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COMMENTARY

The Art of Casting Nets: Fishing for the Prize of Personalized Cancer Prevention

David J. Waters and Emily C. Chiang
The Center on Aging and the Life Course, Purdue University, and Gerald P. Murphy Cancer Foundation West Lafayette, Indiana, USA

David G. Bostwick
Bostwick Laboratories, Glen Allen, Virginia, USA

Now, more than ever, there is great need for personalized cancer prevention. We define personalized cancer prevention as a strategy that will enable each person to reduce his or her risk for lethal cancer by matching the dose, duration, and timing of an intervention with their own cancer risk profile. Most research studies provide us with data on the average person. But who is the average person anyway? The central tenet of personalized cancer prevention is that average is overrated. In this article, we frame what are the major obstacles to developing personalized cancer-reducing interventions: the lack of validated, non-invasive stratifiers of risk; the U-shaped dose response between cancer-fighting nutrients (e.g., selenium) and DNA damage, meaning that more of a good thing is not necessarily a good thing; the relatively brief duration of interventions evaluated in human prevention trials; the challenge of finding populations in which the impact of early life interventions on the incidence of cancers affecting older adults can be studied; and the interindividual differences in gene expression that may influence a person's response to a particular nutrient. Moreover, we contend that those who study personalized cancer prevention will need a unique constellation of expertise, including an understanding of cancer and aging, a passion for prevention, and proven health communication skills. We propose that becoming cross-trained in cancer and aging and taking more responsibility for communicating health-related research to the public in the proper context are two of the most important ways scientists can move us all closer to the goal of personalized cancer prevention. Every fisherman knows that where he casts his net determines his catch. Now, we ask: When it comes to solving the cancer problem, where should we be casting our nets?

Address correspondence to David J. Waters, PhD, DVM, Gerald P. Murphy Cancer Foundation, 3000 Kent Avenue, Suite E2-100, West Lafayette, IN 47906. E-mail: waters@purdue.edu

Every fisherman knows that where he casts his net determines the catch. When it comes to solving the cancer problem, where should we be casting our nets?

Some say the results of two recent, widely publicized studies published in *JAMA* (1) and the *Journal of the National Cancer Institute* (2) cast further doubt on the benefit of nutritional supplements for reducing cancer risk and all-cause mortality. Indeed, the headlines communicated to the public were: "Vitamin pills can help send you to an early grave, say scientists" (3) and "Advanced fatal prostate cancer linked to excessive use of multivitamins" (4). On the contrary, we do not believe these findings cast a long, gloomy shadow over the oxidative stress hypothesis of cancer and aging. Instead, these studies send a much more urgent message—*now, more than ever, there is great need for personalized cancer prevention*.

We define personalized cancer prevention as a strategy that will enable each person to reduce his or her risk for lethal cancer by matching the dose, duration, and timing of an intervention with their own cancer risk profile. Most research studies provide us with data on the "average" person, but who *is* the average person, anyway? The central tenet of personalized cancer prevention is that *average is overrated*. Average may have been a useful concept in the past, but now we are entering a new and exciting era: the era of personalized cancer prevention. And if capturing the essence of personalized data is to be this era's ultimate prize, how much closer do these recent studies move us toward claiming victory?

In a meta-analysis of 68 randomized clinical trials, Bjelakovic et al. (1) found no effect of antioxidant supplements on all-cause mortality [OR and 95% CI = 1.02 (0.98–1.06)]. Approximately two-thirds of the studies were of individuals with pre-existing conditions (i.e., secondary prevention trials) and only 7 studies had all-cause mortality as an intended endpoint. Mean duration of antioxidant supplementation was brief—only 2.7 years—and the age of subjects at time of intervention varied widely, ranging from 18 to 103 years old. The

high doses of nutrients used in some of the trials have already been criticized. The message conveyed to the public—that antioxidant supplements may be harmful—emerged only after investigators further pruned the analysis to 47 so-called low bias risk studies. Only then was there a small but significant increase in all-cause mortality associated with antioxidant supplementation [OR and 95% CI = 1.05 (1.02–1.08)]. Excluded from analysis were more than 400 studies in which there were no deaths in either the antioxidant supplement or placebo arms. Also, the authors failed to obtain the raw data from each study, relying exclusively on summary statistics, a common and often crucial mistake of meta-analyses. "This study does not advance our understanding, and could easily lead to misinterpretation of the data," commented Meir Stampfer, Ph.D., of the Harvard School of Public Health (5).

