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Alcohol drinking cessation and its effect on esophageal and head and neck cancers: A pooled analysis

Jürgen Rehm[2,3,4]*, Jayadeep Patra[1] and Svetlana Popova[1]

[1]*Public Health and Regulatory Policies, Centre for Addiction and Mental Health, Toronto, Ontario, Canada M5S 2S1*
[2]*Public Health Sciences, Faculty of Medicine, University of Toronto, Canada*
[3]*Research Institute for Public Health and Addiction, Zurich, Switzerland*
[4]*Technische Universität Dresden, Klinische Psychologie & Psychotherapie, Germany*

The objective of this study was to conduct a pooled analysis to evaluate the strength of the evidence available in the epidemiological literature on the association between alcohol drinking cessation and reduction in esophageal and head and neck cancer risks. A search using several electronic bibliographic databases was performed for relevant epidemiological literature between 1966 and 2006. A total of 13 unique studies including over 5,000 cases were found. Categorical and third order polynomial (cubic) regression models were fitted to estimate the temporal relationship between years of drinking cessation and risk of cancer. The risk of esophageal cancer significantly increased within the first 2 yr following cessation [odds ratios ($OR_{0-2\ yr}$: 2.50, 95% confidence intervals (CI): 2.23–2.80], then decreased rapidly and significantly after longer periods of abstention ($OR_{15+\ yr}$: 0.37, 95% CI: 0.33–0.41). An elevated risk, although not strong as for esophageal cancer, was observed for head and neck cancer up to 10 yr of quitting drinking ($OR_{5-10\ yr}$: 1.26, 95% CI: 1.18–1.35). Such risk only reduced after 10 yr of cessation ($OR_{10-16\ yr}$: 0.67, 95% CI: 0.63–0.73). After more than 20 yr of alcohol cessation, the risks for both cancers were no longer significantly different from the risk of never drinkers. Our findings demonstrate an important role of alcohol cessation on esophageal and head and neck carcinogenesis.
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Key words: alcohol consumption; cessation; esophageal cancer; head and neck cancer; pooled analysis; polynomial regression

Epidemiological studies have consistently shown an association between alcohol consumption and cancers of the oral cavity, pharynx, larynx and oesophagus,[1–3] with a clear dose-response relationship.[4,5] Consequently, the International Agency for Research on Cancer stated "sufficient evidence" for alcohol consumption being a cause for these cancers already in 1987.[3] Many studies reported that alcohol is one of the major risk factors responsible for increased risk of oesophagus[6–8] and head and neck cancer[9–11] in many countries of the world, especially in countries with heavy alcohol consumption.[12] The risk of head and neck cancer is 3–10 times greater in heavy drinkers (≥80 g/day of pure alcohol) than in abstainers, and the carcinogenic effect of alcohol consumption is strongest in the oral cavity and pharynx.[12,13] Although alcohol consumption and smoking are often correlated, an elevated risk has been demonstrated independently in drinkers who do not smoke.[4,14]

The mechanisms of cancer causation by alcoholic drinks are not understood fully and may differ by target organ.[2] Ethanol may promote carcinogenesis by a variety of mechanisms: DNA damage by acetaldehyde and ethanol; nutritional deficiencies (*e.g.* in vitamin A) associated with heavy drinking; carcinogenic effect of chemicals other than ethanol present in alcoholic beverages (*e.g. N*-nitrosamines); the induction of microsomal enzymes that enhance the metabolic activation of other carcinogens (*e.g.* those in tobacco) and the capacity of alcohol to solubilize carcinogens or enhance their penetration in the tissues.[2,12,15]

Relatively few epidemiological studies have examined the effect of stopping drinking on the risk of malignant neoplasms. The majority of these studies were relatively consistent in their findings of demonstrating a reduction in risk in developing cancers of the oral cavity, pharynx, larynx and esophagus when someone stops drinking; however, the amount of risk reduction and the time periods after which a reduction occurred varied. The purpose of this study was to conduct a pooled analysis to evaluate the temporal sequence and strength of the association between alcohol drinking cessation and reduction in esophageal and head and neck cancer risks. Quantification of the potential beneficial effects of quitting drinking on the risk of developing cancer will have important public health implications for prevention and health promotion and provide further evidence on the causal role of alcohol in developing cancer.

