Nutritional Epidemiology—There’s Life in the Old Dog Yet!

John D. Potter

Abstract
Consideration is given to the idea that the nutritional epidemiology of cancer is dead, as some in the media have claimed. The basis for the claim does not lie in science nor has anyone with relevant knowledge made such a statement—although that, too, has been claimed. Evidence is adduced for the importance of past achievements of nutritional epidemiology. Attention is similarly drawn to recent contributions. In particular, I note the state of play of cancer and plant foods, fat and breast cancer, meat and cancer, vegetarians, intervention studies, migrant studies, and westernization of diet and lifestyle. Some next steps and some currently important questions are outlined. Cancer Epidemiol Biomarkers Prev; 24(2): 323–30. ©2014 AACR.

Introduction
The death of dietary epidemiology has been announced, rather prematurely it would seem (1). It echoes earlier announcements of the demise of epidemiology more generally (2). This, too, was a premature claim, especially given epidemiology’s list of achievements, which include the identification of many of the causes of human cancer, such as ionizing radiation, tobacco, asbestos, solvents, ultraviolet radiation, hepatitis B virus, and human papillomaviruses, as well as causes and prevention of disease more generally, including methyl mercury poisoning, smallpox eradication, sudden infant death syndrome, and HIV/AIDS (3).

Some important achievements of dietary epidemiology include understanding and preventing a variety of nutritional-deficiency states (4), unraveling cardiovascular risk factors (5); understanding and preventing iodine deficiency disorders (6); establishing the associations among the drivers of obesity, obesity itself, and a raft of chronic diseases (7, 8); establishing patterns of dietary factors for specific cancers (9, 10); establishing associations between dietary factors and anatomically defined (11–13) and molecularly defined subsets of cancers (14–16); developing better methods to measure nutrition-related behaviors (17–24); and understanding and accounting for measurement error in self-reported behaviors (25–29).

The recent death notice was provoked by Walter Willett’s presentation at the 2014 AACR annual meeting (30), although what was reported in the New York Times, with its errors of omission and commission, did not even vaguely resemble Willett’s presentation. What he actually concluded was that, from a methodologic perspective (a) all is copacetic with food frequency questionnaires (FFQs), basing his argument on the fact that FFQs are able to identify dietary risk factors for cardiovascular disease, even if the cancer/diet relations are less clear; (b) large-scale prevention trials fail because of limited duration and compliance problems; and (c) case–control studies of dietary behaviors are too biased to take seriously. He also concluded that, from a substantive perspective (a) the 1981 Doll and Peto (31) estimate of 30% to 35% of human cancers being due to nutrition is probably right, but that obesity and inactivity are likely to explain most of this; (b) alcohol is causal in breast and probably other cancers; (c) some other nutrients are problematic, e.g., high dairy intake increases the risk of prostate cancer; and (d) some other nutrients are protective, e.g., lycopene against prostate, folate against colorectal cancer.

Although Willett argued clearly that obesity and exercise explain much of the relationship between diet and cancer, he did not assert that there are no associations except these—and obesity, of course, is intimately linked to both dietary behaviors, in all their complexity, as well as exercise. Central to the case being made here, the achievements that Willett did enumerate are nothing like a claim that we know little and can recommend little as public health policy or personal choice. Indeed, he provided excellent examples from three large studies conducted by his group over many decades. These Harvard studies have generated valuable data regarding, among other relationships, risk of breast cancer in relation to alcohol (32), plant foods (33–35), fat intake (36), meat consumption (37), and body mass, weight gain, and weight loss (38, 39) as well as dietary behaviors in relation to colorectal cancer risk (40) and prostate cancer survival (41). However, to assess the overall status of nutritional epidemiologic research, it is helpful to also consider data generated from other sources.

Plant Foods and Cancer
The 1997 World Cancer Research Fund (WCRF) report (9), with relatively extensive reliance on case–control studies, concluded that there was convincing evidence for a causal association between higher consumption of vegetables and fruit and lower risk of cancers of mouth and pharynx, esophagus, lung, stomach and a similar association between higher consumption of vegetables alone and cancers of the colon and rectum. Further, the report

www.aacrjournals.org
concluded that there was evidence for a probable causal association between higher consumption of vegetables and fruit and lower risk of cancers of the larynx, pancreas, breast, and bladder.

