korean; insufficient data for quantitative analysis; gray literature including non-peer-reviewed publications; full text inaccessible; cancer types other than those under investigation herein; and studies not concerned with alcohol

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consumption and smoking. We also excluded studies that only evaluated specific types of alcoholic beverages or smoking. If the results of the same study were published in multiple articles, only the most recent or complete article was included.

Study selection, data extraction, and quality assessment

Three authors (Jun S, Park H, and Kim UJ) decided if studies should be included based on the inclusion and exclusion criteria. They evaluated the titles/abstracts and full texts of the studies. Disagreements among the authors were resolved through discussion, and if necessary, a final decision was made by an independent expert (Park H).

The general characteristics (author, year, country, and study design), population characteristics (sample size, sex, and age distribution), classification criteria, covariates, and main findings of the studies were recorded for data extraction.

The Risk of Bias for Non-randomized Studies (RoBANS) was used to assess the quality of the studies.[12] For all questions across six domains, risk of bias was classified as low, high, or unclear. Quality was independently assessed by two authors (Jun S and Park H), and any disagreements were resolved through discussion.

Exposure categories

Alcohol consumption was categorized as none, light (< 12.5 g/day), moderate (12.5–49.9 g/day), or heavy (≥ 50 g/day).[13,14] The various alcohol units (g, mL, oz, number of drinks) and time frames (daily, weekly, monthly, yearly) used in the studies were converted to g/day based on unit conversion factors of 0.8 g/mL, 28 g/oz, and 12 g/glass.[15] Smoking levels were classified as none, light (≤ 10 cigarettes/day), moderate (11–19 cigarettes/day), or heavy (≥ 20 cigarettes/day).[16,17] Groups defined by the combination of alcohol consumption and smoking levels were named as follows: 1) non-alcohol and moderate smoking, 2) non-alcohol and heavy smoking, 3) light alcohol and non-smoking, 4) light alcohol and moderate smoking, 5) light alcohol and heavy smoking, 6) moderate alcohol and non-smoking, 7) moderate alcohol and moderate smoking, 8) moderate alcohol and heavy smoking, 9) heavy alcohol and non-smoking, 10) heavy alcohol and moderate smoking, and 11) heavy alcohol and heavy smoking. The number of studies reporting light smoking was insufficient for meta-analysis, so the light and moderate smokers were combined into a single group named moderate smoking.

Statistical analysis

Quantitative analysis was conducted of homogeneous studies in terms of exposure levels and outcomes. Risk estimates were adjusted for confounding factors; crude values were used if there were no adjustments. The relative risk (RR) of cancer for each individual study was computed by alcohol consumption and smoking level (relative to non-drinkers and non-smokers). As incidence of cancer is relatively uncommon, the OR, and hazard ratio were assumed to be analogous to the RR.

Through meta-analysis, the combined effects according to the level of exposure to alcohol consumption and smoking were estimated and interpreted in terms of theoretical definitions of interactions.[18] Accordingly, the interaction effect of alcohol consumption and smoking on cancer risk was investigated relative to the effects of alcohol consumption alone and smoking alone. The interaction magnitude on a multiplicative scale was calculated as; $RR_{11}/RR_{10}RR_{01}$. If $RR_{11}/RR_{10}RR_{01} > 1$, the multiplicative interaction is interpreted as positive. Synergistic interaction was assessed on an additive scale; the relative excess risk due to interaction

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(RERI), attributable proportion due to interaction (AP), and synergy index (SI). This could be calculated by: RERI = $RR_{11} - RR_{10} - RR_{01} + 1$, AP = RERI/$RR_{11}$, and SI = $(RR_{11} - 1)/[(RR_{10} - 1) + (RR_{01} - 1)]$. RR_{11}, RR_{01}, and RR_{10} are considered RR of both exposures together or of each exposure alone. If RERI and AP > 0, and SI > 1, it indicates that there is a synergistic interaction. Additionally, the interaction between alcohol consumption and smoking according to exposure level was evaluated by performing a meta-regression analysis based on the natural logarithm of the RR scale. Statistical tests were also performed to compare the combined effect of alcohol consumption and smoking on cancer risk with the effect of alcohol consumption or smoking alone.

Heterogeneity in meta-analysis was evaluated using the I^2 test and classified as low (≤ 25%), moderate (50%), or high (≥ 75%).[19] A fixed-effects model was used in cases when I^2 was lower than 50%, whereas if I^2 was greater than 50%, the random-effects model was used. Publication bias was examined by Egger's test, a funnel plot, and the trim-and-fill method.[20,21] Subgroup analysis was performed to assess the effect of study design on the results. The statistical analysis was conducted using R Studio (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria), and a P value < 0.05 was considered significant.

RESULTS

A total of 4,452 studies were identified through the literature search and review of the reference lists. After removing duplicates, 2,804 studies remained for the title/abstract and full-text review; 2,420 and 276 studies were excluded after reviewing the title/abstract and full-text according to the eligibility criteria. Out of 108 studies subjected to a systematic literature review, only 24 were included in the meta-analysis. This exclusion was either due to the absence of suitable quantitative data or the inappropriateness of the exposure level for this study in the remaining 84 studies (**Fig. 1**). **Table 1** shows the main characteristics of the 24 final studies included in the meta-analysis according to cancer type. There were 4 cohort and 20 case-control studies. Studies that investigated multiple cancer types or reported multiple outcomes may have been counted more than once.

According to RoBANS, half of the studies evaluated had a high risk of bias concerning self-reported exposure. However, the questions in the other five domains showed low or unclear risk of bias (**Supplementary Fig. 1**).

