Partnerships for Promoting Prevention

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In an elegant analysis from the Atherosclerosis Risk In Communities Study, Rasmussen-Torvik and colleagues demonstrate that a higher degree of adherence to the American Heart Association seven health and behavior factors recommended for prevention of cardiovascular disease was also related to substantially reduced incidence of cancer, over a 17-19 year follow-up\textsuperscript{1}. As one might expect, the strongest common risk factor for these two leading causes of death is smoking. Although it is more strongly associated with lung cancer (in terms of relative risk) than with cardiovascular disease, smoking causes more deaths from cardiovascular disease. However, even after excluding smoking from the seven factors, those meeting the goals for 5-6 of these health metrics had a significant 25% lower risk of cancer compared to those who met none of the goals.

The authors expressed surprise to observe a significant trend for increased prostate cancer incidence among men with a larger number of ideal health metrics. The most likely explanation for this entirely predictable result is that health consciousness – including greater adherence to the ideal health metrics – is associated with more PSA screening. It is not widely appreciated that a large fraction, perhaps even a majority, of older men in the US harbor undiagnosed prostate cancer. As an illustration, in two large randomized trials of low risk middle-aged men (PSA_\textless 3 at baseline), random biopsies were conducted after 4 and 7 years of follow-up, in the placebo arms of those trials 25% of the men were diagnosed with prostate cancer, almost entirely low grade and early stage disease\textsuperscript{2,3}. Similarly, autopsy series of men with no prior symptoms of prostate cancer show an age-related prevalence of undiagnosed prostate cancer that exceeds 50% in the oldest age groups in some studies\textsuperscript{4}. Thus, the major risk factor for the diagnosis of prostate cancer is getting a biopsy after screening. For this reason, epidemiologic studies of total prostate cancer incidence are difficult to interpret in the era of PSA screening, and the focus of such study should be on lethal disease\textsuperscript{5}.
The investigators were unable to evaluate advanced or fatal prostate cancer, but they note substantial evidence that smoking is a strong risk factor for fatal prostate cancer. The apparent relation of smoking with lower risk of non-advanced prostate cancer in that same study likely is an artifact of less PSA screening among smokers, as was seen in the Health Professionals Follow-Up Study. Thus, the impact of adherence to the seven healthy metrics on clinically meaningful cancer is even greater than is estimated by the current study. The AHA metric for smoking is defined as never smoking or quitting more than 12 months before. Much, though not all, of the cardiovascular risk from smoking is removed a year after quitting, but the impact of past smoking on cancer risk remains much longer. Thus, life-long adherence to the smoking guideline – i.e. never smoking – would have an even greater impact on reducing cancer risk.

Apart from smoking, the seven AHA metrics include several other factors of great importance for cancer risk: healthy weight, physical activity and healthy diet. Compelling evidence supports a causal link between overweight and obesity and risk of cancer incidence and mortality at several major cancer sites, including endometrial, post-menopausal breast, colorectal, prostate, esophageal, and pancreatic, among others. In the largest and most comprehensive pooled analysis of major studies of body-mass index (kg in weight/ height in meters squared, BMI) and cancer mortality, de Gonzalez found that apparently healthy individuals with BMI over 27.5 had substantially elevated risks of cancer mortality, and those with BMI of 40-50 had 70% higher risk of cancer mortality as compared with those of healthy weight, BMI 20-25. The interpretation of studies of BMI and health are complicated by investigators who ignore the impact of smoking and preclinical or insidious disease on this relation. Smoking and disease are often linked to lower weight, and are, of course, both related to increased mortality risk. When smokers (including those who quit, as that is often due to
health reasons) and those with illnesses are included in such analyses, the lower BMI categories are enriched with those high-risk individuals resulting in the spurious finding that higher BMI yields better health outcomes. In studies predicting mortality, including smokers and sick people in the population show that both obese and low BMI categories are associated with higher mortality rates\(^9\). In contrast, for studies of BMI geared toward prevention – that is, to identify the ideal body weight that healthy adults should strive to attain – one must exclude smokers and those with prevalent disease, and assess BMI at middle age to avoid the influence of preclinical disease on body weight (reverse causation). Such studies clearly demonstrate healthy weight in the BMI range of about 20-25\(^8\).

Smoking and BMI are measured with a reasonably high degree of precision. Therefore, if one can avoid the methodologic pitfalls described above, one can quantify the impact of these risk factors. In contrast, physical activity is measured much less precisely. To the extent that the imprecision in measurement is unrelated to the health outcomes, the association of estimated activity levels with CVD and cancer are likely to underestimate the true impact. Growing evidence suggests that physical activity may reduce the risk of cancer incidence at various sites (including breast, colorectal and lethal prostate cancer), and may improve survival after cancer diagnosis\(^10\). It is unclear whether the same activity parameters will have similar benefits for cancer and CVD. For example, walking at a moderate pace is strongly protective for CVD\(^10\) but only vigorous activity, including brisk walking, was associated with better survival for prostate cancer\(^11\).

The components of Rasmussen-Torvik’s healthy diet score are: fruits and vegetables, fish, fiber-rich whole grains, and limitations on sodium and sugar sweetened beverages. Although much of the early impetus for promoting intake of fruits and vegetables came from a
goal of cancer prevention, the evidence is stronger for reducing risk of CVD, especially stroke. However, recent data suggests that fruits and vegetables reduce risk of estrogen-receptor negative breast cancer. Chiuve and colleagues have described a more comprehensive dietary index, the alternative healthy eating index, which is strongly associated with lower risk of CVD and diabetes. Interestingly, adherence to that index was significantly associated with lower risk of cancer in women, but not in men. Total cancer is a very heterogeneous outcome, and one might expect different associations for different cancer sites. The overlap of CVD risk factors is perhaps most pronounced for diabetes, colorectal cancer, and perhaps cognitive decline.

Nature has not been so obliging as to arrange all risk factors to move in concert. A notable counter example is moderate alcohol consumption, which is strongly linked to lower risk of heart disease, but also with increased risk of breast cancer. Nonetheless, the finding of so much overlap in preventive strategies for seemingly diverse diseases suggests some common basic molecular pathways or networks, whose perturbations yield pleiotropic effects. A network medicine approach to scrutinize the common elements of these shared risk factors may be fruitful. An example of such work is the finding that genetic alterations in the folate metabolism pathway are associated with higher risk of both CVD and colorectal cancer in those with inadequate folate intake.

In counseling individual patients, clinicians should remind patients that many of the healthy behaviors can reduce risk of multiple diseases, and some patients may be more motivated by cancer prevention and others by CVD prevention. Although the public is likely generally aware of the cardiovascular benefits of physical activity and maintaining a healthy weight, their cancer prevention effects are probably under appreciated. Combined advice for chronic disease prevention could be extended from the individual to the institutional level. Rasmussen-Torvik
and colleagues conclude with the practical suggestion that the AHA form partnerships with cancer and other chronic disease advocacy groups to create a broad and powerful coalition to promote primary prevention of chronic disease. To be maximally effective, such an approach should include not only efforts to promote healthy lifestyle to the public, but also advocate for more research into primary prevention, and effective ways to implement behavior change. One can foresee a variety of institutional political hurdles to overcome. However, moving away from the silo-based disease-specific approach, both for advocacy as well as research, could yield enormous dividends in improving health. One major step in this direction would be the creation of an institute of public health and prevention within the NIH.

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