In May 2007, Lawson et al. (2) reported their findings from almost 300,000 older men in the National Institutes of Health–AARP Diet and Health Study. Men completed a questionnaire on how frequently they used either of three types of multivitamin supplements: Stress Tab; Therapeutic/Theragran; or One-a-Day. In the 5% of men with the highest frequency of multivitamin use (greater than 7 per week), there was an almost 2-fold increase in risk of fatal prostate cancer during the 6-year follow-up period [OR and 95% CI = 1.98 (1.07–3.66)]. However, neither dose nor serum concentration of vitamins was available for any of these men. Moreover, the amount of these nutrients consumed in the diet, which would be expected to influence response to the multivitamin supplements, was unknown. The message conveyed to the public was that taking too many multivitamins may kill you, but should we condemn multivitamin use for all men based on these data? In the original scientific article (2), the authors' conclusion was articulated more thoughtfully: "Excessive use of multivitamin supplements *or a closely related behavior* was associated with an increased risk of advanced and fatal prostate cancer." Undoubtedly, future studies will be targeted at learning more about the health behaviors of this interesting subset of men in the NIH–AARP cohort. In the meantime, we need to be targeting the most fundamental issues surrounding personalized cancer prevention.

PERSONALIZED CANCER PREVENTION: WHO WILL BENEFIT AND AT WHAT DOSE?

Why is it so difficult to design specific interventions to prevent cancer? One of the major obstacles is the lack of validated, non-invasive risk stratifiers for certain cancers. Consider the prevention of prostate cancer. The inability to segregate men into high- versus low-risk groups mandated the enrollment of more than 32,000 subjects to test a single hypothesis in the SELECT prostate cancer prevention study. It is logical that persons at highest risk for cancer are those who could benefit most; low-risk individuals only dilute the power to detect protective effects. But without risk stratifiers, the scientists who interpret clinical trial results put themselves at risk—at risk of concluding an intervention has no benefit, rather than conceding that those individuals who would benefit from the intervention have simply not yet been identified.

Low selenium status is reportedly a risk factor for prostate cancer (6–8). But who will benefit from supplementing their dietary intake of selenium? To get closer to answering this question, we conducted a randomized feeding trial in which elderly beagle dogs received nutritionally adequate or supranutritional selenium for 7 months to simulate the broad range of dietary selenium intake of men in the United States (9). We studied elderly dogs because, like men, they develop naturally occurring prostate cancer (10–12)[1]. By using the aging dog prostate to mimic the aging human prostate, we could study the effects of selenium on prostate cells *in an appropriate context*—amidst the complex environment of an aging prostate gland prior to the onset of cancer. The results of our feeding trial showed an intriguing U-shaped dose-response relationship between selenium status (toenail selenium concentration) and the extent of DNA damage within the prostate (alkaline Comet assay); prostatic DNA damage was most severe at the lowest and highest selenium concentrations. Further, we demonstrated that the concentration of selenium that minimized DNA damage in the aging dog prostate remarkably paralleled the selenium concentration in men that minimized prostate cancer risk (9) (Fig. 1). We might say from this new understanding that additional selenium could potentially benefit only the subgroup of the population with low selenium levels, and that it would not reduce disease in subjects with moderate to high selenium levels. But these are not our words. Instead, they are pirated from the published work of Willett et al. in *Lancet* almost 25 years ago, describing their results from the first prospective cohort study to look at selenium status and subsequent cancer risk (18). Based upon our work and the work of others, we consider the findings of the NIH–AARP study—higher prostate cancer mortality in men with excessive multivitamin use—an expected result. Moreover, we strenuously argue that individuals need to know their baseline levels of cancer-fighting nutrients *prior to supplementation*. In the case of selenium, men should avoid oversupplementation and adjust their selenium intake to an optimal range by periodically measuring the amount of selenium in their toenails.