Head and neck cancer included oral, laryngeal, and pharyngeal cancer. The results for head and neck cancer are shown in **Fig. 2**. The RR of head and neck cancer for the light alcohol and moderate smoking group was 4.26 (95% CI, 2.50–7.26). Moreover, the RR for the heavy alcohol and heavy smoking group was 35.24 (95% CI, 23.17–53.58), which was much higher than those of the heavy alcohol and non-smoking group and non-alcohol and heavy smoking group, indicating a multiplicative interaction. The heavy alcohol and heavy smoking group and the heavy alcohol and moderate smoking group showed a statistically significant difference in risk compared to the group that only considered alcohol consumption or smoking. Even in the moderate alcohol and heavy smoking group, the risk was statistically different compared to the group that only considered alcohol consumption. Synergistic interactions were observed at all levels of head and neck cancer, and it was greater in the heavy alcohol and heavy smoking group (**Table 2**).

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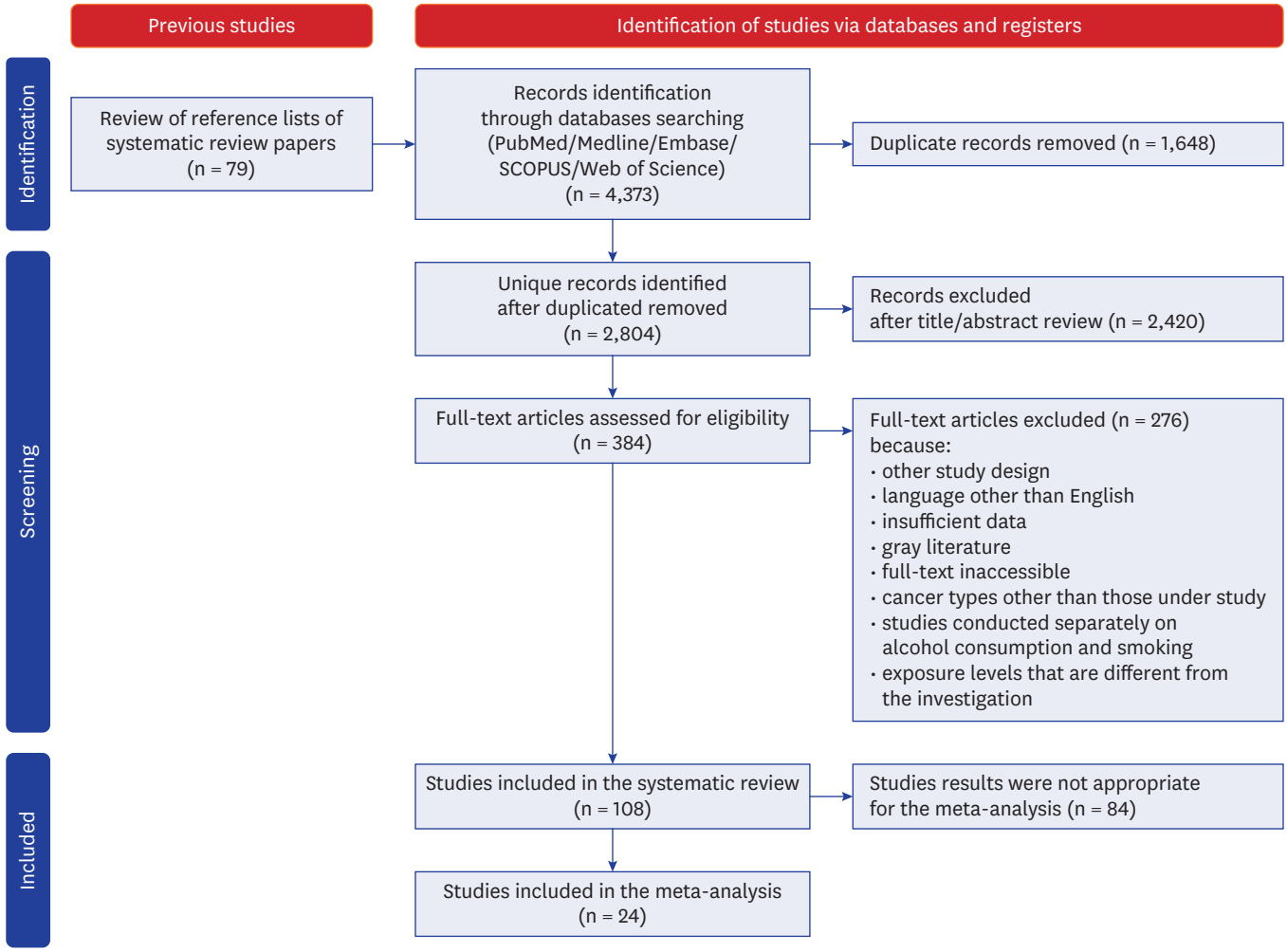

Fig. 1. Flowchart of the selection of studies for inclusion in the meta-analysis.

Table 3 shows the results of the meta-analysis of the risk of different cancer types (oral, pharyngeal, laryngeal, esophageal, and pancreatic cancers) according to alcohol consumption and smoking levels. There were not enough studies reporting light alcohol consumption to conduct a meta-analysis by cancer type, so it was combined with moderate consumption. The risk of cancer types of interest increased when alcohol consumption and smoking co-occurred compared to either alone. Multiplicative interaction effects of heavy alcohol consumption and heavy smoking on oral and laryngeal cancer risk were seen (RR, 36.42; 95% CI, 24.62–53.87 and RR, 38.75; 95% CI, 19.25–78.01, respectively); these RRs were much higher than those of heavy alcohol consumption and heavy smoking alone, respectively.

A subgroup analysis by study design was performed for risk of all alcohol-related cancers (**Supplementary Table 1**). Although the results of cohort and case-control studies differed markedly, a multiplicative interaction effect of heavy alcohol consumption and heavy smoking on cancer risk was observed in both cohort and case-control studies.

