Alcohol: a recently identified risk factor for breast cancer

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Breast cancer is so common that about 10% of women will be diagnosed with this disease during their lifetime. And yet we know little about its causes. Combining all known risk factors for breast cancer — older age at birth of first child, earlier onset of menses, later age at menopause, increased mammographic density and the presence of specific genes, to name a few — accounts for only about 30% of cases.[1] Thus, in the majority of cases, we cannot identify a known or suspected risk factor. Both alcohol and tobacco are known to have important causal roles in a variety of cancers, and breast cancer has not escaped the epidemiologists' critical examination.

Evidence from 53 epidemiologic studies comprising about 80% of the worldwide epidemiologic data on the question of whether alcohol and tobacco are risk factors for breast cancer has been systematically studied by the Collaborative Group on Hormonal Factors in Breast Cancer.[2] Because the consumption of alcohol and tobacco is closely intertwined, the challenge is to disentangle the effects of exposure to these substances. In the simplest scenario, this is done by assessing breast cancer risk associated with alcohol in separate groups of women who never smoked and those who ever smoked, and by assessing the risk associated with tobacco use in separate groups of women who do not drink and those who do drink. This type of subgroup analysis is often difficult to accomplish in individual studies with limited sample sizes. The great advantage of combining the breast cancer studies in the systematic review by the collaborative group is that sufficient statistical power is achieved to address these objectives.

Through this combined analysis, the collaborative group found that alcohol is clearly an independent risk factor for breast cancer, with no confounding by smoking or other risk factors such as parity and age at birth of first child. Furthermore, they found that the risk increased with increasing alcohol consumption, regardless of smoking status. Specifically, there was a 7% increase in risk with each 10 g (about 1 drink) of alcohol per day. This linear dose-response confirms previous findings and argues against a threshold effect for alcohol.[3,4] Among women who reported drinking no alcohol, having ever smoked tobacco was shown to have little or no effect on breast cancer risk compared with having never smoked. Among the women who ever smoked and reported drinking alcohol, the risk of breast cancer increased with increasing alcohol consumption and was higher than the risk among women who ever smoked but reported drinking no alcohol.

Alcohol is a known risk factor for several cancers, including those of the mouth, larynx, esophagus and liver, and it is listed as a known human carcinogen by agencies such as the US National Toxicology Program and the International Agency for Research on Cancer. In terms of mechanisms for causing cancer, it has been postulated that alcohol may alter estrogen levels, themselves known to be associated with breast cancer risk,[5–7] or interfere with DNA repair.[8,9]

Although the systematic review has several methodologic strengths, some limitations are apparent and have been acknowledged by the authors.[2] For example, alcohol was assessed as average consumption, and thus patterns of consumption (e.g., daily compared with "binge" drinking) were not captured. No information was available on the type of alcohol or tobacco consumed, the duration of use, the timing of exposure within the person's lifetime (e.g., age started, age stopped) or passive smoking. These are important limitations and areas of continuing research. Studies published after these data were collected for the combined analysis have looked in much more detail at patterns of alcohol consumption[10–12] and smoking,[13] including passive smoking,[14] and have begun to assess gene–environment interactions.[15,16] This level of precision is what we must strive for to achieve a more in-depth understanding of these relations. For example, women who drink alcohol are more likely than those who do not drink to be in environments with high levels of tobacco smoke, and a recent assessment of 10 studies with breast cancer incidence as the outcome concluded that there may indeed be an association between passive smoking and breast cancer.[17]

Assessment of the effect of potential biases, such as systematic underreporting of alcohol consumption and random misclassification, also raises some questions regarding the precision of the alcohol-related results, but this uncertainty is likely small compared with the weight of the evidence presented. For smoking, the imprecision is greater because measurement of this exposure is crude, assessed only as "ever" compared with "never" having smoked. Other studies, or more in-depth analyses of the 53 included in the combined analysis, will provide better answers on the relation between smoking and breast cancer.

The relation between alcohol and health is even more complex. As noted earlier, most cases of breast cancer have an unknown cause or combination of causes. In this context, is a small (about 10%) increase in breast cancer risk among women who are moderate drinkers, and even a greater increase among those who are heavy drinkers, im-

portant? The association between alcohol consumption and breast cancer risk meets several criteria for causality, such as consistency of results, strength of association and biologic gradient. If alcohol consumption is judged to be a cause of breast cancer, the level of relative risk, because alcohol consumption is relatively common, translates roughly to a population attributable risk of 4% in developed countries. That is, about 4% of new cases of breast cancer can be attributed to drinking alcohol, and in Canada this year, it means that alcohol will account for an astounding 700 new cases. What is important here is that alcohol consumption is one of the few known risk factors for breast cancer that is a potentially modifiable behaviour at both the individual and the societal level.

Mark Twain famously remarked: "Sometimes too much drink is barely enough." Despite the known hazards of drinking, he was at least partially correct: during the past 2 decades, it has become clear that moderate drinking is associated with longer life,[18] reduced rates of myocardial infarction and perhaps decreased risks of stroke and dementia.[19,20]

What does this mean for women? Alcohol almost certainly is a risk factor for breast cancer. When a risk factor is associated with both benefits and harms, should moderate drinking by women be encouraged or discouraged? I believe that public health messages on the benefits of drinking must be heavily weighted by the many negative consequences. According to the World Health Organization, alcohol abuse is estimated to be the fourth leading cause of worldwide disability[21] and accounts for more years of life lost to death and disability than does tobacco or illegal drugs.[22,23] At the individual level, we should also think in terms of who is at risk and direct recommendations accordingly: in general, teens are not at increased risk of heart disease, and consequences of drinking can be tragic; pregnant women should not be encouraged to drink, and men under 40 and women under 50 with no signs of heart conditions are likely not in need of the benefits of alcohol. People who do not drink should not be encouraged to start. However, for some groups, there is a clear benefit of consuming a moderate amount of alcohol. For women, this now must be weighed against increased breast cancer risk. Women who drink should do so at low or moderate levels, and in many cases this will mean drinking less. Although I am wont to agree with Mark Twain, on this occasion I must disagree: *less* drink is enough.

