Commentary

Cancer Prevention Research

Cancer Interception

Elizabeth H. Blackburn

Abstract

A common perception is that cancer risk reduction is passive, such as not smoking. However, advances in the understanding of cancer biology and in cancer treatment modalities suggest that it is now timely to consider anew cancer risk reduction by active, including pharmacologic, approaches. Risk avoidance approaches are certainly important, but other approaches are important as well, as exemplified by the irony that most new lung cancers occur in former smokers, or current avoiders. Cancer interception is the active way of combating cancer and carcinogenesis at earlier and earlier stages. A great challenge is to educate people that the development of cancers, like heart disease, typically takes years and accordingly can potentially be intercepted with risk-reducing agents in the same way that advanced cancers can be treated with drugs or that cardiovascular disease can be intercepted with antihypertensive and other risk-reducing drugs. The cancer biology behind cancer interception is increasingly solid. For example, hedgehog pathway studies of mutations in the patched homolog 1 (*PTCH1*) gene, which constitutively activates Smoothened (SMO), led to development of an oral SMO inhibitor active in advanced basal cell carcinoma and which, in very high-risk Gorlin syndrome patients (germ line *PTCH1* mutation), is nearly completely clinically effective in intercepting basal cell neoplasia. Also, the oral immunomodulator lenalidomide, first found to be active in advanced, relapsed multiple myeloma, was highly effective in intercepting the precursor stage, high-risk smoldering multiple myeloma from progressing. These are but two exciting, recent examples of the many advances in cancer research that have created an optimal time to discover and implement cancer interception. The multifaceted roles of telomere maintenance in both fueling advanced cancers and, at early stages, keeping them at bay, also highlight how the growing knowledge of cancer biology opens avenues for cancer interception. Emerging molecular techniques, including next-generation sequencing platforms, that account for a large part of the remarkable recent advances in cancer biology are now being applied to interception of premalignancy. Keeping the medical community and public at large informed about possibilities for actively intercepting cancer will be important for gaining acceptance of this increasingly powerful approach to lessening the cancer burden. *Cancer Prev Res; 4(6); 787–92. ©2011 AACR.*

Cancer interception is the active way of combating cancer at earlier and earlier stages. Most people not working in or very familiar with the field usually think that cancer "prevention" is somewhat passive, such as smoking avoidance to prevent getting lung cancer, which is an example of primary prevention. Although this category is crucially important, other approaches are needed as well. This need is emphasized by the startling fact that now the majority of new lung cancers develop in *former* smokers where preventive agents appear to be more active (1). The growing science and knowledge of cancer biology and treatment are showing us ways to intercept cancers by new, active approaches. The term "cancer interception" captures this idea: to actively intercept a cancer development process before the damage is done, that is, before the full-blown advanced tumor presents in the clinic (Fig. 1). A great challenge for medicine is to let people know that the development of cancers, like heart disease, can be intercepted with risk-reducing agents, in the same way that cancers can be treated with drugs or that cardiovascular disease (CVD) can be intercepted with antihypertensive and other risk-reducing drugs.

Intercepting, or *actively* preventing, cancer has been a hard sell heretofore, including even among people prone to exploring it for their personal health. Even educated, at-risk people have trouble with adherence to risk reduction; for example, adherence to established effective breast cancer risk–reducing agents has proven challenging despite active adherence promotion. Yet, although confronting similar challenges, risk reduction in other settings such as CVD and osteoporosis has met with widespread acceptance.

Why has pharmacologic CVD risk reduction become so widely accepted, whereas pharmacologic cancer risk