Statistical heterogeneity was observed within the studies. Some studies assessed only light consumption, and not all studies reported the number of abstainers. Additionally, the CIs

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Table 1. Summary of studies characteristics included in the meta-analysis by cancer types

No.	Study (Publish year)	Study design	Country	Cohort/Control size		Case size		Age at baseline or range, yr	Year(s) of baseline	Case identification	Mean duration of follow-up year or recruitment period, yr
				M	F	M	F				
Head and neck cancer											
1	Maasland et al. (2014)[22]	Cohort	The Netherlands	120,852		65	45	61.8	1986	Annual record linkage to the Netherlands Cancer Registry and the nationwide network and pathology registry	17.3
2	Andre et al. (1995)[23]	Case-control	France	645		299		≥ 18	1986–1989	Doubs Cancer Registry	3
3	Hashibe et al. (2009)[9]	Case-control	Multi	11,611		4,557	2,993	Not specified	2004	Face-to-face interviews, self-administered questionnaires, International Head and Neck Cancer Epidemiology consortium	-
4	Franceschi et al. (1999)[24]	Case-control	Italy	1,254	0	274	0	57	1992–1997	Interview and diagnosed at major hospitals	5
5	Castellsagué et al. (2004)[25]	Case-control	Multi	304	71	304	71	60	1996–1999	Interview, diagnosed in participating hospitals	3
6	Lissowska et al. (2003)[26]	Case-control	Poland	72	52	78	44	23–80	1997–2000	Cancer Registry data, interview	3
7	Bundgaard et al. (1995)[27]	Case-control	Denmark	250	150	97	64	Not specified	1986–1990	Aarhus University Hospital, Danish Central Population Register, questionnaire	5
8	De Stefani et al. (2007)[28]	Case-control	Uruguay	1,501	0	335	0	30–89	1988–2000	Four major public hospitals, interviews and questionnaire	2
9	Hayes et al. (1999)[29]	Case-control	Puerto Rico	417	298	104	69	21–79	1992–1995	Central Cancer Registry of the Department of Health of Puerto Rico, personal interview	2.5
10	Olsen et al. (1985)[30]	Case-control	Denmark	978	163	26	6	< 75	1980–1982	Five hospital departments involved in therapy, questionnaire about exposure	2
11	Talamini et al. (2002)[31]	Case-control	Northern Italy and Switzerland	1,027	245	478	49	61	1992–2000	Major local teaching and general hospitals in the area	8
12	Hashibe et al. (2007)[32]	Case-control	Europe	783	180	340	44	Not specified	2000–2002	Diagnosed at designated hospitals or cancer clinics	2
13	Falk et al. (1989)[33]	Case-control	USA	235	0	151	0	60	1975–1980	Ascertained from 56 hospitals in a six-country region, review of state health department records, interview	6
14	Zang et al. (2001)[34]	Case-control	USA	4,436	3,124	352	183	Not specified	1969–1994	Participating hospitals, individual interview	25
15	Guénel et al. (1988)[35]	Case-control	France	4,135	0	411	0	≥ 25	1980–1981	Head and Neck department of the curie institute in Paris, medical consultation and interviews	1
Oral cancer											
1	Maasland et al. (2014)[22]	Cohort	The Netherlands	120,852		65	45	61.8	1986	Annual record linkage to the Netherlands Cancer Registry and the nationwide network and pathology registry	17.3
2	Franceschi et al. (1999)[24]	Case-control	Italy	1,254	0	274	0	57	1992–1997	Interview and diagnosed at major hospitals	5
3	Castellsagué et al. (2004)[25]	Case-control	Multi	304	71	304	71	60	1996–1999	Interview, diagnosed in participating hospitals	3
4	Lissowska et al. (2003)[26]	Case-control	Poland	72	52	78	44	23–80	1997–2000	Cancer Registry data, interview	3

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Table 1. (Continued) Summary of studies characteristics included in the meta-analysis by cancer types

No.	Study (Publish year)	Study design	Country	Cohort/Control size		Case size		Age at baseline or range, yr	Year(s) of baseline	Case identification	Mean duration of follow-up year or recruitment period, yr
				M	F	M	F				
5	Bundgaard et al. (1995)[27]	Case-control	Denmark	250	150	97	64	Not specified	1986–1990	Aarhus University Hospital, Danish Central Population Register, questionnaire	5
6	De Stefani et al. (2007)[28]	Case-control	Uruguay	1,501	0	335	0	30–89	1988–2000	Four major public hospitals, interviews and questionnaire	2
7	Hayes et al. (1999)[29]	Case-control	Puerto Rico	417	298	104	69	21–79	1992–1995	Central Cancer Registry of the Department of Health of Puerto Rico, personal interview	2.5
8	Hashibe et al. (2009)[9]	Case-control	Multi	11,611	4,557	2,993		Not specified	2004	Face-to-face interviews, self-administered questionnaires, International Head and Neck Cancer Epidemiology consortium	-
Pharyngeal cancer											
1	Franceschi et al. (1999)[24]	Case-control	Italy	1,254	0	364	0	56	1992–1997	Interview and diagnosed at major hospitals	5
2	Olsen et al. (1985)[30]	Case-control	Denmark	978	163	26	6	< 75	1980–1982	Five hospital departments involved in therapy, questionnaire about exposure	2
3	De Stefani et al. (2007)[28]	Case-control	Uruguay	1,501	0	441	0	30–89	1988–2000	Four major public hospitals, interviews, and questionnaire	2
4	Hashibe et al. (2009)[9]	Case-control	Multi	11,611	4,557	4,040		Not specified	2004	Face-to-face interviews, self-administered questionnaires, International Head and Neck Cancer Epidemiology consortium	-
Laryngeal cancer											
1	Maasland et al. (2014)[22]	Cohort	The Netherlands	120,852		187	12	61.8	1986	Annual record linkage to the Netherlands Cancer Registry and the nationwide network and pathology registry	7.3
2	Talamini et al. (2002)[31]	Case-control	Northern Italy and Switzerland	1,027	245	478	49	61	1992–2000	Major local teaching and general hospitals in the area	8
3	Hashibe et al. (2007)[32]	Case-control	Europe	783	180	340	44	Not specified	2000–2002	Diagnosed at designated hospitals or cancer clinics	2
4	Falk et al. (1989)[33]	Case-control	USA	235	0	151	0	60	1975–1980	Ascertained from 56 hospitals in a six-county region, review of state health department records, interview	6
5	Zang et al. (2001)[34]	Case-control	USA	4,436	3,124	352	183	Not specified	1969–1994	Participating hospitals, individual interview	25
6	Hashibe et al. (2009)[9]	Case-control	Multi	11,611	4,557	2,965		Not specified	2004	Face-to-face interviews, self-administered questionnaires, International Head and Neck Cancer Epidemiology consortium	-
7	Guénel et al. (1988)[35]	Case-control	France	4135	0	411	0	> 25	1980–1981	Head and Neck department of the curie institute in Paris, medical consultation, and interviews	1
Esophageal cancer											
1	Yaegashi et al. (2014)[36]	Cohort	Japan	46,395	0	42,408	0	40–79	1988–1990	Annually or biannually confirmed dates and causes of death and reviewing population register sheets	20
2	Wu et al. (2011)[37]	Case-control	China	2,916	963	1,191	329	65.3 (male case), 67.4 (female case)	2003–2007	Face-to-face interview, local population-based cancer registries	4

