

Predicting risks genetically by Harvey E. Finkel, MD

Our esteemed editor called to my attention that the complete genetic codes of human cancers have been completely mapped for the first time. Although some have called this a breakthrough, from a more detached perspective it is an important increment in a stepwise progression. Let's speculate on its significance to the effects of drinking.

The mappings of a small-cell lung cancer and of a malignant melanoma, two important and difficult cancers, were accomplished by a group of nine research institutions, led by the Wellcome Trust Sanger Institute near Cambridge, England, and reported in the journal *Nature* (January 14, 2010).

It is hoped that elucidation of the basic genetic makeup of cancers will eventually enable vast improvements in assessing risk, in prevention, and in treatment. Carried a step further, mapping of individual human genomes is likely to be similarly enabling with regard to most diseases.

Let me pose a theoretical though common real-life problem as just one example of how intricate knowledge of an individual's genetics can be of great help. Postulate a 40-year-old woman who enjoys moderate portions of wine with her dinners, but who is informed by a television report that drinking may lead to breast cancer, and by a magazine article that drinking may prevent death from heart attack or stroke. She is confused and conflicted. It seems to her she is being forced to choose between two horrible ends: drink, and die of breast cancer with a healthy heart; don't drink, and die of a heart attack, but with non-cancerous breasts (more on these later). What a choice!

What to do? One solution is not to watch medical TV shows and not to read magazine articles on health. And the internet makes three. But with the jinni out of the bottle, it is sensible to consult one's physician. Right now, the physician's tools in predicting risk are crude: reviewing family history and lifestyle, examining the breasts and cardiovascular apparatus, measuring blood pressure, blood sugar, cholesterol, and so on, perhaps ordering a mammogram and cardiac tests. At best, only gross probabilities of relative risk of breast cancer versus heart attack can be guessed at. It is expected, however, that knowing our woman's genetic makeup will enable accurate predictive assignment of risk, so that she can make a

well-informed decision. The same would go for any number of questions of risk about other diseases. In balancing risks and making choices it is imperative to have reliable, complete data, and to interpret the data soundly. Shall we pursue the nuances of the all-important example set above?

The American Heart Association provides, among others, these thought-provoking statistics (<http://www.americanheart.org/presenter.jhtml?identifier=1200026>). One of three women has some form of cardiovascular disease. Since 1984, the number of deaths of women from cardiovascular disease has exceeded those of men. In 2005, for example, more than 454,000 women in the United States died of cardiovascular diseases, nearly 53 percent of all US cardiovascular deaths. These figures are rising. It was expected that more than 500,000 women will have died of cardiovascular disease in 2009, compared to 41,000 breast-cancer deaths, a ratio of nearly 13:1. It seems clear that moderate drinking greatly reduces cardiovascular risk (Djoussé, et al. *Circulation*, July 21, 2009).

Philip Norrie, in his wise and sober analysis of the effects of drinking upon cancer risk (AIM Digest, July 21, 2009), focused on the Framingham Study and the Million Women Study. The former found a decrease in most cancer risks of 20-30 percent among women drinking, on average, from less than half to one and one-half drinks per day, compared to abstainers. The latter study trumpeted a small increase in cancer risk among drinking women, but did not discuss the six percent decrease in cancer among women drinking one or two units per day. In the entire drinking group, some cancers decreased in frequency (thyroid, non-Hodgkin's lymphoma, kidney). Cancers of the mouth, throat, larynx, and esophagus increased in women who drank and smoked. Liver and rectal cancers increased in some cases with drinking at moderate levels. The statistics for breast cancer are suspect, at least because the population studied was attending breast-screening clinics. Other studies of breast cancer and drinking have reported conflicting data, but the weight of studies do suggest a slight increased risk (6%) for moderate drinking women. The ingestion of the vitamin folic acid (folate) may mitigate alcohol's putative carcinogenic effect on breast tissue, and maintaining a low BMI is also an important mitigating factor.

In general, it is readily apparent that cardiovascular disease constitutes a far greater threat to the health and life of women than does breast cancer, hence the beneficial effects of moderate drinking to the cardiovascular system, should be put in the balance.

It is likely that the statistical muddle we get stuck in when trying to determine whether drinking, especially moderate drinking, might affect breast-cancer risk arises because we are looking at a very heterogeneous population. Genetic analysis ought to be able, some day, to dissect out the differences, and define whose risk is how much.

Going a step further, for those already afflicted with cancer there are often several treatment options, the

efficacy of which can only be confirmed after a trial of what might be unpleasant, perhaps even risky, therapy. The cancer cell's sensitivity or resistance to a given treatment is likely to be engraved in its genome, so genetic mapping may provide a shortcut to optimal treatment that is safe, effective, comfortable, and economical.

Finally, we may daydream about being able to alter genomes to reduce risk or facilitate treatment. We are already witnessing partial, nascent realities. We now know that many of the multiple mutations associated with cancer formation occur, and may even be naturally repaired by the cells, long before a cancer develops. We may eventually be able to do the repair work ourselves, rather than to trust to luck.