Published in final edited form as:

Gastroenterology. 2009 April ; 136(4): 1155. doi:10.1053/j.gastro.2009.02.021.

Alcohol Drinking and the Risk of Barrett's Esophagus and Esophageal Adenocarcinoma

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A little wine sometimes, that's all. Spirits are bad. Alcohol wrong.

-Bob Marley

Esophageal adenocarcinoma (EAC) has acquired an increasingly amount of interest during recent years, prompted by the fact that its incidence has been increasing rapidly in several regions in Europe, North America, and Australia. Most EAC cases arise in the setting of a detectable preneoplastic lesion known as Barrett's esophagus (BE). It has become well established that gastroesophageal reflux disease (GERD) is a common and strong risk factor (i.e., with a large attributable fraction) for both BE and EAC. However, given that GERD symptoms are very common, and that only 5-10% of patients with GERD symptoms develop BE and only a small fraction of those ever develop EAC, there is great interest in additional or modifying risk factors for BE and EAC.

In addition to GERD, previous studies indicated that a high body mass index (BMI) and a large waist circumference are independently and strongly linked with an increased risk of BE as well as EAC, while tobacco smoking increases these risks only to a moderate extent. While heavy alcohol drinking since long has been strongly and consistently linked to increased risk of esophageal squamous cancer, its role in BE and EAC is less studied. For EAC, the more recent large population-based studies consistently show a lack of association with alcohol consumption(1-4). For BE, hospital-based studies reported either a slight increase in BE risk with liquor intake or no association with overall alcohol intake (5-7).

Recently, *Gastroenterology* has published findings from three population-based case-control studies examining the association between alcohol and BE (2 studies) (8;9) and EAC (2 studies) (8;10). The studies were conducted in three different continents (Table 1) and had some differences in the sampling frame, case definition, method of ascertaining alcohol consumption, and the adjustment for possible confounders. There was no overall effect of alcohol intake on BE or EAC. However, modest wine intake was associated with a lower risk of BE and EAC.

The studies had several strengths including the population-based design, the large sample size, and the more detailed analyses of the association between alcohol drinking and BE or EAC. The external validity of having similar results from three unrelated studies strengthens the validity of the results of these studies.

Yet, these findings have to be interpreted with caution due to multiple sources of bias. Case control comparisons are susceptible to selection, information and survival biases. First, residual confounding is possible in all three studies from misclassification or inaccurate analysis of known confounders (e.g., GERD symptoms), or from unknown or unmeasured confounders (e.g., food items that accompany wine consumption, additives, socioeconomic status). Second, patients with GERD, and especially those with BE who typically have the physiological and pathological changes of severe GERD, are likely to avoid wine drinking if it precipitates GERD symptoms. Alcohol has been demonstrated to reduce the LES pressure and to precipitate GERD symptoms. Hence, the seemingly protective effect of wine may be an aversion effect. Third, heavy alcohol drinking adversely affects survival following the diagnosis of esophageal adenocarcinoma, thus participants in the study are less likely to be alcohol drinkers than the overall population of cases with EAC. The effects of survival bias are likely to be greater in studies with low participation. Fourth, it is notoriously difficult to assess the true exposure to alcohol consumption, particularly if the data collection is retrospective. The misclassification is therefore likely considerable. Whether or not this misclassification is differential or not is not clear. Cases and controls in all three studies were aware of their diagnoses and therefore recall bias may be present. Differential responses in cases and controls and potentially biased recall estimates of exposure in cases could have influenced the results (Table 1). Lastly, the internal consistency was not strong in these studies; for example, in the study by Kubo et al. protective effect was observed only in comparison to population-based controls and not endoscopy controls(9), and in the study by Anderson et al. wine was inversely associated with BE and EAC in Northern Ireland but not in the Republic of Ireland(8). Logical but complicated explanations of this finding include the fact that endoscopy controls may also reduce their wine intake because of underlying GERD/dyspepsia thus making them similar in that regard to patients with BE.

The three studies combined, but none individually since none was designed primarily to address alcohol consumption, are informative about the extent of detailed alcohol intake history required to enable calculation of life time intake, timing of the intake in relationship to age (20s, 30s, etc.) or diagnosis of disease (1 or 5 years prior) and type of alcohol. In addition, the pattern of drinking (binge, steady) may need to be examined. Previous studies indicated that moderate consistent rather than episodic or binge wine drinking was associated with a beneficial reduction in the risk of heart disease. The studies also demonstrate the options for analytic technique including the use of predefined cutoffs, empirically derived cutoffs from the distributions found in the study population, and non-linear assumptions. The relationship between wine consumption and risk of BE or EAC seems to follow a J shaped curve, where both very low and very high intake are associated with increased risk. Where to draw the cutoffs for the transitions in this curve is unclear. There is also a risk that previous (or current) high consumers of alcohol falsely report that they are non-users of alcohol or that previous alcoholics have a history of high alcohol consumption that is not assessed in the data collection of the studies. Such information bias might explain the J shaped curve. To obtain a more detailed picture of alcohol drinking, questions should target lifetime consumption, as well as timing of this consumption, preferably for different types of alcoholic beverages.

Do the secular trends in the amount and type alcoholic beverages fit within the temporal trends of BE and EAC, and with a protective effect of wine drinking? Not really! In the US, the per capita alcohol consumption in the US has fallen by 20% between 1979 and 2000, mainly because of reduced spirits consumption, and less so for beer(11;12). However, wine drinking has remained steady and possibly increased slightly in recent years. While secular trends are prone to ecological bias, they do not indicate a widespread protective effect for wine drinking.

The putative benefits of the ingestion of wine on cardiovascular risks has been well publicized. However, its possible effect on cancer risk is less examined. Wine drinking has been associated

with reduced risk of lung cancer (13). If wine drinking was to be protective from BE or EAC, the authors could only speculate about mechanisms. For example, wine consumption may reduce direct damage of a simultaneous food passage through the esophagus, or the presence of polyphenols may reduce oxidative stress. The anticancer effect of resveratrol, present in red grape skin, has also been raised by the authors. In the one study that distinguished red from white wine, there was a significant reduction associated with modest intake (<40 g/week) of red wine (OR.78, 95% CI.67-.91) but not white wine (8).

Although these interesting findings are suggestive of a protective effect of modest intake of wine with regard to the risk of developing BE or EAC, there are several biases, some of which are practically impossible to control, that make it important to maintain a healthy skepticism of these findings. Possibly, more definitive data will become available from cohort studies and experimental data.

Acknowledgments

Dr. El-Serag by NIH NIDDK K24DK078154-03. Dr. Lagergren by Swedish Research Council and Swedish Cancer Society.

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Table 1

Description of three studies that examined the association between alcohol drinking and the risk of Barrett's esophagus and or esophageal adenocarcinoma

Study	Country	Cases	Controls (source)	Participation Rate	Wine Drinking	Odds Ratio (95% Confidence Intervals)
Pandeya(10)	Australia	362 EAC	1574 (Population)	35% for cases, 51% for controls	Life time	* .84 (.75-.94)
Kubo(9)	USA	320 BE	317 (population); 316 (GERD)	NA	One year prior to the diagnosis	** .44 (.20-.99)
Anderson(8)	Ireland	224 BE, 227 EAC	260 (population)	41% controls, and 74% EAC, 84% BE	5 years prior to diagnosis	*** .45 (.20-1.01)

* Per additional 10g/week

** ≥ 7 drinks/week vs. none

*** >5.5 glasses/week vs. none