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Table 1. (Continued) Summary of studies characteristics included in the meta-analysis by cancer types

No.	Study (Publish year)	Study design	Country	Cohort/Control size		Case size		Age at baseline or range, yr	Year(s) of baseline	Case identification	Mean duration of follow-up year or recruitment period, yr
				M	F	M	F				
3	Sewram et al. (2016)[38]	Case-control	South Africa	621	567	334	336	Not specified	2001–2003	Interview, three major public referral hospitals	1.5
4	Zambon et al. (2000)[39]	Case-control	Northern Italy	593	0	275	0	60	1992–1997	Major hospital of the areas, interview	5
Pancreatic cancer											
1	Partanen et al. (1997)[40]	Case-control	Finland	1,770		662		40–74	1984–1987	Identified at the Finnish Cancer Registry	3
2	Talamini et al. (2010)[41]	Case-control	Italy	348	304	174	152	63	1991–2008	Major general hospitals, questionnaire	18
Lung cancer											
1	Zang et al. (2001)[34]	Case-control	USA	4,436	3,124	1,763	1,205	Not specified	1969–1994	Participating hospitals, individual interview	25
Liver cancer											
1	Kuper et al. (2000)[42]	Case-control	Greece	298	62	283	50	Not specified	1995–1998	Identified from 3 teaching hospital in Athens, interviewed in the hospital	4
Stomach cancer											
1	Sung et al. (2007)[43]	Cohort	Korea	669,570	0	3,452	0	44	1996–2002	Questionnarie, Korea Central Cancer Registry	6.5
Colorectal cancer											
1	Tsong et al. (2007)[44]	Cohort	Singapore	61,321		845		67.4	1993–1998	In-person interviews and population-based Singapore Cancer Registry and Registry of Births and Deaths	8.9

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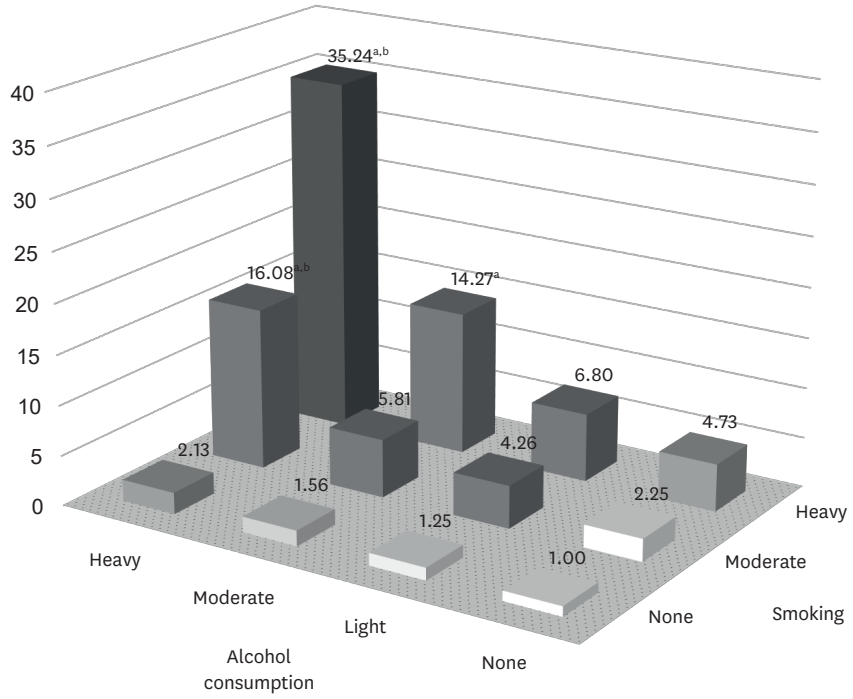

Fig. 2. Relative risks of head and neck cancer associated with the combined effects of alcohol consumption and smoking. Head and neck cancer included cancers of the oral, pharyngeal, and laryngeal. Alcohol consumption was classified as none, light (< 12.5 g/day), moderate (12.5–49.9 g/day), or heavy (≥ 50.0 g/day). Smoking was classified as none, moderate (< 20 cig/day), or heavy (≥ 20 cig/day).
[a]When comparing the pooled relative risk of the combination of alcohol consumption and smoking group and the corresponding alcohol consumption group alone, the *P* value was smaller than 0.05.
[b]When comparing the pooled relative risk of the combination of alcohol consumption and smoking group and the corresponding smoking group alone, the *P* value was smaller than 0.05.