Material and methods

Identification of relevant studies

Search of the literature on time dependent risks after reduction/quitting of drinking for esophageal cancer and head and neck cancer was performed in November–December 2006. The following key search terms were used: (["mouth cancer" OR "oral cavity cancer" OR "oropharynx cancer" OR "oropharyngeal cancer" OR "pharyngeal cancer" OR "head and neck cancer" OR "esophageal cancer"] AND "alcohol") AND ("risk" OR "association") AND ("cessation" OR "stopping drinking" OR "quitting drinking" OR "abstinence"). This search was performed in multiple electronic bibliographic databases, including: Ovid MEDLINE (1966–2006), PubMed (1980–2006), EMBASE (1980–2006), Web of Science (including Science Citation Index, Social Sciences Citation Index, Arts and Humanities Citation Index) and PsychINFO (1980–2006). In addition, manual reviews of the content pages of major epidemiology journals were conducted as well as citations in any of the relevant articles. The search was restricted to the English language only.

A total of 39 studies were found for esophageal cancer and 56 studies for head and neck cancers in the initial broad search. Of these studies, only 19 contained topic matter on odds ratios (ORs) and its corresponding 95% confidence intervals (CI) or underlying number of cases and controls for esophageal cancer, and 27 for head and neck cancer. Nine studies on esophageal cancer and 18 studies of head and neck cancer were eliminated because they did not assess quantitative risk estimates after quitting of drinking in time. One study[16] was conducted on both esophageal and head and neck cancers. The remaining studies were not unique. The data from a series of 4 case-control esophageal cancer studies[17–20] were included and published in a pooled study by Castellsague

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***Correspondence to:** Centre for Addiction and Mental Health, 33 Russell Street, room 2035B, Toronto, Ontario, Canada M5S 2S1.
Fax: +416-260-4156. E-mail: jtrehm@aol.com

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TABLE I – CHARACTERISTICS OF IDENTIFIED CASE-CONTROL STUDIES ON ALCOHOL CESSATION AND OESOPHAGEAL AND HEAD AND NECK CANCER RISK

Reference	Country of study	Year of study	Cancer	Specification of gender			Cases	Controls
				M	W	Both		
Oesophagus								
Bosetti *et al*., 2000[4]	Italy & Switzerland	1992–1999	Squamous-cell carcinoma			√	403	1,069
Castelletto *et al*., 1994[17a]	Argentina	1986–1989	Squamous-cell carcinoma			√	131	261
Castellsague *et al*., 1999[21]	Argentina, Brazil, Paraguay & Uruguay	1986–1992	Squamous-cell carcinoma	√	√		739	1,647
Castellsague *et al*., 2000[31b]	Argentina, Brazil, Paraguay & Uruguay	1986–1992	Squamous-cell carcinoma			√	550	1,195
Cheng *et al*., 1995[23]	Hong Kong	1989–1990	Not specified			√	396	1,589
De Stefani *et al*., 1990[18a]	Uruguay	1985–1988	Squamous-cell carcinoma	√			199	398
Martinez, 1969[16]	Puerto Rico	1966	Epidermoid carcinoma	√			61	87
Rolon *et al*., 1995[19a]	Paraguay	1988–1991	Not specified			√	131	381
Victora *et al*., 1987[20a]	Brazil	1985–1986	Squamous-cell carcinoma			√	172	342
Zambon *et al*., 2000[24]	Italy	1992–1997	Squamous-cell carcinoma	√			274	593
Head and neck								
Altieri *et al*., 2002[22]	Italy & Switzerland	1992–2000	Squamous-cell carcinoma of larynx			√	526	1,297
Balaram *et al*., 2002[25]	India	1996–1999	Oral cavity (not specified)			√	251	230
Castellsague *et al*., 2004[26]	Spain	1996–1999	Oral cavity & oropharynx (not specified)			√	375	375
De Stefani *et al*., 2004[27]	Uruguay	1997–2003	Squamous-cell carcinoma of hypopharynx	√			85	640
De Stefeni *et al*., 2004[27]	Uruguay	1997–2003	Squamous-cell carcinoma of larynx	√			235	640
Franceschi *et al*., 2000[28]	Italy & Switzerland	1992–1997	Oral cavity & pharynx (not specified)			√	754	1,775
Garrote *et al*., 2001[29]	Cuba	1996–1999	Oral cavity & oropharynx (not specified)			√	200	200
Hayes *et al*., 1999[30]	Puerto Rico	1992–1995	Oral cavity (not specified)	√	√		649	904
Martinez, 1969[16]	Puerto Rico	1966	Epidermoid carcinoma of pharynx			√	43	43
Martinez, 1969[16]	Puerto Rico	1966	Epidermoid carcinoma of oral cavity			√	136	138
Talamini *et al*., 2002[5c]	Italy & Switzerland	1992–2000	Squamous-cell carcinoma of larynx			√	526	1,297