Our strategy of using dogs to search for non-invasive stratifiers of risk has yielded other promising leads. We have shown that the sensitivity of peripheral blood lymphocytes to oxidative stress challenge in the laboratory predicts those individuals with the most extensive DNA damage in the prostate (19). After isolating lymphocytes from blood, we first evaluated whether the amount of endogenous damage in lymphocytes could predict which dogs had the highest DNA damage in their prostate. The answer was no. But then we borrowed a page straight out of the cardiologist's playbook. Cardiologists successfully stratify

[1]For a review of the similarities between the cancers of dogs and humans, the reader is referred to the article by Waters and Wildasin published in *Scientific American* (13).

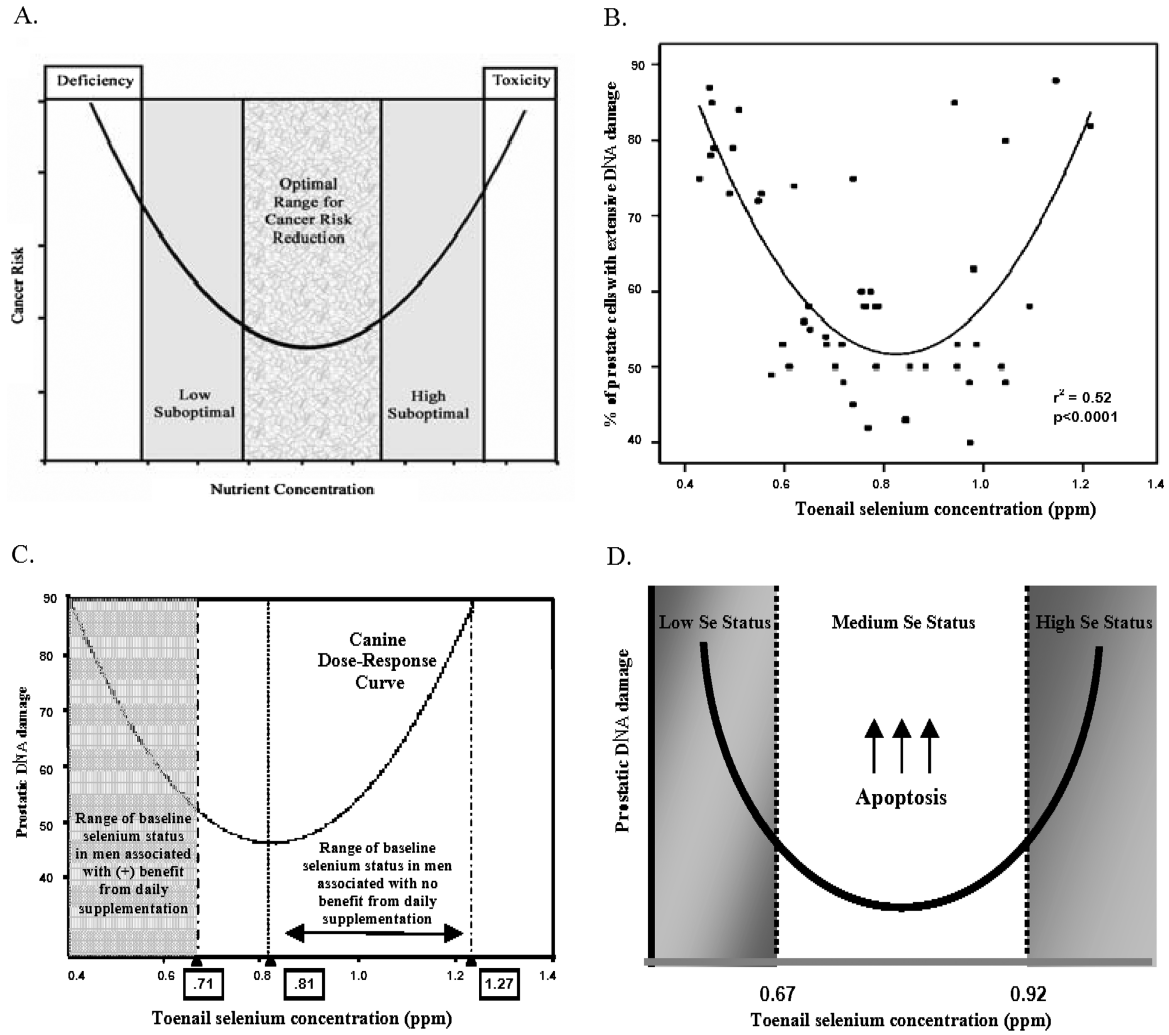

FIG. 1. It's a U-shaped World: More Is Not Necessarily Better. (**A**) Model adapted from Mertz (14) predicting the biological response to an essential nutrient. The model predicts more is not necessarily better. Our data from dogs (Panel B) provided the first in vivo confirmation that the Mertz model fits for selenium and carcinogenic events within the prostate. (**B**) U-shaped dose-response relationship between toenail selenium concentration and prostatic DNA damage in 49 elderly dogs that were physiologically equivalent to 62- to 69-year-old men (9). (**C**) Canine dose-response curve from Panel B explains the effect of baseline selenium status on human prostate cancer risk reduction in the Nutritional Prevention of Cancer Trial (15). Men with baseline selenium status <0.71 ppm (shaded region) had lower than the optimal selenium concentration predicted by the dog model; these men had a statistically significant 92% reduction in prostate cancer risk after selenium supplementation. Men with baseline selenium status >0.81 ppm were already within the optimal or high suboptimal range predicted by the dog model *prior to supplementation*; these men had no significant reduction in prostate cancer after selenium supplementation. Following selenium supplementation, men in the highest baseline selenium tertile had a median selenium level of 1.27 ppm, a value clearly exceeding the selenium concentration that minimized DNA damage within the dog prostate. These men had an alarming and statistically significant 88% increase in total cancer incidence compared with men with the lowest baseline selenium (16). (D) Selenium has been shown to induce apoptosis