Table 2. Alcohol and smoking multiplicative interaction and synergistic interaction for head and neck cancer

Alcohol	Smoking	RR_{01}	RR_{10}	RR_{11}	Multiplicative interaction	RERI	AP	SI
Heavy	Heavy	2.13	4.73	35.24	3.50	29.38	0.83	7.05
Moderate	Heavy	1.56	4.73	14.30	1.94	9.01	0.63	3.10
Light	Heavy	1.25	4.73	6.80	1.15	1.82	0.27	1.46
Heavy	Moderate	2.13	2.25	16.10	3.36	12.72	0.79	6.34
Moderate	Moderate	1.56	2.25	5.81	1.66	3.00	0.52	2.66
Light	Moderate	1.25	2.25	4.26	1.51	1.76	0.41	2.17

RERI = relative excess risk due to interaction, AP = attributable proportion due to interaction, SI = synergy index. RR_{01}, RR_{10}, and RR_{11} are the exposure level of alcohol consumption, the exposure level of smoking, and the exposure level of both factors.

and I^2 statistics varied widely. Publication bias was revealed by the funnel plot and Egger's test. The trim-and-fill method was used to determine the unbiased effect on the results and adjust for publication bias (**Supplementary Table 2**). The combined effects according to the level of exposure to alcohol consumption and smoking were found to decrease in all groups except the heavy alcohol and non-smoking group, but most results were meaningful. Large effect sizes were seen for small studies, and publication bias was likely due to their small study effects.

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Table 3. Pooled relative risks estimated by cancer types associated with the combined effects of alcohol consumption[a] and smoking[b]

Smoking[b]	Alcohol consumption[a]		
	None	Moderate	Heavy
Oral (8 studies)			
None	1.00	1.77 (1.06–2.97)	2.78 (1.10–7.03)
Moderate	1.92 (1.41–2.61)	4.71 (2.37–9.38)	18.18 (12.32–26.84)
Heavy	4.41 (2.64–7.37)	8.08 (4.32–15.09)	36.42 (24.62–53.87)
Pharynx (4 studies)			
None	1.00	1.22 (0.91–1.63)	1.54 (0.29–8.19)
Moderate	2.03 (1.48–2.80)	5.70 (2.79–11.64)	13.74 (8.79–21.50)
Heavy	NA	11.69 (3.74–36.54)	26.73 (12.73–56.11)
Larynx (7 studies)			
None	1.00	1.66 (1.40–1.97)	2.45 (1.21–4.98)
Moderate	5.80 (3.89–8.66)	5.54 (2.55–12.04)	14.70 (4.50–48.08)
Heavy	12.59 (8.22–19.27)	19.23 (11.59–31.90)	38.75 (19.25–78.01)
Esophagus (4 studies)			
None	1.00	1.10 (0.83–1.46)	1.75 (0.90–3.39)
Moderate	1.81 (1.09–2.99)	2.89 (2.19–3.82)	4.59 (1.87–11.26)
Heavy	2.62 (1.46–4.72)	6.46 (4.28–9.75)	8.11 (6.00–10.97)
Pancreas (2 studies)			
None	1.00	1.28 (0.93–1.75)	1.63 (0.60–4.44)
Moderate	NA	1.98 (1.45–2.72)	2.88 (1.83–4.55)
Heavy	NA	2.50 (1.63–3.85)	2.80 (1.35–5.82)

Only one study included lung, liver, stomach, and colorectal cancers, so meta-analysis of these cancer types was not performed.
NA = not available.
[a]Alcohol consumption was classified as none, moderate (< 49.9 g/day), or heavy (≥ 50.0 g/day).
[b]Smoking was classified as none, moderate (< 20 cig/day), or heavy (≥ 20 cig/day).

DISCUSSION

This study found that there was an increased cancer risk with combined alcohol consumption and smoking compared to alcohol consumption alone. Individuals in the light alcohol and moderate smoking group had a 4.3 times higher risk of head and neck cancer, and there was multiplicative interaction effect. In addition, an interaction was observed at above moderate alcohol consumption with smoking, and the interaction was even stronger with heavy alcohol consumption for head and neck cancer, as well as in detailed cancer types such as oral and laryngeal cancer.

Many studies have discussed the interaction between alcohol consumption and smoking, and previous studies have mainly focused on cancers of the upper aerodigestive tract.[9,45,46] Some studies have investigated the interaction between light drinking and light smoking, but evidence supporting it has not been found, which is consistent with our findings.[22,24,29,39] Studies have shown an interaction effect between drinking and smoking on upper aerodigestive tract cancers, including oral, pharyngeal, laryngeal, and esophageal cancers.[7-9,22,24,29,31,39,47-48] In a meta-analysis,[8] the synergistic consumption of both alcohol and tobacco was associated with an increased probability of developing oral squamous cell carcinoma (OR, 5.37; 95% CI, 3.54–8.14). Another meta-analysis indicated that the risk of cancer increases with greater alcohol and cigarette consumption; the risk of laryngeal cancer increases approximately 35-fold with high levels of alcohol and smoking.[45] Similarly, we observed a multiplicative interaction effect of heavy alcohol and heavy smoking group on head and neck, oral and laryngeal cancer.