The 2007 WCRF report (10) concluded, based on data that included more cohort studies, that there was a evidence for a probable causal association between higher consumption of vegetables and lower risk of cancers of the mouth, pharynx, larynx, esophagus, and stomach, similar probable inverse associations between garlic consumption and cancer of the colon and rectum and allium vegetables and cancer of the stomach, and a probable inverse association between higher fruit consumption and cancers of the mouth, pharynx, larynx, esophagus, and stomach. This report also concluded that there was a probable causal relationship between lower risk of prostate cancer and higher intake both of foods containing lycopene and foods containing selenium.

Willett, in his 2014 AACR presentation concluded, as noted above, that case-control studies were too prone to bias to be useful in deciding about dietary behaviors and specifically denied that vegetables and fruit exert much influence on cancer risk. However, since 2005 there have been about 30 published articles reporting cohort studies of site-specific cancers and vegetable and fruit intake and related topics. Among these recent articles, cancers fall into two clear groups: those showing consistent beneficial associations with vegetable and fruit intake, namely head and neck, esophageal squamous cell, stomach, colorectal, liver, lung, and breast cancers, and those showing consistent null associations, namely esophageal adenocarcinoma and cancers of the pancreas, bladder, and prostate. Specifically, the following cohort studies showed consistent inverse associations: two of two studies of head and neck cancer (42, 43); two of two on esophageal squamous cell cancer (44, 45); five of five (one study was reported on twice with greater numbers) on stomach (refs. 45–50; perhaps particularly distal/non-cardia cancer in men); five of five on colorectal cancer (refs. 51–55; although this was seen only in men in two studies (52, 55)); there were also two further studies showing reduced risk specifically of MLH1-deficient colon cancer (55) and of adenoma (55); one of one on liver (56); three of three on lung (refs. 57–59); and a further study showing reduced risk with greater diversity of intake of both vegetables and fruit (60)—the lung studies show varying evidence of interaction with smoking; and five of five on breast cancer (refs. 15, 33–35, 61; four showing an association more strongly, or only, with estrogen receptor–negative cancers with the exposure variable ranging across vegetables, vegetables and fruit, some specified fruits, and serum carotenoids). In contrast, cohort studies were null for the following cancers: two of two on pancreas (62, 63); two of two on esophageal adenocarcinoma (44, 45); two of three on bladder (refs. 64–66; one study showed reduced risk among men; ref. 65); and one on prostate cancer (ref. 67; although it did find a reduced risk of extra-prostatic cancers).

Given the definable heterogeneity reported here, studies of total cancer are problematic but at least two such studies reported a reduced risk, one showing reduced incidence with higher intake of a Mediterranean diet (68) and the other reduced cancer mortality with higher consumption of total vegetables and fruit (69).

During this same period, at least five meta-analyses were undertaken. For prostate cancer, a meta-analysis of 16 cohort studies showed no association with vegetable and fruit intake (70). Two meta-analyses of stomach cancer were dominated by case-control studies and showed lower risk respectively with higher cruciferous intake (borderline for the cohort studies) and with both higher vegetable intake and higher fruit intake (71, 72). A meta-analysis of 19 cohort studies of colorectal cancer showed reduced risk with both higher fruit intake and higher vegetable intake (73). A meta-analysis of lung cancer studies showed reduced risk in association with higher combined intake of vegetables and fruit, consistent across both case-control and cohort studies (74).

Since 2005, there have been at least four studies on survival and intake of vegetables and fruit. One study of breast cancer showed improved survival associated with a greater variety in consumption of vegetables and fruit and of fruit alone (75) and one showed reduced recurrence with higher intake of vegetables (76). A third breast cancer study showed no association between survival or recurrence and intake of cruciferous vegetables (77). One study of prostate cancer showed reduced likelihood of progression associated with higher intake of cruciferous vegetables (78).

What is important about these recent studies is that they show that vegetable and fruit intake is consistently associated with a reduced risk of a number (although not all) epithelial cancers, and that a specific subset of breast, but not prostate, cancer is similarly associated. This is still an area for research and for clear public health messages, particularly in the light of consistent and substantial associations between plant food intake and cardiovascular disease (79).