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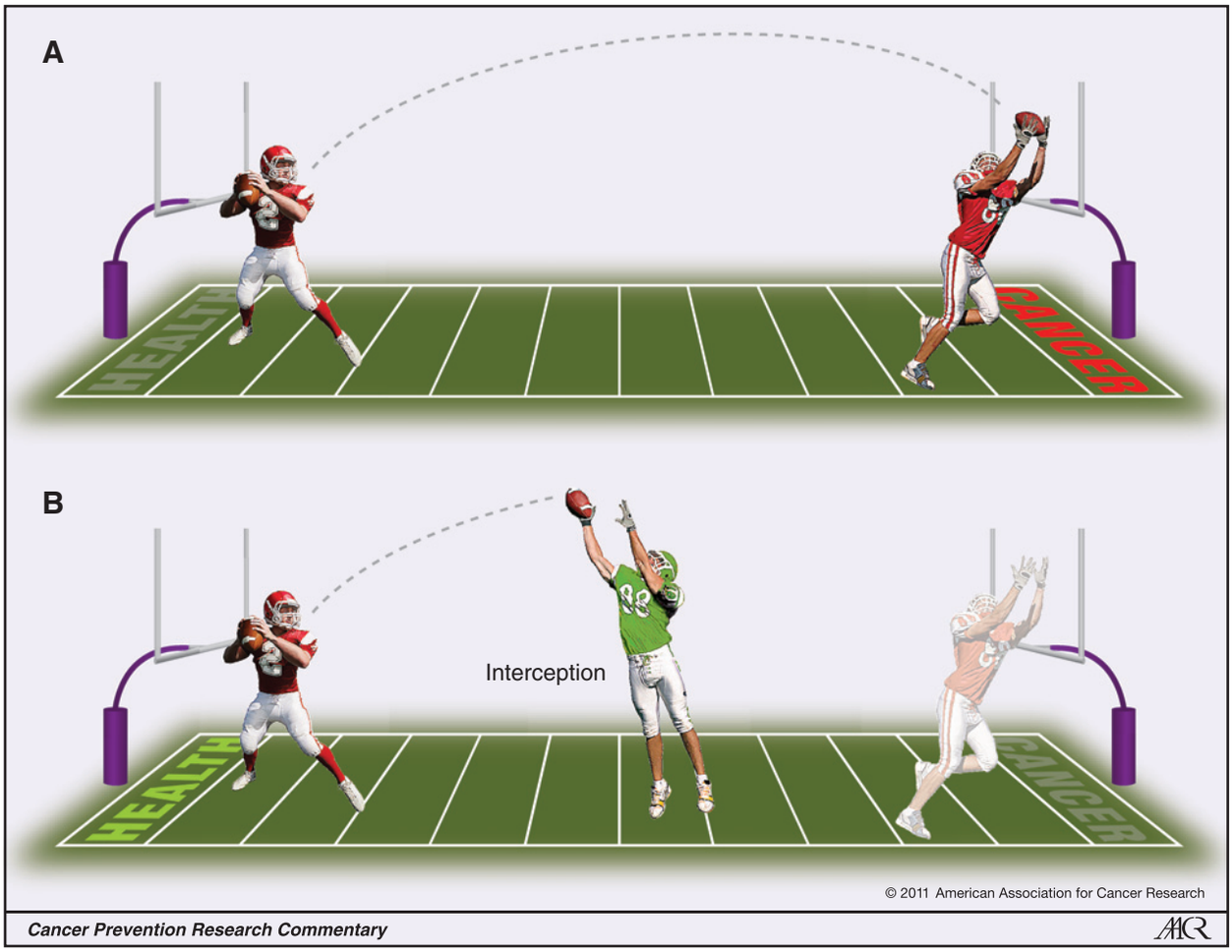

Figure 1. Cancer interception. As in a game of American football, the Cancer touchdown (top) can be prevented by interception (bottom), thus preserving good health. Intercepting cancer can be accomplished by various means including oral small molecules, vaccines, and physical activity.

reduction has not? One proposed reason is that CVD risk reduction treats measurable conditions—notably, hypertension and high cholesterol levels—that patients can follow to assess effectiveness. Cancer interception or risk reduction actually also has at least one good example of a marker of success. Aspirin can reduce the number of detectable colorectal adenomas (the measurable condition) and has been shown to reduce colorectal cancer mortality and incidence in long-term follow-up of randomized controlled CVD trials; aspirin also is associated with the reduced mortality of several other common cancers (2, 3). In this case, surgical control of colorectal adenomas has established this lesion as a biomarker of cancer risk and mortality reduction (4). Another proposed obstacle to public acceptance of cancer risk reduction is the risk of toxic effects. This concern may be allayed, in part, by a new study of celecoxib and other nonsteroidal anti-inflammatory drugs (NSAID), which, like aspirin, were shown to be active in intercepting colorectal neoplasia but, unlike aspirin, to also produce adverse CV effects. The new data indicate that low-baseline CVD risk or low-baseline C-reactive protein level eliminates the risk of NSAID-associated CVD toxicity (5). This example, furthermore, emphasizes another important concept: More "personalized" cancer interception may be the most effective. It is notable that CVD risk reduction with antihypertensive agents also has risks of substantial toxicity. Nevertheless, these proposed reasons have a sound basis and speak to a lack of effective public education about the parallels of cancer risk reduction with CVD risk reduction, and the need to remedy this lack (6).