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References

1. Friedenreich C, Aronson KJ, DeKoning K, Goldberg M, Heisey R, Hepburn V, et al. Summary report: review of lifestyle and environmental risk factors for breast cancer. Report of the Working Group on Primary Prevention of Breast Cancer. Ottawa: Health Canada; 2001. Cat no H39-586/2001E. Available: www.hc-sc.gc.ca/pphb-dgspsp/publicat/cbci-iccs01/pdf/cbci_summary_report.pdf (accessed 2003 Mar 28).
2. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW Jr, et al. Alcohol, tobacco and breast cancer — collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Collaborative Group on Hormonal Factors in Breast Cancer. *Br J Cancer* 2002;87(11):1234-45.
3. Longnecker M. Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. *Cancer Causes Control* 1994;5(1):73-82.
4. Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* 1998;279(7):535-40.
5. Reichman ME, Judd JT, Longcope C, Schatzkin A, Clevidence BA, Nair PP, et al. Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. *J Natl Cancer Inst* 1993;85:722-7.
6. Ginsburg ES, Mello NK, Mendelson JH, Barbieri RI, Teoh SK, Rothman, M et al. Effects of alcohol ingestion on estrogens in postmenopausal women. *JAMA* 1996;276:1747-51.
7. Dorgan JF, Baer DJ, Albert PS, Judd JT, Brown ED, Corle DK, et al. Serum hormones and the alcohol–breast cancer association in postmenopausal women. *J Natl Cancer Inst* 2001;93(9):710-5.
8. Wright RM, McManaman JL, Repine JE. Alcohol-induced breast cancer: a proposed mechanism. *Free Radic Biol Med* 1999;26(3-4):348-54.
9. Sellers TA, Vierkant RA, Cerhan JR, Gapstur SM, Vachon SM, Olson J, et al. Interaction of dietary folate intake, alcohol, and risk of hormone receptor-defined breast cancer in a prospective study of postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2002;11(10 Pt 1):1104-7.
10. Lenz SK, Goldberg MS, Labrèche F, Parent ME, Valois MF. Association between alcohol consumption and postmenopausal breast cancer: results of a case–control study in Montreal, Quebec, Canada. *Cancer Causes Control* 2002;13:701-10.
11. Baumgartner KB, Annegers JF, McPherson RS, Frankowski RF, Gillila FD, Samet JM. Is alcohol intake associated with breast cancer in Hispanic women? The New Mexico Women's Health Study. *Ethn Dis* 2002;12(40):460-9.
12. Chen WY, Colditz GA, Rosner B, Hankinson SE, Hunter DJ, Manson JE, et al. Use of postmenopausal hormones, alcohol, and risk for invasive breast cancer. *Ann Intern Med* 2002;137(10):798-804.
13. Terry PD, Miller AB, Rohan TE. Cigarette smoking and breast cancer risk: a long latency period. *Int J Cancer* 2002;100(6):723-8.
14. Kropp S, Chang-Claude J. Active and passive smoking and risk of breast cancer by age 50 years among German women. *Am J Epidemiol* 2002;156(7):616-26.
15. Zheng T, Holford TR, Zahm SH, Owens PH, Boyle P, Zhang Y, et al. Cigarette smoking, glutathione-s-transferase M1 and t1 genetic polymorphisms, and breast cancer risk (United States). *Cancer Causes Control* 2002;13(7):637-45.
16. Chang-Claude J, Kropp S, Jager B, Bartsch H, Risch A. Differential effect of NAT2 on the association between active and passive smoke exposure and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2002;11(8):698-704.
17. Morabia A. Smoking (active and passive) and breast cancer: epidemiologic evidence up to June 2001. *Environ Mol Mutagen* 2002;39(2-3):89-95.
18. Thun MJ, Peto R, Lopez AD, Monaco JH, Henley J, Health CW, et al. Alcohol consumption and mortality among middle-aged and elderly US adults. *N Engl J Med* 1997;337(24):1705-14.
19. Djousse L, Ellison RC, Beiser A, Scaramucci A, D'Agostino RB, Wolf PA. Alcohol consumption and risk of ischemic stroke. The Framingham Study. *Stroke* 2002;33(4):907-12.
20. Ruitenberg A, van Sweiten JC, Witteman JC, Mehta KM, van Duijn CM, Hofman A, et al. Alcohol consumption and risk of dementia. The Rotterdam Study. *Lancet* 2002;359(9303):281-6.
21. Lowenfels AB. Epidemiologic studies of alcohol-related disease in the 20th century. *J Epidemiol Biostat* 2000;5(1):61-6.
22. World Health Organization. *Global status report on alcohol*. Geneva: The Organization; 1999. Cat no WHO/HSC/SAB/99.11. Available: www.who.int/substance_abuse/pubs_alcohol.htm (accessed 2003 Mar 28).
23. Monteiro MG. A World Health Organization perspective on alcohol and illicit drug use and health. *Eur Addict Res* 2001;7(3):98-103.

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