M, men; W, women.

[a]Not included in the analysis because this study was a part of the larger study by Castellsague *et al*., 1999.–[b]Not included in the analysis because the same cases and controls were included in Castellsague *et al*., 1999.–[c]Not included in the analysis because the same cases and controls were included in Altieri *et al*., 2002.

TABLE II – ODDS RATIOS BY YEARS SINCE DRINKING CESSATION

Study	Years since drinking cessation[a]	Odds ratio
Oesophageal cancer		
Bosetti *et al*., 2000[4]	1–5 yr	0.85
	6–14 yr	1.72
	≥15 yr	0.53
	Never drinker	0.31
Castellsague *et al*., 1999; M[21]	1–4 yr	0.90
	5–9 yr	0.80
	≥10 yr	0.60
	Never drinker	0.23
Castellsague *et al*., 1999; W[21]	1–4 yr	1.30
	≥5 yr	0.60
	Never drinker	0.50
Cheng *et al*., 1995[23]	0–1 yr	2.50
	1–4 yr	1.50
	5–9 yr	0.50
	10–14 yr	0.80
	≥15 yr	0.20
	Never drinker	0.60
Martinez, 1969; M[16]	10 yr or more	0.29
	Never drinker	0.35
Martinez, 1969; W[16]	10 yr or more	1.45
	Never drinker	0.66
Zambon *et al*., 2000[24]	<10 yr	2.38
	≥10 yr	0.54
	Never drinkers	0.10
Head and Neck cancer		
Altieri *et al*., 2002[22]	1–5 yr	1.24
	6–19 yr	1.29
	≥20 yr	0.53
	Never drinker	0.56
Balaram *et al*., 2002[25]	<10 yr	0.94
	≥10 yr	0.62
	Never drinker	0.35
Castellsague *et al*., 2004[26]	1–2 yr	1.22
	3–7 yr	0.58
	8–13 yr	0.68
	≥14 yr	0.48
	Never drinker	0.29
De Stefani *et al*., 2004 (Hypopharynx)[27]	1–4 yr	1.35
	5–9 yr	1.30
	10+ yr	0.43
	Never drinker	0.16
De Stefani *et al*., 2004 (Larynx)[27]	1–4 yr	1.94
	5–9 yr	1.19
	10+ yr	0.47
	Never drinker	0.64
Franceschi *et al*., 2000[28]	1–3 yr	1.21
	4–6 yr	1.82
	7–10 yr	3.29
	≥11 yr	1.91
	Never drinker	0.52
Garrote *et al*., 2001[29]	<10 yr	0.74
	≥ 10 yr	0.28
	Never drinker	0.50
Hayes *et al*., 1999; M[30]	Up to 2 yr	0.95
	2–9 yr	1.61
	10–19 yr	1.07
	20+ yr	0.55
	Never drinker	0.40
Hayes *et al*., 1999; W[30]	Up to 2 yr	0.77
	2–9 yr	1.70
	10–19 yr	1.42
	20+ yr	1.13
	Never drinker	0.91
Martinez, 1969; M; (Pharynx)[16]	10 yr or more	0.22
	Never drinker	0.19
Martinez, 1969; Both M & W; (Pharynx)[16]	10 yr or more	0.22
	Never drinker	0.53
Martinez, 1969; M; (Oral cavity)[16]	10 yr or more	0.32
	Never drinker	0.64
Martinez, 1969; Both M & W; (Oral cavity)[16]	10 yr or more	2.67
	Never drinker	1.33

M, men; W, women.

