Editorial
Health Policy

Cancer Prevention Research

Cancer Chemoprevention—the Cardiovascular Model

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In considering the potential for and hurdles in the development of cancer chemoprevention drugs, Meyskens and colleagues, elsewhere in this issue of the journal (1), look somewhat longingly at the success of drug development efforts in the area of preventing cardiovascular disease. And well they might. Treatment of levels of elevated blood pressure (BP) and low-density lipoprotein (LDL) cholesterol, as well as use of aspirin and other platelet inhibitors, postinfarction β-blockade, improved treatment of heart failure, treatment of acute myocardial infarctions with thrombolytic agents, angioplasty and stenting, and coronary artery surgery, have reduced heart disease mortality (as shown in Fig. 1 of ref. 1) despite growing problems with obesity and diabetes. This reduction has not been a cakewalk, however. The cardiovascular disease community has a long history of insisting on actual evidence of benefit, as opposed to accepting an effect on a plausible biomarker, and this approach has been buttressed repeatedly by unwelcome and largely unpredictable (or at least unpredicted) failures of treatments that many believed simply "had to be effective" before studies proved otherwise. The cardiovascular experience will therefore not reveal shortcuts to success, but it can suggest how success might be achieved through selection of appropriate high-risk patients, study of sample populations of seemingly daunting size, perhaps with simplified protocols, and carrying out studies long enough to evaluate convincing endpoints.

Although long forgotten, in the early 1960s, the so-called "New York School" contested the value of lowering BP, arguing that the elevated BP level was an adaptive response to vascular disease and that lowering the pressure would cause even more strokes, heart attacks, renal failure, etc., than people with elevated BP levels already had. Most people did not agree with the New York School in this view, believing instead that elevated BP levels caused these events, but it was only when the Veterans Administration (VA) studies of 1967 and 1970 (2, 3) showed unequivocal beneficial effects of BP control on death, heart attack, and stroke that the value of BP treatment was unequivocally established. (Note that the studies could not ethically have been conducted if the answer had been clear.) Even in the case of BP control, we did not (and still do not) know all we need to. Epidemiologic data show a continuous increase in cardiovascular risk starting at below normal pressures, but the ideal BP treatment goal is not really known from controlled trials, and there is concern about going too low (4), although this remains a matter of debate. Moreover, there is good reason to think that the typical high diuretic doses (100 mg of hydrochlorothiazide or chlorthalidone) strongly urged until the mid-1980s caused an excess of cardiovascular death (5) by causing hypokalemia. Meta-analyses of BP trials using high doses of diuretics showed the epidemiologically predicted reduction of stroke but a less than expected effect on cardiovascular mortality (6, 7). Only when the dose was lowered (e.g., 12.5–25 mg of chlorthalidone) was the full epidemiologically predicted benefit of BP control on cardiovascular mortality seen (8).

Lowering LDL cholesterol levels, at least with 3-hydroxy-3-methylglutaryl-coenzyme A HMGCA reductase inhibitors, is now widely accepted as markedly beneficial. Reaching that point was not easy, however, and even now there is not complete agreement on the benefit despite many trials showing outcome benefits even in patients without markedly elevated LDL levels. Just before the Scandinavian Simvastatin Survival Study (4S trial; ref. 9) triggered the avalanche of favorable outcome studies, much of an entire book was devoted to denial of any established outcome benefit (10).

In many other cardiovascular areas, expected outcome benefits of biomarker modulation and even symptomatic clinical modification were not found. The inability to date to show favorable effects of blood sugar control on macrovascular events in diabetics is a well-recognized example, as is the failure of antiarrhythmic drugs to improve survival in treating ventricular arrhythmias (11) despite their clear ability to decrease ventricular premature beats and episodes of nonsustained ventricular tachycardia, both recognized markers of the risk of fatal ventricular arrhythmias. The failure of inotropic (heart-muscle–strengthening) agents to improve survival, and indeed their effect of increasing mortality, in heart failure remains well-documented but not well-explained (12, 13), and agents with negative inotropic effects (β-blockers) have proved beneficial in heart failure, all reminders that what seems obvious is not necessarily true. The replicated failure of oral iib/iiia inhibitors of platelet function to provide expected cardiovascular benefits in long-term use in coronary artery disease

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(14, 15)–indeed, some had an adverse effect (15)–when the parenteral short-term use of these drugs did reduce heart attacks and death (16, 17), is yet another example of the unexpected, as was the adverse mortality effect of torceptrapib (18), a high-density lipoprotein (HDL)-raising drug (low HDL being as well-established a cardiovascular risk factor as could be imagined).