in prostatic cancer cells in vitro (17). In a randomized feeding trial in which elderly beagle dogs received daily supplementation with nutritional or supranutritional doses of selenium to mimic the wide range of selenium status seen in U.S. men, we found that apoptosis in the prostate was highest at mid-range selenium concentration (toenail conc., .67–.92 ppm) (Waters et al., unpublished data). Highest apoptosis was accompanied by lowest DNA damage suggesting that mid-range selenium concentration is the optimal dose for the preferential elimination of DNA damaged cells by apoptosis. This "homeostatic housecleaning" effect of selenium leaves open the possibility that *intermittent* selenium supplementation might curb accumulation of cancer-causing genetic damage within the aging prostate.

patients into low-, medium-, and high-risk categories for heart attack based upon a *challenge*—a stress test—not by measuring resting heart parameters. So we devised our own version of a stress test. We exposed lymphocytes to a brief ex vivo challenge with oxidative stress, because this kind of stress bombards a man's prostate every day and is believed to contribute to prostate cancer development. Now, after oxidative stress challenge, we found that dogs whose blood cells were sensitive to oxidative stress were 7 times more likely to harbor high prostatic DNA damage than dogs whose blood cells were resistant to the stress test. Our results from dogs support recent findings from a case-control study of 158 men with prostate cancer, which showed

that men with the most sensitive peripheral blood lymphocytes to oxidative stress had a 2-fold increased risk of prostate cancer after adjusting for age, race, smoking, and family history (20). Current studies in our laboratory are now focusing on the extent to which changes in a man's lifestyle, including taking antioxidant supplements, can restore the resistance of his lymphocytes—and presumably target organs—to oxidative stress.

PERSONALIZED CANCER PREVENTION: HOW LONG AND WHEN?

Two other factors, the duration and timing of intervention, are key issues in developing cancer preventives. Unfortunately, much of our experience with cancer preventives in humans relates to relatively brief interventions. Additionally, for practical reasons, the timing of intervention has usually been restricted to older adults—quite similar to the age range in which cancer is most frequently diagnosed. So how should we interpret the results of such studies?