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The interaction between drinking and smoking has been discussed in biological terms. Alcohol enhances the cellular penetration of carcinogens associated with smoking and potentially acts as a solvent.[50,51] Additionally, alcohol affects the hepatic enzymes responsible for metabolizing smoking-related carcinogens.[52] Our study showed interaction effects, especially in oral and laryngeal cancer. Alcohol and smoking are both class 1 carcinogens and independent risk factors for oral and laryngeal cancer.[2] The interaction may occur in oral and laryngeal cancer as follows: alcohol is believed to increase the solubility of tobacco carcinogens and, in turn, promote their penetration into the oral mucosa, potentially exacerbating the impact of smoking.[53] In vitro experiments have demonstrated that ethanol can boost the penetration of nitrosonornicotine, a carcinogen associated with tobacco, through porcine oral mucosa.[54]

Regarding the guidance on alcohol use, the Australian Cancer Society Alcohol Working Group reported that alcohol consumption and smoking had a synergistic effect on some cancer risks, considering scientific evidence.[55] Since then, guidelines for cancer prevention have been introduced in Europe and the United States, considering the risk of concurrent alcohol consumption and smoking.[56,57] Our findings support these guidelines. However, cancer prevention guidelines in many countries including Korea do not address the risk of concurrent alcohol consumption and smoking.[58] According to data from Korea, the proportion of adult men who were current smokers and high-risk drinkers in 2015 was 7.8%.[59] Alcohol consumption and smoking are linked, and people who drink have cravings to smoke and are more likely to do so than non-drinkers.[60,61] Given these findings, addressing the combined effects of drinking and smoking may be a key strategy for preventing cancer.

Our study had some limitations. It focused on alcohol-related cancers and may have excluded some smoking-related cancers. Moreover, the duration and type of exposure, which could have affected the effect sizes, were not considered, and the definition of exposure varied among studies. The study selection process may have resulted in potential selection bias due to inaccessibility to full-texts or language restrictions. Among the studies that evaluated the interaction effect of alcohol consumption and smoking on cancer risk, 71 were excluded due to a failure to report exposure levels or because the exposure level did not meet the inclusion criteria. There was high heterogeneity among the studies, and a random-effects model was thus used.[62] Heterogeneity in study design was also observed. We interpreted the interactions based on theoretical definitions. No statistical significance of the interaction was observed in the meta-regression analysis (data not shown). This may be due to insufficient number of studies, differences in the amount of information between combination groups[63] and methodological weaknesses in meta-regression analysis of aggregate data.[64] Additionally, despite including the latest available data, evidence from previous studies was insufficient to evaluate various cancer. Lastly, evidence is limited since there are relatively few prospective studies that have been evaluated to be more reliable regarding exposures investigation than retrospective studies. To draw more reliable and accurate conclusions in the future, evidence through sufficient research based on prospective studies is needed.

This study also had several strengths. As stated above, we included the latest data. While previous meta-analyses focused on alcohol consumption and smoking as risk factors for specific cancer types, we included a more comprehensive range of cancers, and we also considered a wider range of consumption amounts, including light consumption. Lastly, our study highlights that individual who smoke while consuming alcohol, including light level, elevate the risk of head and neck cancer. It also shows that as alcohol consumption

and smoking increase, the effect on cancer risk becomes greater. The results of this study provide additional evidence for the combined effects of smoking in alcohol guidelines. Our findings can serve as evidence supporting efforts to prevent cancers associated with alcohol consumption and smoking, underscoring the importance of public health interventions.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Subgroup analysis by study design of the combined effect of alcohol consumption[a] and smoking[b] on alcohol-related cancer risk

Supplementary Table 2

Funnel plots of the meta-analysis examining the relationship between alcohol consumption and smoking on alcohol-related cancer

Supplementary Fig. 1

Assessment of study quality included in the meta-analysis.

REFERENCES

1. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396(10258):1223-49. PUBMED | CROSSREF
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol drinking. *IARC Monogr Eval Carcinog Risks Hum* 1988;44:1-378. PUBMED
3. GBD 2019 Cancer Risk Factors Collaborators. The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2022;400(10352):563-91. PUBMED | CROSSREF
4. Rumgay H, Shield K, Charvat H, Ferrari P, Sornpaisarn B, Obot I, et al. Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. *Lancet Oncol* 2021;22(8):1071-80. PUBMED | CROSSREF
5. Union for International Cancer Control. Cancer and alcohol. https://www.uicc.org/what-we-do/areas-focus/cancer-and-alcohol. Updated 2023. Accessed October 2023.
6. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoking. *IARC Monogr Eval Carcinog Risks Hum* 1986;38:1-395. PUBMED
7. Prabhu A, Obi KO, Rubenstein JH. The synergistic effects of alcohol and tobacco consumption on the risk of esophageal squamous cell carcinoma: a meta-analysis. *Am J Gastroenterol* 2014;109(6):822-7. PUBMED | CROSSREF
8. Mello FW, Melo G, Pasetto JJ, Silva CA, Warnakulasuriya S, Rivero ER. The synergistic effect of tobacco and alcohol consumption on oral squamous cell carcinoma: a systematic review and meta-analysis. *Clin Oral Investig* 2019;23(7):2849-59. PUBMED | CROSSREF
9. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev* 2009;18(2):541-50. PUBMED | CROSSREF