TABLE III – POOLED ODDS RATIO (OR) AND COORESPONDING 95% CONFIDENCE INTERVALS (CI) ASSOCIATED WITH ALCOHOL CESSATION[1]

Years since cessation	OR (95% CI)	*p*-value
Oesophageal cancer		
>0–2 yr	2.50 (2.23–2.80)	<0.001
2–5 yr	1.10 (1.03–1.17)	<0.006
5–10 yr	0.85 (0.78–0.92)	<0.001
10–15 yr	0.85 (0.79–0.92)	<0.001
15+ yr	0.37 (0.33–0.41)	<0.001
Never drinker	0.37 (0.35–0.39)	<0.001
Head and neck cancer		
>0–5 yr	1.12 (1.06–1.19)	<0.001
5–10 yr	1.26 (1.18–1.35)	<0.001
10–16 yr	0.67 (0.63–0.73)	<0.001
16+ yr	0.72 (0.65–0.78)	<0.001
Never drinker	0.46 (0.43–0.48)	<0.001

[1]Current drinker being reference category.

et al.[21]; as a result, information from the pooled study were taken for analysis, as these data were sex-specific. Similarly, both the Talamini *et al*.[14] and Altieri *et al*.[22] studies were based on the same data. Only the latter study was included in the analysis because of availability of ORs with current drinkers as a reference group. The final list of included articles in the analyses was comprised of 5 studies of esophageal cancer[4,16,21,23,24] and 8 studies of head and neck cancer[16,22,25–30] that examined the effect of cessation of alcohol drinking on the risk of these malignant neoplasms (See Table I for an overview).

Statistical analysis

We extracted the ORs and 95% CIs around it, adjusted for smoking where possible, using the current drinker group as a reference category. A sensitivity analysis was carried out containing only smoking adjusted ORs. Where available, ORs adjusted for sociodemographic factors were also used. Where a "never drinker" category was available as a reference category, other categories were rescaled to make current drinkers the reference group. Pooled estimates were derived from logarithmized OR, weighted by reciprocals of squared standard errors (SEs).[32] SEs were calculated based on Rothman and Greenland.[33]

We assigned the midpoint of the corresponding range of time since cessation of alcohol (in years) to each category as the exposure value. When the highest category was open-ended (*e.g*., 10 yr or more, 15 yr or more *etc*), we assumed the width of the interval to be the same as in the preceding category. For estimation, we ran 2 types of regression analyses to explore the influence of number of years since cessation of alcohol on cancer. First, a multiple regression analysis through the origin with years after cessation, sex and never drinker as categorical independent variables was used (see also Ref. 34 for similar analytic strategies). Second, a third order polynomial (cubic) regression analysis through the origin was used with years after cessation as continuous independent variable. For "never drinker" we assumed 30 yr since cessation. All statistical analyses were done with SPSS Statistical software, version 15.0.

Results

We identified 13 unique case-control studies with a total of over 5,000 cases to separately evaluate the associations of years of drinking cessation with 5 unique studies of esophageal cancer (1,873 cases) and 8 unique studies of head and neck cancer (3,254 cases) (see Table II).

In Table III we present the pooled OR of esophageal cancer and head and neck cancer comparing the risk for different categories of alcohol cessation with the current drinkers.

The results showed that apart from an increased risk among those who recently stopped, there was a clear decrease in risk with longer periods of abstention. Alcohol cessation was negatively and

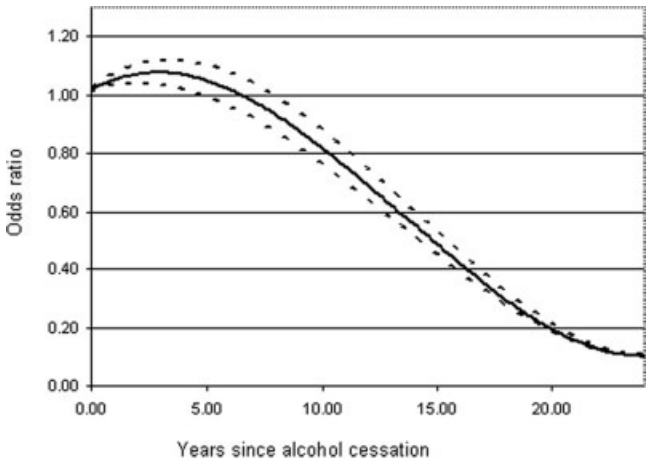

FIGURE 1 – Effect of drinking cessation on esophageal cancer risk by duration (cubic regression).