Fat and Breast Cancer

The association between dietary fat intake and breast cancer risk has been extensively studied. Results, however, have been controversial. Recent data, even those from Nurses Health Study II, have shown that (36) there is evidence of a role for fat intake: during 8 years of follow-up of more than 90,000 women, 714 developed incident invasive breast cancer. Women in the highest (compared with lowest) quintile of fat intake had a borderline increased risk of breast cancer [relative risk (RR) = 1.25; 95% confidence interval (CI), 0.98–1.59; P for trend = 0.06], explained by an association with animal but not vegetable fat: across increasing quintiles of animal fat intake, relative risks were 1.00, 1.28, 1.37, 1.54, and 1.33 (95% CI, 1.02–1.73; P for trend = 0.002). Red meat and high-fat dairy foods were each associated with higher risk, as were intakes of both saturated and monounsaturated fat.

The European Prospective Investigation into Cancer and Nutrition (EPIC) data, too, show an association with fat consumption (80). Among almost 320,000 women followed for 8.8 years, 7,119 developed breast cancer. There was an association between high saturated fat intake and greater breast cancer risk [hazard ratio (HR), 1.13; 95% CI, 1.00–1.27; P for trend = 0.038] for the highest, compared with the lowest, quintile of saturated fat and HR = 1.02 (1.00–1.04) for a 20% increase in saturated fat consumption. There was no association with other fat variables. Among menopausal women, the association with saturated fat was confined to non-users of hormone therapy at baseline: HR = 1.21 (95% CI, 0.99–1.48; P for trend = 0.044) for the highest quintile compared with the lowest quintile and HR = 1.03 (95% CI, 1.00–1.07) for a 20% increase in saturated fat.

In the National Institutes of Health/American Association of Retired Persons (NIH/AARP) Diet and Health Study (81), of 188,736 postmenopausal women who completed a 124-item food-frequency questionnaire in 1995 to 1996, after an average follow-up of 4.4 years, there were 3,501 cases of invasive breast cancer. The HR for breast cancer among the highest quintile of total fat intake (approximately 40% energy from total fat) compared...
with the lowest (approximately 20% energy from total fat) was 1.11 (95% CI, 1.00–1.24; P for trend = 0.017). The corresponding HR for a 2-fold increase in percent energy from total fat as a continuous variable was 1.15 (1.05–1.26). Associations were also reported for subtypes of fat: HR for a 2-fold increase in percent energy from saturated fat was 1.13 (1.05–1.22); from monounsaturated fat was 1.12 (1.03–1.21); and from polyunsaturated fat was 1.10 (1.01–1.20). Correction for measurement error in nutrient intakes, on the basis of a calibration substudy that used two 24-hour dietary recalls, strengthened the associations, yielding an estimated HR for total fat of 1.32 (1.11–1.58). Secondary analyses showed that associations between total, saturated, and monounsaturated fat intakes were confined to women who were not using menopausal hormone therapy at baseline.

Of course, the most celebrated data come from the Women’s Health Initiative (WHI) dietary intervention. After 10 years intervention among 48,835 women, those in the low-fat arm showed an HR of 0.91 (95% CI, 0.83–1.01) and, among the high compliers, 0.85 (0.71–1.02; ref. 82). Whatever else is true, the empirical observation is that breast cancer incidence fell in the low-fat intervention group. Something about the intervention worked: even if it was not fat per se but rather weight loss, it still provides us with a 15% decline in breast cancer risk among the most adherent.

What other intervention, except Tamoxifen, achieves that? We surely would not recommend universal Tamoxifen prophylaxis!

However, other recent cohort studies do not show an association between dietary fat and breast cancer (83, 84). In a Canadian intervention study among 4,690 women with elevated mammographic density (a known risk factor), the intervention arm received intensive dietary counseling to reduce fat intake to a target of 15% and increase carbohydrate to 65% of calories. The women were followed for an average of 10 years. The proportion of calories from fat in the intervention group remained 9% to 10% lower than the comparison group throughout. There was no difference in outcome between intervention and comparison arms (85). To further complicate matters, in one of the few studies to examine the impact of dietary fat on survival, the risk of dying among 516 breast cancer cases was elevated more than 3-fold (HR, 3.12; 95% CI, 1.79–5.44) in those in the highest tertile compared with the lowest tertile of total fat intake (75).