The reasons for these failures to show expected benefits are often not known even long after the observation. They could represent pathophysiologic misunderstandings, but they may well reflect so-called "off-target effects," unrecognized adverse effects of drugs that can matter greatly when very small benefits are being sought, as is often the case in prevention settings. It is critical to remember that even drugs well-targeted to a receptor, including naturally occurring hormones, may have effects other than the desired one, as the Women's Health Initiative randomized trial has surely reminded us with its array of reported effects of an estrogen plus progestin combination on cardiovascular events and various malignancies including significantly increased breast cancer incidence and significantly reduced colorectal cancer incidence (19, 20). It would be hard to imagine a more targeted molecule than the naturally occurring hormone erythropoietin (as the name tells you, it stimulates development of red cells), yet it seems to have adverse effects on cardiovascular event rates (21–23) and makes many tumors grow faster (24).

All this leads to the conclusion that reliance on anything but real outcomes, especially in a prevention setting, where well people are being treated, is a treacherous business. But in cancer chemoprevention, in most cases, event rates are very low and events may be years or decades away. How, then, can we progress? The cardiovascular field and some illustrations from cancer suggest a pathway.

The earliest studies of clinical outcomes in cancer prevention should follow the cardiovascular example of being in very high-risk populations for the following 2 reasons:

- There will be enough events and perhaps enough early events to detect an effect if one is present, allowing smaller, shorter studies.
- Risks, including unrecognized ones, will be more acceptable in the very high-risk people who gain most from prevention because the benefit (events prevented) will be larger even if the risk reduction is the same as that in lower-risk people.

High-risk populations are therefore valuable for detecting effects and making the adverse event risk of prevention agents acceptable. In the cardiovascular area, the earliest successful outcome studies have almost always been in very high-risk populations:

- People with diastolic BP of 115 to 129 were in the first VA study (2).
- People with class III/IV heart failure were included in the first outcome study, CONSENSUS, that showed an effect on survival of the angiotensin-converting enzyme inhibitor enalapril (the study needed only 253 patients; ref. 25).
- People who had already had a myocardial infarction and had very high LDL were included in the 4S study of simvastatin (9), the first study showing a survival effect of LDL lowering.
- An important predictor of cardiovascular and cerebrovascular risk is the prior occurrence of a heart attack or stroke. People with a prior heart attack [acute myocardial infarction (AMI)] or stroke (a high-risk population) were entered into "secondary prevention" trials of aspirin that showed a decreased rate of recurrent infarction and stroke, leading to physician-directed labeling of aspirin that recommends these uses. The increased risk of gastrointestinal and intracranial bleeding caused by aspirin treatment was clearly acceptable in that population. Trials of primary prevention in lower-risk populations (no prior AMI or stroke) have been much less clear in showing benefit, and aspirin is not currently labeled for such uses. In addition, bleeding risk is a greater concern. The benefit of aspirin thus seems clearly easier to show as cardiovascular risk increases. Nevertheless, in this case, as in others, once benefit was established in high-risk patients, studies in lower-risk patients were carried out, obviously made more attractive and feasible by the prior success, and although not yet clearly successful, they are continuing.

There is some suggestion of similar approaches in oncology, in cases cited by Meyskens and colleagues, notably in the initial conduct of studies in the adjuvant setting, an obviously high-risk population for which events of interest are near-term, not usually delayed. Of course, it remains to be seen whether preventing or delaying recurrence of existing disease would predict prevention of a first cancer. In at least 1 case, however, a drug, tamoxifen, shown to delay recurrence of breast cancer after local therapy, also was shown to decrease the rate of apparently new tumors in the opposite breast (the population was plainly at a high risk for a second primary tumor). This result led to a successful study of tamoxifen for primary prevention in patients at high risk for breast cancer (a high Gail model score; ref. 26) and U.S. Food and Drug Administration (FDA) approval for this use despite tamoxifen toxicity. It is of note that this primary prevention effect was observed in a study of just 5-year treatment duration. The tamoxifen experience is also instructive with respect to risks people find acceptable. Meyskens and colleagues note the lack of wide use of tamoxifen for this prevention/risk-reduction purpose, presumably because of its toxicity (including an increased risk of endometrial cancer), but this toxicity did not prevent wide acceptance of tamoxifen as an adjuvant treatment option for preventing breast cancer recurrence. Presumably, these different levels of acceptance reflect a difference in attitude toward a tumor that was known to be present and one that has a greater risk of occurring but has not yet been seen. Raloxifene was equivalent to tamoxifen

in preventing invasive breast cancer in women with a high Gail model risk score and had a more favorable safety profile (particularly with regard to endometrial cancer risk; ref. 27), leading to an FDA approval of this agent for breast cancer risk reduction in 2007. It will be of interest to see whether this drug proves more acceptable.