Perhaps Sir Arthur Eddington's story, *The Parable of the Fishing Net*, may provide some valuable insight here (21). An ichthyologist, who is attempting to learn about the creatures living in the ocean, casts his net into the sea. After carefully examining the catch, he concludes: (1) no sea creature is more than 2 inches long; and (2) all sea creatures have gills. It is from this starting point that he proceeds to systematically categorize fishes. An onlooking non-scientist remarks: "You are not studying all of the fishes that live in the sea, just those that are in your net." The scientist quickly rejects this possibility, saying: "*What my net can't catch isn't fish*."

Cancer prevention scientists must not adopt the attitude of the ichthyologist in Eddington's fish tale. Instead, we must craft our conclusions based upon an open-minded assessment of what is in our net and what net we are using. For certain, our results are contingent upon the context of each experiment, and this context includes the duration and timing of the intervention. For example, in the Women's Health Initiative Dietary Modification Trial, no association was found between dietary fat intake and colon or breast cancer incidence in 50- to 79-year-old women who were randomized to receive a low-fat diet or continue their usual diets for an average of 8 years (22,23). From these results, should we conclude that at no time during a woman's life does modification of dietary fat intake reduce her risk of these cancers? We should not. Instead, we are obliged to acknowledge that whether or not dietary fat intake during the third or fourth decade of life influences colon or breast cancer risk is still up for grabs (24).

While our certainty for just how to interpret the studies of older adults is waning, the idea that early life events can influence adult health outcomes, such as cancer, is building momentum (25,26). Investigators are faced with a conundrum: Where can we find a study population which lends itself to measuring the possible preventive effects of early life interventions on the cancers that affect older adults? The answer might just be sleeping at the foot of your bed. Capitalizing on the compressed lifespan of dogs compared to humans, we have designed a randomized clinical trial to test if antioxidants can reduce the incidence of naturally occurring cancer in pet dogs (13). Our trial circumvents the restrictive context of studying a brief intervention in an older population that is characteristic of most human cancer prevention trials. Starting at 4 years of age—equivalent to people in their thirties—dogs will receive antioxidant supplements for the rest of their lives. That means dogs taking antioxidant supplements for 8 to 9 years, which is equivalent to a 60-year intervention in humans.

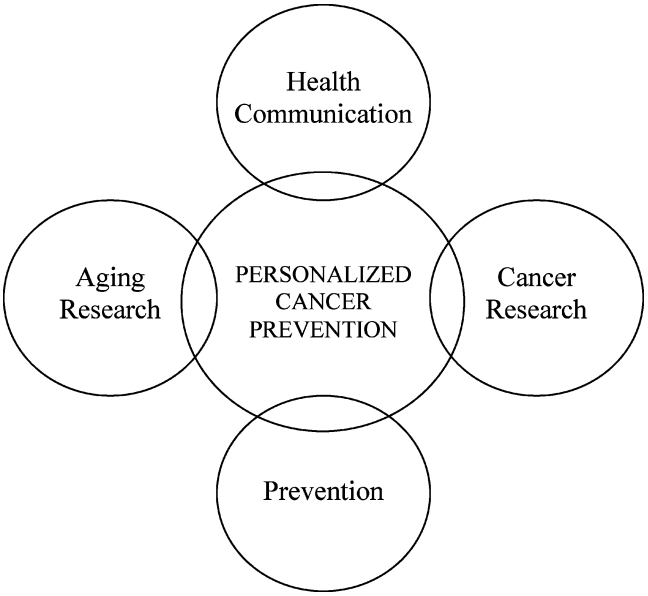

FIG. 2. The Essential Elements of Personalized Cancer Prevention.

PERFECTING THE ART OF CASTING NETS: CROSS-TRAINING, COMMUNICATION, AND CONTEXT

Those who study personalized cancer prevention will need a unique constellation of expertise, including an understanding of cancer and aging, a passion for prevention, and proven health communication skills (Fig. 2). Cardiologists, firefighters, and undoubtedly the lion's share of the readers of *Nutrition and Cancer* already recognize the power of prevention. But the sobering reality is that, at least so far, far too much cancer research has been focused on treatment rather than prevention (27). As a consequence, and not surprisingly, few scientists are cross-trained in the fields of cancer and aging. As long as our sights are set on *killing cancer cells*, little attention is paid to the biology of aging. But as more and more cancer scientists turn their attention toward prevention, what we will need is a more complete understanding of what exactly happens in old tissues—the tissues in which most cancers arise. That is why we should commit ourselves to cross-training young scientists in both cancer and aging so that they will be better prepared to "play" in that intersection. In February 2007, the AACR organized "Translational Research at the Aging-Cancer Interface," its first meeting to bring together scientists from these two

disciplines. At Purdue University's Center on Aging and the Life Course, faculty are cultivating an interdisciplinary training environment that integrates the biomedical and psychosocial sciences, while emphasizing the importance of using a life course perspective to study aging and adult health outcomes.