**Meat and Cancer**

Consistent with the observations made in the Harvard cohorts, the 2007 WCRF report concluded that the evidence for an association between red and processed meat consumption and colorectal cancer was convincing (10) with further support emerging from the WCRF/American Institute for Cancer Research (AICR) Continuous Update Project on colorectal cancer in 2011 (86). The 2007 report concluded that cancers of the esophagus, lung, pancreas, prostate, stomach, and endometrium may also be linked to red and processed meat but that the evidence was limited and inconsistent.

Abid and colleagues (87) recently reviewed studies published since the 2007 report on meat consumption and most of the cancers common in the United States and elsewhere. They also summarized meta-analyses from the same period. They noted that red meat intake was positively associated with incident colorectal adenomas in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) (88) and in a meta-analysis of red meat intake in 5 cohort and nested case–control studies (89). Abid and colleagues (87) also noted an elevated risk of colorectal cancer in the NIH-AARP study (90) and in a meta-analysis of 22 cohort and case–control studies (91).

Furthermore, as noted by Abid and colleagues (87), the NIH-AARP study showed a statistically significantly increased risk of cancers of the lung, esophagus, liver (92–95), kidney (96), and, in men, pancreas (97) and prostate (98) in association with red meat intake. In contrast, this exposure was not associated with cancers of the bladder, stomach, breast, or with glioma and non-Hodgkin lymphoma (87). In other cohort studies, including the PLCO trial and the Agricultural Health Study, red meat intake was not associated with either lung or prostate cancer, but it was positively associated with breast cancer (87). Thus as Abid and colleagues noted (87), the results from these 3 cohort studies are inconsistent for lung, prostate, and breast cancer.

Meat consumption is also well established as a risk factor for planetary health (99, 100) so despite the continued obfuscation of the issue by the meat industry—they learned well from the tobacco merchants—meat should continue to be a focus of public health action, even as we continue to improve our understanding of mechanisms.

**Vegetarians**

As with populations in transition (discussed below), there can be arguments about whether real protection among vegetarians is derived from dietary practices alone or whether there is a package of lifestyle behaviors that jointly contribute to lower risk and better outcomes. For instance, it has been argued that Seventh-day Adventists (SDA) not only espouse (largely) lacto-ovo-vegetarian diets but also eschew (rather than chew) tobacco, as well as alcohol—and that it is these behaviors that are more important than vegetarianism (101). However, contrasting SDAs with individuals with similar social status and healthy behaviors who were not vegetarians provided evidence of extra benefit for the SDAs (102). Although this was not the pattern reported in the UK where vegetarians experienced mortality rates considerably below those of the general population but similar to those of nonvegetarians with healthy habits (103). Other nonsectarian vegetarians show similar benefits (104–106). Finally, at least some of the low risk seen in India and among emigrant Indians (see section below on Westernization) is plausibly due to a similar package. As no one would seriously suggest taking up smoking or heavy alcohol consumption or becoming sedentary or obese in conjunction with a vegetarian diet, perhaps it is this more global or patterned approach we should be recommending as public policy and personal choice.

**Intervention Studies**

Data from intervention studies other than WHI have also been highly informative, not often in the direction predicted. For instance, folate is clearly important as part of diet from as early as in utero, but folic acid is deleterious when used as a dietary supplement or in fortification (107–109). Similar caveats apply to other enthusiastically promoted food-derived “chemoprevention agents”: the data provide clear evidence that high doses of almost all single nutrients are deleterious in relation to cancer (110).

**A More Global View**

Epidemiology has always taken careful account of patterns and changes across populations, as well as investigating individual-level associations or undertaking interventions within populations. This has been a fruitful source of clues that allow
the pursuit of more finely tuned research at the individual level. However, such studies provide some data that are very difficult to obtain in studies of single populations or even pooling studies, particularly information on populations and individuals in transition.

**Migrant Data**

What migrant data show consistently is that the risks of specific cancers move toward those of the new host country and do so, sometimes, within the migrating generation. This identifies the relevant exposures as environmental, not genetic. The fact that some rates change within the migrating generation, e.g., colorectal cancer, and others in later generations, e.g., breast cancer, suggests two possible interpretations: (a) that early-life exposure is key for some cancers and later exposure for others, and (b) that the degree to which family and social customs are retained determines the rate of change of risk. It is this pattern of changes in risk (which have been shown in multiple migrant settings; ref. 111) that led to specific questions about the role of dietary practices and, consequently, the development of the first robust food frequency questionnaire (17). Observations on migrating populations were tested at the individual level in studies, for instance, on Japanese migrants to the United States (112–114) and European migrants to Australia (115) and provided insight into relevant changes and causes. The initial impression that diet is important has been borne out by subsequent observations, although clearly, a multitude of factors change with migration—and dietary behaviors represent only one set of these. Minimally, populations in transition are not like populations under more stable conditions and hold additional data for our interpretation.