It would clearly be useful if it were possible in more settings to identify populations at increased risk for cancer so that initial trials could be carried out in those populations, perhaps followed, after success, by studies in lower-risk populations. Apart from the use of the Gail model to identify populations at elevated risk of breast cancer, it is well known that *BRCA1* mutation carriers are a population at very high risk of breast cancer, so high that prophylactic mastectomy is sometimes utilized. A group of drugs, PARP inhibitors (28), considered promising in the therapeutic breast cancer setting are also currently in clinical trials in the prevention setting. Use of the *BRCA1* mutation to enrich breast cancer prevention trials of PARP inhibitors is discussed recently in a perspective by de Bono and Ashworth (29). It seems possible that the *BRCA1* mutation could also be used to identify patients for ovarian cancer prevention studies.

Attempts to reduce the risk of colorectal cancer with nonsteroidal anti-inflammatory drugs (NSAID) further illustrate the advantages of early studies of high-risk patients in whom (i) an effect may be demonstrable and (ii) different kinds of evidence may be persuasive. The NSAID celecoxib was shown to reduce the number of polyps in patients with familial adenomatous polyposis (FAP; ref. 30), patients with a nearly 100% risk of colorectal cancer. FDA approved this use (there was no other treatment aside from prophylactic colectomy) under the Accelerated Approval (Subpart H) rule in 1999. Subpart H allows approval of a drug for treating a disease with no available therapy on the basis of a documented effect on a surrogate endpoint "reasonably likely" to predict a clinical benefit. Under the rule, further studies were required to show actual clinical benefit of celecoxib in FAP patients. Such a trial is ongoing in pediatric FAP patients (to assess the clinical benefit of delayed surgery) but has not yet been completed. Trials of celecoxib also have shown a reduction in the risk of colorectal adenomas in patients at an elevated risk but without FAP; these trials, however, have been complicated by concerns about adverse cardiovascular effects of cyclooxygenase-2–selective NSAIDs (31). An ongoing, large cardiovascular outcome trial (in arthritis patients) comparing celecoxib, naproxen, and ibuprofen may clarify this aspect of risk (32). The situation reminds us that prevention, at least in people not at very high risk, demands a very high level of safety assurance. There is little doubt that if aspirin were convincingly shown to reduce colorectal cancer risk, the vast controlled trial experience in the cardiovascular area would be very reassuring. Furthermore, the acceptance level for aspirin, celecoxib, or potentially other NSAIDs likely would increase markedly if they were shown to be effective in high-risk populations such as patients with a history of advanced colorectal neoplasia (i.e., cancer or advanced adenomas).

Subpart H also raises the issue of useful surrogate endpoints, such as those (e.g., BP and LDL cholesterol level) accepted for cardiovascular drug testing. The bar for accepting a surrogate as a basis for long-term use in a healthy population is high, even in the face of convincing epidemiologic data supported by animal data showing biological plausibility. Even when the rationale is strong, there is always the possibility of unexpected "off-target" effects that undermine, or even reverse, any plausibly expected benefit (11–13, 18). Thus, although reduction of polyps was an acceptable surrogate (under Subpart H) in FAP, a question yet to be determined is whether a reduced risk of adenomas would be considered an acceptable endpoint for clinical benefit in patients with colorectal neoplasia.

An important problem in most prevention settings is the absence of good predictors of risk so that studies must be large and long and many people who will never develop cancer must be treated. The adjuvant, high-risk breast cancer and FAP cases show how advantageous (for clinical research) it is to have disease develop in a large proportion of the patients. It seems very likely that the identification of new genomic markers of risk (e.g., *BRCA* mutations), together with historical markers (previous tumor), will provide opportunities for the conduct of initial studies of prevention. Syndromes such as FAP and hereditary breast and ovarian cancer, characterized in general by germline mutations in *APC* and *BRCA*, respectively, are also situations in which standard prevention is extraordinarily invasive, for example, removal of the colon or both breasts, so that the need for alternatives is high and acceptable risks might be higher than in other settings.

One advantage cardiovascular risk reduction has had is that in many cases improvements occur rapidly, beginning in under a year (BP, LDL cholesterol, postinfarction β-blockers). This has been seen in adjuvant breast cancer, but, at least so far, preventing or delaying new cancer development is a longer-term process.

It seems clear that effective cancer prevention drug development will depend on finding clinical features and biomarkers that identify high-risk states and, if possible, markers that predict a high likelihood of response. As in the cardiovascular area, such markers greatly facilitate a showing of benefit, but, almost as important, they identify a population in which the drug risk can be balanced against a high likelihood of benefit.

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