A critical aspect of personalized cancer prevention is the communication of new findings to the public *in the correct context*. Health-related news is too often sensationalized—selected for its apparent entertainment value, rather than providing the public with news they can use. Too often the media exhibit a stance that can be described as "the writer's divided self"—living in limbo between communication and artistic self-expression (28).

Clearly, realizing the goal of personalized cancer prevention will demand improved communication to the public. The take-home message of the NIH–AARP study (2) should not be that multivitamin supplements are dangerous and have no health benefits. This is an oversimplification, one that fails to address how the findings advance our understanding of nutrition and cancer prevention. Context matters. Even a hot dog vendor at the ballpark knows that the meaning of "Make me one with everything" is different from when someone at a spiritual gathering in Tibet says "Make me One with everything." And certainly a healthier, contextually correct message of the NIH–AARP study is: When it comes to dietary supplements and prostate cancer protection, *more is not necessarily better.* As the public divorce themselves from their beloved but toxic metaphor "More is better," they will come to see a world that is less linear, more U-shaped.

We may also come to see what the *Dictionary of Modern Thought* says about metaphor—"a form of reasoning that is particularly liable to yield false conclusions from true premises" (29)—may very well pertain to meta-analysis. Gene V. Glass, credited with publishing the first paper on the meta-analytic process more than 30 years ago (30), reflected: "What I've come to think meta-analysis really is—or, rather, what it ought to be—is not single-number summaries such as "This is what psychotherapy's effect is," but a whole array of study results that show how relationships between treatment and outcome change as a function of all sorts of other conditions—the age of the people in treatment, what kind of problems they had, . . . how long after therapy you're measuring change . . . That's what we really want to get—a *total portrait* of all those changes and shifts, a complicated landscape . . . " (31). Using meta-analysis to generate a single central point, such as "Treatment with beta-carotene may increase mortality" (1), does not move us closer to personalized cancer prevention. Instead, we should be harnessing the power of meta-analysis to create a total portrait that captures the essence of personalized data—the extent to which changes in dose, duration, or timing of specific interventions protect or endanger specific populations.

Now we are just beginning to appreciate how much individuals differ in terms of their metabolic capacity—their ability to activate pro-carcinogens, to detoxify and excrete cancer-causing agents, and to handle bioactive food components. Inquiries at the level of protein expression (proteomics) and at the level of molecular signals (metabolomics) are attempting to better define the nature of these differences (32). Investigators in the field of nutrigenomics are forging ahead in an effort to understand whether these differences actually translate into different responses to dietary change (32,33). And if diet and other lifestyle factors significantly alter the epigenome—the chromatin configuration and DNA methylation patterns that influence gene expression—then it opens up the possibility that specific strategies targeted at reprogramming the epigenome might provide us with the most bang for our cancer-fighting buck (34–37). But some scientists remain pessimistic that any cancer-reducing dietary intervention will cut the mustard because Western populations are so maladapted to caloric overabundance—obesity has become the not-so-welcome physiological context of our increasingly sedentary lifestyle (38). Yet amidst the pessimism, other scientists are betting on the prospect that tailored strategies for reducing a person's risk of cancer will someday be a reality. Unfortunately, as this story of steady scientific progress unfolds, the public is growing increasingly frustrated with what sounds to them like a muddled message.

PIPELINE TO THE PUBLIC

What can we do to unmuddle the message? Scientists and non-scientists must band together to create a pipeline to the public—a dynamic information pipeline of what we know about the "good things" that enhance health. First, scientists must help the public become more savvy consumers of science. The public must come to realize that science is all about uncertainty, not certainty (39). Different scientists chop up the world differently and hence the fact that their results are not identical, or even consistent, is to be expected. The public wants the truth about what is swimming in the sea of cancer prevention research. They must realize, however, that the scientist can only tell them what is in his net.