Cancer interception has never been more desirable or necessary. In the United States, for example, 44% of men and 38% of women will develop cancer in their lifetimes. Eighty-four percent of all cases are diagnosed after age 60; 31% of all cases are diagnosed after age 80. The population is aging, and an increased fraction of the population in the United States and world is reaching cancer-prone ages. Early detection increases cancer diagnosis rates. Treatment has improved, increasing the life spans of cancer patients; survivors are at increased cancer risk. These factors all point to a significantly increasing cancer burden that can only be

mitigated by a double-pronged approach: interception as well as treatment.

Advances in cancer research have created an optimal time to discover and implement cancer interception. Lessons can be learned from risk reduction drug development in the CVD setting (7). The first advances in CVD prevention derived from (a) antihypertensive agents in treating patients with high-risk severe hypertension (diastolic blood pressure: 115–129) or with class III/IV heart failure, (b) statins in treating patients with prior myocardial infarction (MI) and very high LDL (low-density lipoprotein) cholesterol, and (c) aspirin in treating patients with prior MI or stroke. All these therapies were effective in advanced disease and subsequently were tried and became standard in lower risk settings of CVD prevention (7).

This reverse migration (from therapy and established disease to intercepting disease before it becomes established; Fig. 2; refs. 8–10) is illustrated in several settings. Both selective estrogen receptor modulators (SERM) and aromatase inhibitors were pursued for treating advanced breast cancer before showing activity in preventing it. SERMs were developed as a result of the early discoveries of the ER and its role in breast cancer (11). These agents first proved active in advanced cancer (30% activity in ER-positive tumors), then worked back through the adjuvant setting (resected ER-positive early breast cancer, where they reduced recurrence by 50%, ER-negative recurrence by 6%),