**Westernization**

The strong index of suspicion regarding diet and migration has led to further explorations of what happens as populations undergo transitions within their country of origin, especially seeking to understand rapidly changing rates of cancers as countries “westernize.” Some interesting patterns have emerged (116). Stomach cancer rates are falling everywhere across Asia, even in India, where, for decades, rates have been similar to the low incidence seen in Australasia and North America. By comparison with the United States, Australasia, and European countries, incidence rates of prostate cancer are quite low in Asia. They began to rise in Singapore and Japan in the early 1990s and in China in the late 1990s. Incidence rates of prostate cancer are low and flat in India. From 1975, colorectal cancer rates showed different patterns in men and women in Asia. Among men, incidence climbed rapidly in Japan and then stabilized in the early 1990s. Rates continue to rise in China and Singapore, and have recently begun to rise in Thailand. In India, however, incident rates have remained flat from the 1980s to 2006. In women, colorectal cancer incidence rates rose rapidly in Singapore and Japan until about 1990 and have remained flat since then. Chinese incidence is quite high but more or less flat from 1990 onwards. As in men, incidence rates in India are low and flat and beginning to rise in Thailand. Breast cancer incidence has been rising steadily in many Asian countries, especially Japan, Singapore, and China. However, the slope is more gentle in India and rates remain low.

These data suggest that diet may well be a key influence on changing rates across Asia. India, with a very large proportion of vegetarians in the population, shows little change across 30 years, whereas those countries where westernization of diet is most marked show the earliest and largest changes. That this is not a phenomenon just related to greater poverty is attested to by the low and falling rates of stomach cancer in India and the patterns of differences among populations in Singapore. Indians tend to maintain dietary patterns for multiple generations after migration, and the incidence rates per 100,000 population among Singaporean Chinese and Indians in 1998 to 2002 were, respectively, for cancers of the colorectum (male: 46.0; female: 31.7 and male: 15.8; female: 13.7), breast (56.4 and 45.0), and prostate (18.6 and 11.1; ref. 117). There is much still to be learned by studying the Indian diaspora.

Specifically in relation to dietary changes in Japan, Kono (118) explored the secular trend in colon cancer from 1950 to 2000 in relation to changing diet, focusing particularly on fat and meat consumption. As noted above, he found that incidence and mortality each increased almost linearly on a log scale until the early 1990s, after which the increase stopped. The temporal changes in fat and meat intake coincided with the incidence of colon cancer with a lag of approximately 20 years. Cereal consumption declined continuously across the whole period and intake of vegetables showed little change. Kono concluded that meat intake explained most of the increases in Japan in the second half of the 20th century, although it is notable that alcohol also increased in a manner similar to meat (118). A further intriguing observation is that the sex difference in colon cancer in Japan is the most marked in the world (119)—a difference that perhaps provides relevant clues regarding obesity, alcohol, tobacco, or differences in the degree to which men and women have changed their diets.

In a cohort study of 80,658 Japanese men and women ages 45 to 74, Takachi and colleagues (120) examined associations between the consumption of red and processed meat and the risk of colorectal cancer. They found, consistent with Kono’s time-trend analysis, that higher consumption of red meat (but not processed meat) was associated with a higher risk of colon cancer among women (HR, 1.48; 95% CI, 1.01–2.17; \( P \) for trend = 0.03) and men (HR, 1.44; 95% CI, 1.06–1.98; \( P \) for trend \( P = 0.07 \)). The authors note, however, that the highest quintile of red meat intake in this population could be considered moderate by Western standards (120).