Second, scientists should develop their skills as storytellers. Stories provide information in context. Stories stick (40). The public always loves a good story; in that sense, they are child-like. When a child insists "Daddy, tell me a story," she is craving entertainment, not instruction. Unfortunately, most scientists today are more comfortable instructing than entertaining—they have no training in entertaining. But the most creative scientists are playful and, like children, they frequently engage in metaphorical thinking. Scientists telling stories—emotionally engaging stories—just might provide the public and scientists the common ground they need. We realize the reader might find it paradoxical that, after criticizing the media for being too focused on entertainment, we would be advocating scientists become a bit more "entertaining." But seasoned scientists will recognize this as the wisdom that comes from embracing paradox.

Finally, as they become more savvy consumers of science, the public will come to expect more from scientists. They will expect to see cancer prevention scientists casting a variety of nets—nets that will catch the elusive answers to who will benefit,

what is the best dose, what duration is sufficient, and when is the right time. These high expectations might be the nudge we need to re-focus our artistic talents—the way we do science—on the prize of personalized cancer prevention. No longer will it be good enough to say "Selenium is good for you." That doesn't really give anyone anything they can use. The public already embraces the notion that cancer prevention can save lives. We believe personalized cancer prevention will save more.

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REFERENCES

1. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, and Gluud C: Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA* **297,** 842–857, 2007.
2. Lawson KA, Wright ME, Subar A, Mouw T, Hollenneck A, et al.: Multivitamin use and risk of prostate cancer in the National Institutes of Health–AARP diet and health study. *J Natl Cancer Inst* **99,** 754–764, 2007.
3. Vitamin pills can help send you to an early grave, say scientists. *Daily Mail,* February 28, 2007.
4. Paddock C: Advanced fatal prostate cancer linked to excessive use of multivitamins. *Medical News Today,* May 16, 2007.
5. Advanced fatal prostate cancer linked to excessive use of multivitamins. *MSNBC* http://www.msnbc.msn.com/id/17364607/from/ET/. Accessed March 26, 2007.
6. Bostwick DG, Burke HB, Djakiew D, Euling S, Ho SM, et al.: Human prostate cancer risk factors. *Cancer* **101,** 2371–2490, 2004.
7. Yoshizawa K, Willett WC, Morris SJ, Stampfer MJ, Spiegelman D, et al.: Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst* **90,** 1219–1224, 1998.
8. Combs GF Jr: Current evidence and research needs to support a health claim for selenium and cancer prevention. *J Nutr* **135,** 343–347, 2005.
9. Waters DJ, Shen S, Glickman LT, Cooley DM, Bostwick DG, et al.: Prostate cancer risk and DNA damage: translational significance of selenium supplementation in a canine model. *Carcinogenesis* **26,** 1256–1262, 2005.
10. Cornell KK, Bostwick DG, Cooley DM, Hall G, Harvey HJ, et al.: Clinical and pathologic aspects of spontaneous canine prostate carcinoma: a retrospective analysis of 76 cases. *Prostate* **45,** 173–183, 2000.
11. Waters DJ, Sakr WA, Hayden DW, Lang CM, McKinney L, et al.: Workgroup 4: spontaneous prostate carcinoma in dogs and nonhuman primates. *Prostate* **36,** 64–67, 1998.
12. Waters DJ, Patronek GJ, Bostwick DG, and Glickman LT: Comparing the age at prostate cancer diagnosis in humans and dogs. *J Natl Cancer Inst* **88,** 1686–1687, 1996.
13. Waters DJ and Wildasin K: Cancer clues from pet dogs. *Sci Am* **295,** 94–101, 2006.
14. Mertz W: The essential trace elements. *Science* **213,** 1332–1338, 1981.