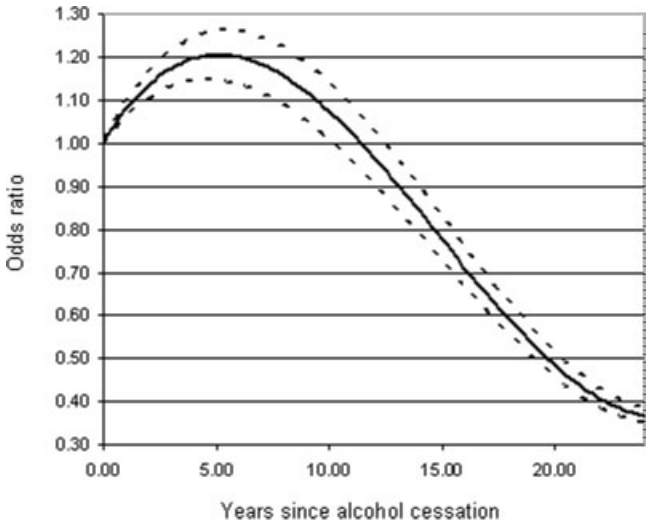

FIGURE 2 – Effect of drinking cessation on head and neck cancer risk by duration (cubic regression).

significantly ($p < 0.001$) associated with the esophageal cancer risk ($OR_{\text{highest category } vs. \text{ current drinker}} = 0.37$, 95% CI: 0.33–0.41) and head and neck cancer risk ($OR_{\text{highest category } vs. \text{ current drinker}} = 0.72$, 95% CI: 0.65–0.78) after 15 or 16 yr. However, within 2 yr of drinking cessation the esophageal cancer risk increased (esophageal $OR_{>0–2 \text{ yr}} = 2.50$, 95% CI: 2.23–2.80) before it started to decrease rapidly. A weaker yet significant increase was found in esophageal cancer in 2–5 yr after cessation ($OR_{2–5 \text{ yr}} = 1.10$, 95% CI: 1.03–1.17). After 15 yr of quitting drinking the risk estimate for esophageal cancer ($OR_{15+ \text{ yr}} = 0.37$, 95% CI: 0.33–0.41) almost reached the level of risk of the never-drinkers ($OR_{\text{never drinkers}} = 0.37$, 95% CI: 0.35–0.39). The exact shape of the curve was sex-specific. Figure 1 summarizes the overall effect of drinking cessation on reducing esophageal cancer risk.

The risk for head and neck cancers stayed elevated for a time period of 5–10 yr of drinking cessation ($OR_{5–10 \text{ yr}} = 1.26$, 95% CI: 1.18–1.35). For exdrinkers the required minimum cessation time for a statistically significant risk reduction was 10–16 yr ($OR_{10–16 \text{ yr}} = 0.67$, 95% CI: 0.63–0.73), and this risk reduction prevailed for longer periods of quitting ($OR_{16+ \text{ yr}} = 0.72$, 95% CI: 0.65–0.78). The level of risk of the never-drinkers was still smaller ($OR_{\text{never drinkers}} = 0.46$, 95% CI: 0.43–0.48). Again, the exact shape of the curve was sex-specific. Figure 2 summarizes the overall effect of drinking cessation on reducing head and neck cancer risk.

