



## Alcohol, smoking and risk of oesophago-gastric cancer



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### ABSTRACT

Oesophago-gastric cancers (oesophageal and gastric cancers) are common, highly fatal cancers. Oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC) are the two main histological subtypes of oesophageal cancer. Globally, OSCC remains the most common histological subtype of oesophageal cancer, with the highest burden occurring along two geographic belts, one from north central China through the central Asian republics to northern Iran, and one from eastern to southern Africa. In Western countries, the incidence of OAC has increased dramatically over the past 40 years. OAC is now the most common subtype of oesophageal cancer in the United States, United Kingdom, and Australia. Approximately 90% of gastric cancers are adenocarcinoma, with the majority of cases diagnosed in Eastern Asia, Eastern Europe, and some Latin American countries. Smoking is an established risk factor for both oesophageal (OSCC and OAC) and gastric cancers. Alcohol consumption, however, is strongly associated with increased risk of OSCC and probably increases the risk of gastric cancer, but is not associated with OAC. Here, we review the current epidemiological evidence on associations between alcohol consumption, smoking and the risk of developing oesophago-gastric cancer, and emphasize the importance of focusing efforts on controlling the worldwide burden of oesophago-gastric cancer by reducing alcohol and tobacco use.

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### 1. Introduction

Oesophago-gastric cancer refers to cancers of the oesophagus or the stomach. Globally, oesophageal and gastric cancers are common, highly fatal cancers with overall mortality to incidence ratios greater than 0.75. Alcohol and smoking, alone and in combination, are associated with increased risks of cancers at various sites. Here, we review the current epidemiological evidence on associations between alcohol consumption, smoking and the risk of developing oesophago-gastric cancer (Table 1).

### 2. Oesophageal cancer

According to the most recent world estimates, 456,000 new cases of oesophageal cancer (representing 3.2% of all cancers cases)

and 400,000 deaths from oesophageal cancer occur annually. Oesophageal cancer is therefore responsible for about five percent of all deaths from cancer worldwide and is the eighth most common cancer worldwide in 2012 [1]. However, a marked geographical variation exists in both the incidence and mortality rates for oesophageal cancer [1]. The highest incidence rates of oesophageal cancer are seen along two geographic belts, one from north central China through the central Asian republics to northern Iran, and one from eastern to southern Africa. Despite many recent advances in diagnosis and treatment, the prognosis for persons diagnosed with oesophageal cancer is poor. The average overall 5-year survival rate for person diagnosed with oesophageal cancer in developed countries remains <20% [2].

There are two main histological subtypes of oesophageal cancer: oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC). The aetiologies of OSCC and OAC are very different [3]. Globally, OSCC remains the most common histological subtype of oesophageal cancer, representing ~87% of all oesophageal cancer cases diagnosed worldwide in 2012. While this is due largely to high incidence rates in many developing countries, the incidence rates for OSCC are significantly higher than the rates for OAC in 90% of all countries presented in the International Agency

Abbreviations: BEACON, Barrett's and Esophageal Adenocarcinoma Consortium; BO, Barrett's oesophagus; OAC, Oesophageal adenocarcinoma; OSCC, Oesophageal squamous cell carcinoma.

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**Table 1**  
Summary of the associations between alcohol consumption and smoking and the risk of oesophago-gastric cancer.

Risk factor	Cancer Type	Subtype	Magnitude of risk	
Alcohol Consumption	Oesophageal cancer	Barrett's oesophagus (precursor)	0	
		Oesophageal adenocarcinoma	0	
		Oesophageal squamous cell carcinoma	++	
Smoking	Gastric cancer		+	
		Oesophageal cancer	Barrett's oesophagus (precursor)	+
			Oesophageal adenocarcinoma	+
Oesophageal squamous cell carcinoma	++			
Smoking cessation > 10 years	Gastric cancer		++	
		Oesophageal cancer	Barrett's oesophagus (precursor)	0
			Oesophageal adenocarcinoma	-
Oesophageal squamous cell carcinoma	-			
Multiplicative effects	Gastric cancer		-	
		Oesophageal cancer	Barrett's oesophagus (precursor)	0
			Oesophageal adenocarcinoma	0
Oesophageal squamous cell carcinoma	+++			
	Gastric cancer		+	

0, no association; +, low to moderate increase in risk; ++, moderate to high increase in risk; +++, high increase in risk; -, low to moderate inverse association; --, moderate to high inverse association; ---, strong inverse association.

for Research on Cancer GLOBOCAN project (Fig. 1). The highest burden of OSCC occur in developing countries, such as Eastern/South-East Asia, sub-Saharan Africa and Central Asia [4]. However, the highest burden of OAC occurs in Northern and Western Europe, Northern America and Oceania [4,5]. Over the past 40 years, there has been a dramatic shift in the epidemiology of oesophageal cancer in Western populations. The incidence of OSCC has decreased, while the incidence of OAC has increased sharply in most Western countries [6,7]. As described in detail below, studies have consistently shown that alcohol consumption and smoking are the main risk factors for OSCC; however, while smoking is associated with increased risk of OAC, there is no association between alcohol consumption and the risk of OAC [8].

