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## Moderate alcohol intake and cancer incidence in women

by Professor R. Curtis Ellison, Boston University School of Medicine

Authors of a recent study state that with the exception of breast cancer, little is known about the effect of moderate intakes of alcohol, or of particular types of alcohol, on cancer risk in women. This study is based on a total of 1,280,296 middle-aged women in the United Kingdom who were enrolled in the Million Women Study and were routinely followed for incident cancer. Cox regression models were used to calculate adjusted relative risks and 95% confidence intervals (CIs) for 21 site-specific cancers according to amount and type of alcoholic beverage consumed. All statistical tests were two-sided.

A quarter of the cohort reported drinking no alcohol; 98% of drinkers consumed fewer than 21 drinks per week, with drinkers consuming an average of 10g alcohol per day. During an average 7.2 years of follow-up, 68,775 invasive cancers occurred. Increasing alcohol consumption was associated with increased risks of cancers of the oral cavity and pharynx (increase per 10g/d = 29%, 95% CI = 14% to 45%, P trend < .001), esophagus (22%, 95% CI = 8% to 38%, P trend = .002), larynx (44%, 95% CI = 10% to 88%, P trend = .008), rectum (10%, 95% CI = 2% to 18%, P trend = .02), liver (24%, 95% CI = 2% to 51%, P trend = .03), breast (12%, 95% CI = 9% to 14%, P trend < .001), and total cancer (6%, 95% CI = 4% to 7%, P trend < .001). The trends were similar in women who drank wine exclusively and other consumers of alcohol. For cancers of the upper aerodigestive tract, the alcohol-associated risk was confined to current smokers, with little or no effect of alcohol among never and past smokers (P heterogeneity < .001). Increasing levels of alcohol consumption were associated with a decreased risk of thyroid cancer (P trend = .005), non - Hodgkin lymphoma (P trend = .001), and renal cell carcinoma (P trend = .03). The authors conclude that low to moderate alcohol consumption in women increases the risk of certain cancers. For every additional drink regularly consumed per day, the increase in incidence up to age 75 years per 1,000 for women in developed countries is estimated to be about 11 for breast cancer,

1 for cancers of the oral cavity and pharynx, 1 for cancer of the rectum, and 0.7 each for cancers of the esophagus, larynx, and liver, giving a total excess of about 15 cancers per 1,000 women up to age 75.

**Professor R. Curtis Ellison comments:** This might be considered an important paper because of its size (more than 1.2 million women enrolled and alcohol consumption assessed in a follow-up survey 3 years later in 700,000) and because of its apparently high level of ascertainment of cancer during an average of 7.2 years of follow up. A total of 68,775 cases of cancer were identified, including 28,380 breast cancers, 5,203 lung cancers, and 4,169 colon cancers. Little difference in effect was noted between consumption of wine and consumption of other beverages containing alcohol. The key findings of the study are shown in Figure 1 from the paper (on the following page) which presents multivariable-adjusted linear relations of the “Percent increase in relative risk per 10-g/day increase in alcohol.”

It is unfortunate that the investigators apparently used only linear analysis. This would be inappropriate for studying the association of alcohol intake with CVD and many other diseases, although data are not as clear for the association with cancer. Using this approach does not permit evaluation for a possible “U-shaped” or “J-shaped” relation between alcohol and cancer, and it is not possible to judge if there is a “threshold” of alcohol intake that may increase the risk of certain cancers. Most previous studies have suggested that only heavy drinkers, usually alcoholics, show an increase in risk of upper aerodigestive cancers. Use of a spline or other such analysis would be helpful in evaluating a dose-response pattern in this study.

There are a number of other problems in interpreting the results. Importantly, no data were available on the pattern of drinking: regular drinking versus binge drinking. It has been demonstrated that for the same total alcohol intake, protection against cardiovascular and other diseases is associated with regular drinking,

but such protection is lost if the alcohol is consumed only on weekends.

Comparisons with lifetime abstainers cannot be made from the data presented. Apparently many (probably most) of the “non-drinkers” in this study were ex-drinkers, as they had the highest smoking rates and higher cancer mortality than most moderate drinking groups. Hence, we cannot evaluate differences in cancer risk between true abstainers and light drinkers.