TABLE IV – POOLED ODDS RATIO (OR) AND COORESPONDING 95% CONFIDENCE INTERVALS (CI) ASSOCIATED WITH ALCOHOL CESSATION[1]—SENSITIVITY ANALYSIS OF STUDIES ADJUSTED FOR SMOKING

Years since cessation	OR (95% CI)	*p*-value
Oesophageal cancer		
>0–2 yr	2.50 (2.23–2.80)	<0.001
2–5 yr	1.10 (1.03–1.18)	<0.004
5–10 yr	0.85 (0.79–0.92)	<0.001
10–15 yr	0.85 (0.79–0.92)	<0.001
15+ yr	0.35 (0.31–0.39)	<0.001
Never drinker	0.37 (0.35–0.39)	<0.001
Head and neck cancer		
>0–2 yr	1.43 (1.31–1.56)	<0.001
5–10 yr	1.34 (1.22–1.46)	<0.001
10–16 yr	0.83 (0.76–0.91)	<0.001
16+ yr	0.53 (0.39–0.72)	<0.001
Never drinker	0.48 (0.45–0.51)	<0.001
–	–	–

[1]Current drinker being reference category.

The results of the sensitivity analyses based on only smoking adjusted ORs can be found in Table IV. There are no substantially different conclusions, although for head and neck cancers the OR in the first years after drinking cessation is slightly higher.

Discussion

Malignant neoplasms take years to develop. According to different sources the latency period between exposure to the carcinogen and the development of signs and symptoms of cancer is from 15 to 30 yr or longer.[12,35] Thus, stopping consumption of alcohol does not immediately reduce the risks for neoplasms to the risk of never drinkers; instead it may take decades before this risk has decreased to this level. This result is also consistent with previous findings.[36,37] For both cancers, we found an elevated risk among recent abstainers. The explanation for this phenomenon lies probably in the so-called "sick quitter" behavior,[38,39] *i.e.* people stopped drinking alcohol after they felt symptoms and/or other health effects. This result was similar to findings in prospective and case-control studies on the cessation of smoking and the risks of lung cancer.[40–42]

This work has some limitations. It was based on a dichotomous variable (drinking *vs.* not drinking) and did not take into consideration either the amount of alcohol consumption before quitting or type of alcoholic beverages. While type of beverage may not be important, as recent systematic evaluations found no beverage-specific effects, both for esophageal and head and neck cancers, a clear dose-response relationship has been reported.[1] Whether this dose-response relationship is also evident in overall volume over the years is an unanswered question.[13,43] Apart from this, please note that the results from this study are entirely from retrospective studies. While case-control studies are the simplest and cost-effective study designs to estimate effects of behavioral changes in the past, they are also susceptible to a number of information and selection biases.[44] Most notably in our case is recall bias, *i.e.* the possibility, that the status being a case or a control person may have influenced recall of alcohol consumption. While this bias cannot be excluded, the public awareness of alcohol as a risk factor for cancer is not very high, so there may not be a large bias in this direction (*e.g.* Ref. 45). However, in any case, the current literature does not allow any more refined analysis on cessation of alcohol consumption than the one presented here (see Ref. 46 for a more general critique).

In spite of the limitations discussed earlier, this pooled analysis is based on a comprehensive search of the published literature on alcohol cessation and esophageal and head and neck cancers, and

consequently provides the most accurate OR estimates after quitting drinking for both cancers studied. The analyses indicate that cessation of alcohol is strongly linked to a reduction of risks in esophageal and head and neck cancers on the long run, giving further evidence to the role of alcohol consumption as carcinogenic, as reversal of risk after removal of harmful exposure is a classic criterion for causality.[47]

The risk reductions are quite large, especially for esophageal cancer, with a 63% risk reduction after 15 yr of quitting, virtually identical with the risk of never drinkers. It should be noted that quitting drinking also eliminates any risk resulting from an interaction of drinking and smoking.[48] Thus, in terms of cancer prevention, cessation of drinking may play an important role. If drinking is stopped because of policy measures rather than individual decision based on symptoms, we also would not expect the dip in increased risk shortly after cessation, because of the "sick quitter" effect. As consumption of alcohol is deeply ingrained in many cultures[49] and has a cardioprotective effects in light doses,[50] cessation may not be an option for many drinkers. For these people not willing to give up drinking completely, given the monotonic dose-response curve for the cancers examined,[13] reduction of volume also would help in reducing the cancer risk.

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