10. International Agency for Research on Cancer. *World Cancer Report 2014*. Lyon, France: International Agency for Research on Cancer; 2014.
11. Cooke A, Smith D, Booth A. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. *Qual Health Res* 2012;22(10):1435-43. PUBMED | CROSSREF
12. Kim SY, Park JE, Lee YJ, Seo HJ, Sheen SS, Hahn S, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol* 2013;66(4):408-14. PUBMED | CROSSREF
13. Choi YJ, Myung SK, Lee JH. Light alcohol drinking and risk of cancer: a meta-analysis of cohort studies. *Cancer Res Treat* 2018;50(2):474-87. PUBMED | CROSSREF
14. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer* 2015;112(3):580-93. PUBMED | CROSSREF
15. Patra J, Taylor B, Irving H, Roerecke M, Baliunas D, Mohapatra S, et al. Alcohol consumption and the risk of morbidity and mortality for different stroke types--a systematic review and meta-analysis. *BMC Public Health* 2010;10(1):258. PUBMED | CROSSREF
16. Husten CG. How should we define light or intermittent smoking? Does it matter? *Nicotine Tob Res* 2009;11(2):111-21. PUBMED | CROSSREF
17. Government of Canada. Tobacco use statistics, terminology. https://www.canada.ca/en/health-canada/services/health-concerns/tobacco/research/tobacco-use-statistics/terminology.html. Updated 2008. Accessed May 2022.
18. VanderWeele TJ, Knol MJ. A tutorial on interaction. *Epidemiol Methods* 2014;3(1):33-72. CROSSREF
19. Higgins JP. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. https://handbook-5-1.cochrane.org/. Updated 2011. Accessed May 2023.
20. Pustejovsky JE, Rodgers MA. Testing for funnel plot asymmetry of standardized mean differences. *Res Synth Methods* 2019;10(1):57-71. PUBMED | CROSSREF
21. Duval S, Tweedie R. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. *J Am Stat Assoc* 2000;95:89-98.
22. Maasland DH, van den Brandt PA, Kremer B, Goldbohm RA, Schouten LJ. Alcohol consumption, cigarette smoking and the risk of subtypes of head-neck cancer: results from the Netherlands Cohort Study. *BMC Cancer* 2014;14(1):187. PUBMED | CROSSREF
23. Andre K, Schraub S, Mercier M, Bontemps P. Role of alcohol and tobacco in the aetiology of head and neck cancer: a case-control study in the Doubs region of France. *Eur J Cancer B Oral Oncol* 1995;31B(5):301-9. PUBMED | CROSSREF
24. Franceschi S, Levi F, La Vecchia C, Conti E, Dal Maso L, Barzan L, et al. Comparison of the effect of smoking and alcohol drinking between oral and pharyngeal cancer. *Int J Cancer* 1999;83(1):1-4. PUBMED | CROSSREF
25. Castellsagué X, Quintana MJ, Martínez MC, Nieto A, Sánchez MJ, Juan A, et al. The role of type of tobacco and type of alcoholic beverage in oral carcinogenesis. *Int J Cancer* 2004;108(5):741-9. PUBMED | CROSSREF
26. Lissowska J, Pilarska A, Pilarski P, Samolczyk-Wanyura D, Piekarczyk J, Bardin-Mikołłajczak A, et al. Smoking, alcohol, diet, dentition and sexual practices in the epidemiology of oral cancer in Poland. *Eur J Cancer Prev* 2003;12(1):25-33. PUBMED | CROSSREF
27. Bundgaard T, Wildt J, Frydenberg M, Elbrønd O, Nielsen JE. Case-control study of squamous cell cancer of the oral cavity in Denmark. *Cancer Causes Control* 1995;6(1):57-67. PUBMED | CROSSREF
28. De Stefani E, Boffetta P, Deneo-Pellegrini H, Ronco AL, Acosta G, Ferro G, et al. The effect of smoking and drinking in oral and pharyngeal cancers: a case-control study in Uruguay. *Cancer Lett* 2007;246(1-2):282-9. PUBMED | CROSSREF
29. Hayes RB, Bravo-Otero E, Kleinman DV, Brown LM, Fraumeni JF Jr, Harty LC, et al. Tobacco and alcohol use and oral cancer in Puerto Rico. *Cancer Causes Control* 1999;10(1):27-33. PUBMED | CROSSREF
30. Olsen J, Sabroe S, Ipsen J. Effect of combined alcohol and tobacco exposure on risk of cancer of the hypopharynx. *J Epidemiol Community Health* 1985;39(4):304-7. PUBMED | CROSSREF
31. Talamini R, Bosetti C, La Vecchia C, Dal Maso L, Levi F, Bidoli E, et al. Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. *Cancer Causes Control* 2002;13(10):957-64. PUBMED | CROSSREF
32. Hashibe M, Boffetta P, Zaridze D, Shangina O, Szeszenia-Dabrowska N, Mates D, et al. Contribution of tobacco and alcohol to the high rates of squamous cell carcinoma of the supraglottis and glottis in Central Europe. *Am J Epidemiol* 2007;165(7):814-20. PUBMED | CROSSREF

33. Falk RT, Pickle LW, Brown LM, Mason TJ, Buffler PA, Fraumeni JF Jr. Effect of smoking and alcohol consumption on laryngeal cancer risk in coastal Texas. *Cancer Res* 1989;49(14):4024-9. PUBMED

34. Zang EA, Wynder EL. Reevaluation of the confounding effect of cigarette smoking on the relationship between alcohol use and lung cancer risk, with larynx cancer used as a positive control. *Prev Med* 2001;32(4):359-70. PUBMED | CROSSREF

35. Guénel P, Chastang JF, Luce D, Leclerc A, Brugère J. A study of the interaction of alcohol drinking and tobacco smoking among French cases of laryngeal cancer. *J Epidemiol Community Health* 1988;42(4):350-4. PUBMED | CROSSREF

36. Yaegashi Y, Onoda T, Morioka S, Hashimoto T, Takeshita T, Sakata K, et al. Joint effects of smoking and alcohol drinking on esophageal cancer mortality in Japanese men: findings from the Japan collaborative cohort study. *Asian Pac J Cancer Prev* 2014;15(2):1023-9. PUBMED | CROSSREF

37. Wu M, Zhao JK, Zhang ZF, Han RQ, Yang J, Zhou JY, et al. Smoking and alcohol drinking increased the risk of esophageal cancer among Chinese men but not women in a high-risk population. *Cancer Causes Control* 2011;22(4):649-57. PUBMED | CROSSREF

38. Sewram V, Sitas F, O'Connell D, Myers J. Tobacco and alcohol as risk factors for oesophageal cancer in a high incidence area in South Africa. *Cancer Epidemiol* 2016;41:113-21. PUBMED | CROSSREF