### 2.1. Oesophageal squamous cell carcinoma

OSCC occurs mostly in flat cells lining the upper two-thirds of the oesophagus [8]. During the period when rates of OAC were increasing dramatically in many Western populations, rates of OSCC declined in these same populations. Worldwide, 398,000 new cases of OSCC were diagnosed in 2012 (278,000 in men, 120,000 in women) with highest incidence in Eastern/South-East Asia (8.8 per 100,000 persons), followed by sub-Saharan Africa (5.1 per 100,000 persons) and Central Asia (4.7 per 100,000 persons) (Fig. 2) [4]. Approximately 80% of OSCC cases (315,000 cases) occurred in the Central and South-East Asian region, especially in China - the country alone accounted for 53% of the global burden of OSCC cases. The overall burden of OSCC in the United States is low, with higher incidence rates observed among African Americans than among Caucasians [4,9].

The regional distributions of OSCC roughly mirror the rates of alcohol consumption and smoking. China, the country with the highest incidence rates for OSCC, consumes the most cigarettes per person; an estimated 45% of men and 2% of women in China are current smokers (The Tobacco Atlas, <http://www.tobaccoatlas.org/topic/cigarette-use-globally/>). Studies from high-incidence regions in Africa also suggest that alcohol consumption and smoking contribute substantially to the high burden of OSCC in that region [10,11]. In Western populations, heavy alcohol consumption and smoking are the main risk factors for OSCC, such that alcohol consumption and smoking have been estimated to account for 80% and 40% of OSCC cases in men and women, respectively [12]. The declining incidence of OSCC in many Western populations is thought to be due to the decreasing consumption of alcohol and

lower rates of smoking.

#### 2.1.1. Risk associated with alcohol consumption

Epidemiological studies have consistently linked higher alcohol consumption with increased risk of OSCC, and reported a strong dose-response relationship [13–15]. Compared to people who have never consumed alcohol, the risk of OSCC is three to five times higher among people who have ever consumed alcohol [14,16]. A pooled analysis of individual level data from 7 studies (5 case-control and 2 cohort studies) participating in the International Barrett's and Oesophageal Adenocarcinoma Consortium (BEACON) found increased risk for OSCC associated with increasing numbers of drink-years [13]. Compared to lifelong non-drinkers of alcohol, the risk of OSCC among persons who reported consuming 3–<5, 5–<7 and  $\geq 7$  drinks per day were 5-fold (Odds Ratio [OR], 4.56; 95% confidence interval [CI], 2.32–8.96), 7-fold (OR, 7.17; 95% CI, 2.98–17.25) and 10-fold (OR, 9.62; 95% CI, 4.26–21.71) higher, respectively. In their meta-analysis of 40 case-control studies and 12 cohort studies, Islami et al. showed that moderate and high alcohol drinking were associated with an increased risk of OSCC in studies conducted in both Asian (Relative Risk [RR], 2.17; 95% CI, 1.58–2.96; RR, 4.02; 95% CI 2.76–5.83; respectively) and non-Asian (RR, 2.34; 95% CI, 1.90–2.88; RR, 5.73; 95% CI, 4.41–7.44; respectively) countries [15]. These associations were also present among never-smokers (RR, 1.54; 95% CI, 1.09–2.17 for moderate, and RR, 3.09; 95% CI, 1.75–5.46 for high intakes) [15]. While for light alcohol drinking, increased OSCC risk was observed only for studies conducted in Asian countries (RR, 1.63; 95% CI, 1.20–2.22), however, a dose-response relationship between alcohol consumption and the risk of OSCC was observed in both Asian and non-Asian countries [15]. Another meta-analysis of 34 studies from Asia, Europe and South America assessed the effect of alcohol consumption on the risk of OSCC and found no differences in the effect of association by race [17].

Studies investigating associations with specific types of alcoholic beverages (e.g., beer, wine, etc.) have shown inconsistent patterns of association. In several large studies, heavy consumption of beer or liquor has been associated with significantly increased risks of OSCC [14], whereas in populations where beer consumption was much lower than other types of alcoholic beverages, an inverse association with beer has been observed [18]. A J-shaped relationship has been observed with wine consumption, where the risks were lower among those consuming less than three drinks per day on average and then shifted towards a significantly increased

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