**Next Steps**

I agree with Willett that the continued study of human dietary behaviors in longitudinal studies, well supported by better biologic measures of both exposure and metabolic responses, is very important if we are to best understand diet and cancer. However, it is not enough. There are some poorly understood human exposures that are currently changing rapidly. Some of these directly impact health. Others do so because they alter aspects of the food supply. Still other changes are occurring that are related to the food supply but that affect other aspects of human, animal, and planetary health. Many of the relevant questions occur at the interface of environmental and nutritional epidemiology, for instance what are pesticides, genetically modified organisms, and their complex interaction doing to human health in general and cancer in particular? How will continually rising human demand for meat impact human health (including cancer), climate change, deforestation,
biodiversity, water quality, etc.? How does exposure to endocrine disruptors in the diet impact cancer and other health risks?

Another set of research questions arises out of the industrialization of the food supply and the increasing centralization of food production in fewer and fewer hands. What is actually happening to food quality, nutrient content, variety—not just of different food items but of strains and subtypes of fruits, vegetables, nuts, and seeds? The impact of this and other changes in the food supply are little studied in relation to cancer and other disease, even though we know, as noted above, that the variety of foods consumed is related to risk. If the quality of food is indeed declining, is this changing differently in different countries and among different social classes?

Other research questions relate to aspects of human development and biology in cancer risk: how important are early exposures (already established in risk of cardiovascular disease and strongly suspected in cancer, e.g., breast cancer)? How do gastrointestinal (and other) microbiomes interact with diet to determine cancer risk? How do we best study the complex mixtures that are the foods we eat? What human variation is there in the capacity for buffering against deleterious exposures and how can we exploit that to improve protection against cancer?

Finally, we will continue to deal with trying to quantitate intakes of a complex mix of exposures that is subject to variation via many influences: geography, season, agricultural practices, soil, climate, weather, changing fashions, etc. as well as reporting variability related to human behavior and memory. Accordingly, we need to continue to look for measures of exposure, metabolism, and biologic and pathologic effect, focusing on signatures that are readable via changes in metabolomics, in affected tissues, in human microbiomes, etc. (121–127).

Some Final Questions

Food and water security will be key issues in the 21st century (128). It may mean that public-health policy will be much more focused on these issues in the coming decades than on the nutritional causes of cancer, although we know that, as well as impairing health in many other ways, undernutrition (like overnutrition) is a risk factor for cancer (129).

Nonetheless, there are important questions that remain to be answered if we are to build on what we already know about diet and cancer. One question that has been asked is why nutritional epidemiology seems to have been more successful in unraveling cardiovascular disease and diabetes than cancer. At least part of the answer involves the fact that cardiovascular diseases are much more homogeneous, in their more systemic nature, in their pathobiology, and in their international epidemiology, than are cancers. However, other differences involve competing risks, timing of exposures versus disease (incubation period), cohort effects, elimination of susceptibles, and interactions among risk factors. Equally important, however, is whether the best theory of carcinogenesis currently underpins how we think about questions in nutrition and cancer. Nutritional epidemiologists have long followed the dominant model that is focused on mutation as the central driver of the carcinogenic process—best exemplified currently by the formulation of Hanahan and Weinberg (130, 131)—even though we struggle with the fact that almost all the exposures that we study in diet, nutrition, exercise, and obesity are not mutagenic. There are other models of cancer (132), perhaps we should be reorienting our view so that our questions are not continually bent through an inappropriate prism (133).

A second key issue involves the very real problems that underlie the translation of studies on humans to recommendations regarding what humans should eat and how they should live. We are comfortable with mechanistic animal studies identifying deleterious (or sometimes beneficial) single exposures in the development of cancer, but these studies are largely unhelpful when the issue involves complex patterns of behavior that are heavily determined not just by biology, but by culture, family, religious and other beliefs, advertising, wealth, education, early-life experience, pathology, and a host of other factors. Undertaking well-defined dietary modification in humans, either as feeding studies or as large-scale interventions, provides somewhat more relevant data, but the complex web of influences on nutrition and lifestyle remains. As noted above, we do have evidence that some definable patterns of behaviors (vegetarianism, food variety, matching energy intake and output, relative abstemiousness) are more beneficial than others, but, because so much of human diet is not dependent on rational choice, there is still much to be learned about how to implement change as a public-health program and as individual choice.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The author thanks Rashmi Sinha, NCI, and Wei Zheng, Vanderbilt University, for their helpful comments and suggestions on this commentary.

Received December 2, 2014; accepted December 2, 2014; published OnlineFirst December 16, 2014.