39. Zambon P, Talamini R, La Vecchia C, Dal Maso L, Negri E, Tognazzo S, et al. Smoking, type of alcoholic beverage and squamous-cell oesophageal cancer in northern Italy. *Int J Cancer* 2000;86(1):144-9. PUBMED | CROSSREF

40. Partanen TJ, Vainio HU, Ojajärvi IA, Kauppinen TP. Pancreas cancer, tobacco smoking and consumption of alcoholic beverages: a case-control study. *Cancer Lett* 1997;116(1):27-32. PUBMED | CROSSREF

41. Talamini R, Polesel J, Gallus S, Dal Maso L, Zucchetto A, Negri E, et al. Tobacco smoking, alcohol consumption and pancreatic cancer risk: a case-control study in Italy. *Eur J Cancer* 2010;46(2):370-6. PUBMED | CROSSREF

42. Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami HO, et al. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. *Int J Cancer* 2000;85(4):498-502. PUBMED | CROSSREF

43. Sung NY, Choi KS, Park EC, Park K, Lee SY, Lee AK, et al. Smoking, alcohol and gastric cancer risk in Korean men: the National Health Insurance Corporation Study. *Br J Cancer* 2007;97(5):700-4. PUBMED | CROSSREF

44. Tsong WH, Koh WP, Yuan JM, Wang R, Sun CL, Yu MC. Cigarettes and alcohol in relation to colorectal cancer: the Singapore Chinese Health Study. *Br J Cancer* 2007;96(5):821-7. PUBMED | CROSSREF

45. Zeka A, Gore R, Kriebel D. Effects of alcohol and tobacco on aerodigestive cancer risks: a meta-regression analysis. *Cancer Causes Control* 2003;14(9):897-906. PUBMED | CROSSREF

46. Oze I, Charvat H, Matsuo K, Ito H, Tamakoshi A, Nagata C, et al. Revisit of an unanswered question by pooled analysis of eight cohort studies in Japan: does cigarette smoking and alcohol drinking have interaction for the risk of esophageal cancer? *Cancer Med* 2019;8(14):6414-25. PUBMED | CROSSREF

47. Pelucchi C, Gallus S, Garavello W, Bosetti C, La Vecchia C. Cancer risk associated with alcohol and tobacco use: focus on upper aero-digestive tract and liver. *Alcohol Res Health* 2006;29(3):193-8. PUBMED

48. Taylor B, Rehm J. When risk factors combine: the interaction between alcohol and smoking for aerodigestive cancer, coronary heart disease, and traffic and fire injury. *Addict Behav* 2006;31(9):1522-35. PUBMED | CROSSREF

49. Flanders WD, Rothman KJ. Interaction of alcohol and tobacco in laryngeal cancer. *Am J Epidemiol* 1982;115(3):371-9. PUBMED | CROSSREF

50. Saracci R. The interactions of tobacco smoking and other agents in cancer etiology. *Epidemiol Rev* 1987;9(1):175-93. PUBMED | CROSSREF

51. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol consumption and ethyl carbamate. *IARC Monogr Eval Carcinog Risks Hum* 2010;96:3-1383. PUBMED

52. Ardies CM, Smith TJ, Kim S, Yang CS. Induction of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) activation in rat lung microsomes by chronic ethanol consumption and repeated running exercise. *Cancer Lett* 1996;103(2):209-18. PUBMED | CROSSREF

53. Wight AJ, Ogden GR. Possible mechanisms by which alcohol may influence the development of oral cancer--a review. *Oral Oncol* 1998;34(6):441-7. PUBMED | CROSSREF

54. Squier CA, Cox P, Hall BK. Enhanced penetration of nitrosonornicotine across oral mucosa in the presence of ethanol. *J Oral Pathol* 1986;15(5):276-9. PUBMED | CROSSREF

55. Winstanley MH, Pratt IS, Chapman K, Griffin HJ, Croager EJ, Olver IN, et al. Alcohol and cancer: a position statement from Cancer Council Australia. *Med J Aust* 2011;194(9):479-82. PUBMED | CROSSREF

56. World Health Organization (WHO). *Alcohol and Cancer in the WHO European Region: An Appeal for Better Prevention*. Geneva, Switzerland: WHO; 2020.
57. City of Hope Cancer Treatment Centers. Alcohol and cancer risk. https://www.cityofhope.org/living-well/alcohol-and-your-cancer-risk. Updated 2023. Accessed September 2023.
58. National Cancer Center. 10 Action codes of cancer prevention. https://www.ncc.re.kr/main.ncc?uri=manage01_3. Updated 2021. Accessed November 8, 2023.
59. Korea Disease Control and Prevention Agency. 2022 KDCA report on harmful effects of tobacco: an overview of tobacco use and its effects on health. https://www.kdca.go.kr/contents.es?mid=a20205010900. Updated 2022. Accessed October 2023.
60. Motschman CA, Tiffany ST. Combined smoking and alcohol cues: effects on craving, drug-seeking, and consumption. *Alcohol Clin Exp Res* 2021;45(9):1864-76. PUBMED | CROSSREF
61. Garnett C, Oldham M, Shahab L, Tattan-Birch H, Cox S. Characterising smoking and smoking cessation attempts by risk of alcohol dependence: a representative, cross-sectional study of adults in England between 2014-2021. *Lancet Reg Health Eur* 2022;18:100418. PUBMED | CROSSREF
62. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002. PUBMED | CROSSREF
63. Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. *Cochrane Handbook for Systematic Reviews of Interventions. Version 6.4 (Updated August 2023)*. London, UK: Cochrane; 2023.
64. Geissbühler M, Hincapié CA, Aghlmandi S, Zwahlen M, Jüni P, da Costa BR. Most published meta-regression analyses based on aggregate data suffer from methodological pitfalls: a meta-epidemiological study. *BMC Med Res Methodol* 2021;21(1):123. PUBMED | CROSSREF