15. Duffield-Lillico AJ, Dalkin BL, Reid ME, Turnbull BW, Slate EH, et al.: Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *BJU Int* **91,** 608–612, 2003.
16. Duffield-Lillico AJ, Reid ME, Turnbull BW, Combs GF, Slate EH, et al.: Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. *Cancer Epidemiol Biomarkers Prev* **11,** 630–639, 2002.
17. Menter DG, Sabichi AL, and Lippman SM: Selenium effects on prostate cell growth. *Cancer Epidemiol Biomarkers Prev* **9,** 1171–1182, 2000.
18. Willett WC, Polk BF, Morris JS, Stampfer MJ, Pressel S, et al.: Prediagnostic serum selenium and risk of cancer. *Lancet* **2,** 130–134, 1983.
19. Waters DJ, Shen S, Xu H, Kengeri SS, Cooley DM, et al.: Non-invasive prediction of prostatic DNA damage by oxidative stress challenge of peripheral blood lymphocytes. *Cancer Epidemiol Biomarkers Prev* **16,** 1906–1910, 2007.
20. Lockett KL, Hall MC, Clark PE, Chuang SC, Robinson B, et al.: DNA damage levels in prostate cancer cases and controls. *Carcinogenesis* **27,** 1187–1193, 2006.
21. Eddington A: Parable of the fishing net. In: *The Armchair Science Reader*, Gordon IS and Sorkin S (eds.). New York: Simon and Schuster, 1959, pp. 387–388.
22. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, et al.: Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* **295,** 629–642, 2006.
23. Beresford SA, Johnson KC, Ritenbaugh C, Lasser NL, Snetselaar LG, et al.: Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* **295,** 643–654, 2006.
24. Low-fat diet not a cure-all. *Harvard School of Public Health* http://www.hsph.harvard.edu/nutritionsource/low_fat.html. Accessed June 19, 2007.
25. Shu XO, Jin F, Dai Q, Wen W, Potter JD, et al.: Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. *Cancer Epidemiol Biomarkers Prev* **10,** 483–488, 2001.
26. Eason RR, Velarde MC, Chatman L, Till SR, Geng Y, et al.: Dietary exposure to whey proteins alters rat mammary gland proliferation, apoptosis, and gene expression during postnatal development. *J Nutr* **134,** 3370–3377, 2004.
27. Leaf C: Why we're losing the war on cancer and how to win it. *Fortune* March 22, 2004, pp. 76–97.
28. Boorstin DJ. *Cleopatra's Nose: Essays on the Unexpected*. New York: Random House, 1994, p. 41.
29. Holton G: *Einstein, History, and Other Passions*. Melville: American Institute of Physics Press, 1995, p. 94.
30. Glass GV: Primary, secondary, and meta-analysis of research. *The Educational Researcher* **10,** 3–8, 1976.
31. Hunt M: *How Science Takes Stock: The Story of Meta-analysis*. New York: Russell Sage Foundation, 1997, p. 163.
32. Milner JA: Diet and cancer: facts and controversies. *Nutr Cancer* **56,** 216–224, 2006.
33. Davis CD: Nutritional interactions: credentialing of molecular targets for cancer prevention. *Exp Biol Med* **232,** 176–183, 2007.
34. Szyf M: The dynamic epigenome and its implications in toxicology. *Toxicol Sci* **100,** 7–23, 2007.
35. Ross SA: Diet and DNA methylation interactions in cancer prevention. *Ann NY Acad Sci* **983,** 197–207, 2003.
36. Dashwood RH, Myzak MC, and Ho E: Dietary HDAC inhibitors: time to rethink weak ligands in cancer chemoprevention? *Carcinogenesis* **27,** 344–349, 2006.
37. Liu H, Zhou Y, Boggs SE, Belinsky SA, and Liu J: Cigarette smoke induces demethylation of prometastatic oncogene synuclein-gamma in lung cancer cells by downregulation of DNMT3B. *Oncogene* **26,** 5900–5910, 2007.
38. Wargovich MJ and Cunningham JE: Diet, individual responsiveness, and cancer prevention. *J Nutr* **133,** 2400S–2403S, 2003.
39. Feynman RP: The uncertainty of science. In: *The Meaning of It All, Thoughts of a Citizen-Scientist*. Boston: Addison Wesley, 1998, pp. 3–28.
40. Heath C and Heath D: *Made to Stick: Why Some Ideas Survive and Others Die*. New York: Random House, 2007.

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