The authors used “floating absolute risks, yielding floating confidence intervals” in their analyses. This is a very controversial approach, and leading epidemiologists have argued that it artificially narrows the calculated confidence intervals, and hence would tend to make borderline relations statistically significant.

Overall, however, the results of this large study largely support previous findings: an increase in upper aerodigestive cancers with alcohol (although a threshold for effect cannot be assessed in the present study), a lesser but positive association between alcohol and cancer of the breast and rectum, and an inverse association between alcohol and thyroid and kidney cancer, and with non-Hodgkins lymphoma.

It is interesting that in these analyses, alcohol did not show an association between alcohol and upper aerodigestive cancers (generally assumed to be “alcohol-related cancers”) among non-smokers. Stratified analyses by level of smoking (light, moderate, heavy smoking, pack-years, etc.) are not presented, and there could also be residual confounding by smoking status. A tendency for an increase in cancer among ex-smokers was shown, but no increase in cancer risk at all among never smokers (as shown in Figure 4 from the report, below). The increase in cancer risk with increasing alcohol intake among current smokers suggests a smoking-alcohol interaction for the development of such cancers.

**Lauer MS, Sorlie P. Alcohol, cardiovascular disease, and cancer: Treat with caution. Editorial. J Natl Cancer Inst 2009;101:282-283**

This editorial accompanying the Allen et al paper did not point out some of the problems in the analyses from that study (e.g., failure to test other than a linear association, not assessing pattern of drinking). Professor Ellison and colleagues from Boston University school of medicine comment on statements from the editorial:

“From a standpoint of cancer risk, the message of this report could not be clearer. There is no level of alcohol consumption that can be considered safe.”

The main analyses of the Allen et al paper are based only on drinkers, as lifetime abstainers could not be identified in their study. The “non-drinking” category undoubtedly contained many ex-drinkers (perhaps explaining why the rates of cancer among non-drinkers were almost always higher than those of light drinkers). This does not mean that “non-drinking” increases your risk of cancer, but at the same time it points out that the publication does not include data making it possible to say that “There is no level of alcohol consumption that can be considered safe.”

“The authors provide no information on all-cause mortality or incident cardiovascular disease events, despite the ability of their data to provide this information. We must hope that the authors plan to report on these outcomes in future publications.”

We agree strongly with this observation. Before anyone considers guidelines for drinking, it is essential that the net effects on health be considered. As an example, in the latest final death statistics from the CDC (for 2005), there were 7,773 deaths in the US from cancer of the lip, oral cavity, or pharynx, diseases generally associated with very heavy drinking. For comparison, there were 856,030 deaths from major cardiovascular diseases, and data strongly indicate that light-to-moderate drinking is associated with a considerable lowering of risk. Basing drinking guidelines or recommendations only on the risk of upper aerodigestive cancers would obviously be inappropriate. We look forward to learning more of the net health effects of alcohol from the authors of the Allen study.

“...the only reasonable recommendation we can make (for middle-aged women) is that there is no clear evidence that alcohol had medical benefits.”

There are no data presented in the Allen et al paper that justifies such a statement. It will be important to see the net health effects of alcohol use among these women in future publications.

Quoting Professor Albus’s statement to Harry Potter (from Rowling JK, *The Tales of Beedle the Bard*) regarding truth: “It is a beautiful and terrible thing, and should therefore be treated with great caution.”

It is indeed important when discussing alcohol to treat the subject with great caution. However, unless regular moderate drinking is differentiated from binge drinking or other abusive use of alcohol, and unless the net effects of alcohol consumption on health are known, one has great difficulty learning the “truth.”

**Figure 1.** Estimated increase in the relative risk (95% confidence interval) of incident cancer per 10-g/d increase in alcohol intake (drinkers only). Analyses are adjusted for age, region of residence, socioeconomic status, body mass index, smoking, physical activity, use of oral contraceptives and hormone replacement therapy. CI=confidence interval. ICD-10=International Classification of Diseases, 10th Revision (the C00-C97 codes refer to malignant neoplasm codes as defined in ICD-10).