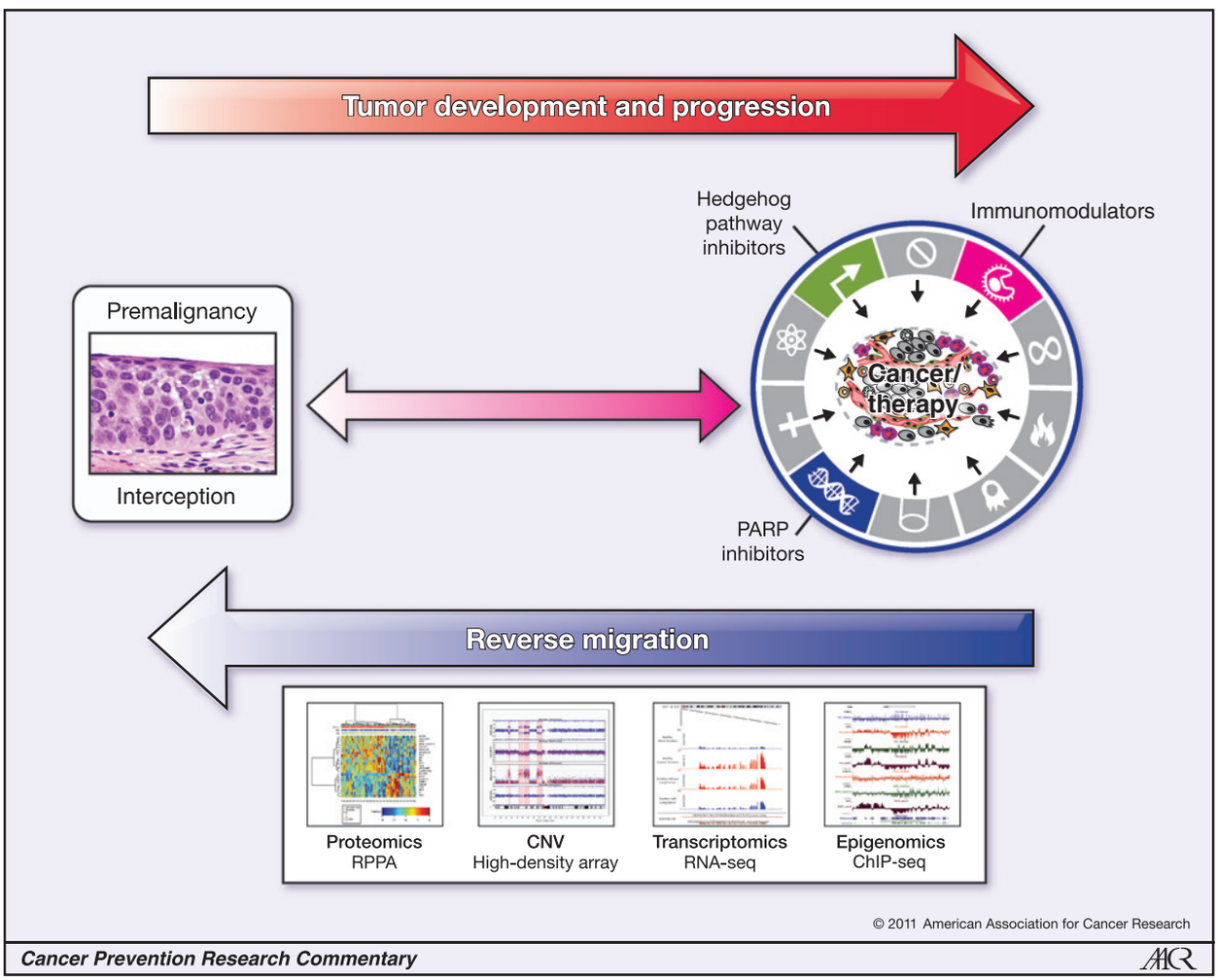

Figure 2. Advances in the biology and interception of premalignancy derive from advances in the biology and therapy of cancer. The color saturation at the right-hand side of the horizontal arrows reflects the greater body of work in cancer biology and therapy. The reverse migration arrow reflects the movement of small molecules and other agents from therapy to interception. The cancer-hallmarks diagram (9) at the right shows three examples of hallmarks that were originally targeted in malignant cancer by small molecules currently on the path of reverse migration toward interception (see text). Molecular techniques (bottom; ref. 10) that account for a large part of the remarkable recent advances in cancer biology are now being applied to interception of premalignancy. In particular, next-generation sequencing platforms, an emerging technology that has been used to profile the epigenome and transcriptome in cancer tissue, are now being applied to the study of premalignant cells (RNA-seq, bottom right; ref. 46). RPPA, reverse-phase protein array; CNV, copy number variance; ChIP-seq, chromatin immunoprecipitation sequencing. (The cancer-hallmarks diagram in this figure was adapted with permission from Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.)

and next worked back to effective prevention with the SERM raloxifene in moderate-risk women with no cancer history (50% prevention overall, 80% prevention of ER-positive breast cancer, and ineffective in preventing ER-negative disease; refs. 12, 13). Androgen suppression therapies in prostate cancer also have reverse migrated from metastatic to locally advanced (14) to interception of disease (15, 16). Breast research has also shown that molecular subtypes, which are intensively studied in invasive breast cancer biology and treatment, are now known to exist in premalignant breast disease (17) and are becoming increasingly clear in pre-premalignant cells, driven in large part by cellular stress and molecular heterogeneity (18, 19). This work has major implications for risk profiles and targeted interception. Human papilloma virus 16 (HPV16) was linked to cervical cancer (20), leading to the development of an active HPV16 vaccine (21, 22), followed by the development of bivalent and quadravalent HPV vaccines for standard interception of cervical premalignancy and cancer. More recently HPV, particularly HPV16, has been linked to oropharyngeal cancer, and the reverse migration development of vaccination to intercept oropharyngeal cancer is now in progress (23). Reverse migration in myeloma has involved lenalidomide, which is an immunomodulator capable of enhancing immune cell function via activation of T cells and natural killer cells and via increased expression of death effector molecules. Standard-dose lenalidomide plus high-dose dexamethasone produced an approximately 60% response rate (and median time to progression of 12 months) in advanced, relapsed multiple myeloma (24). A very recent phase III trial randomly assigned patients with the precursor stage, high-risk smoldering multiple myeloma to no treatment (the standard approach for this disease) versus treatment with standard-dose lenalidomide plus low-dose dexamethasone induction followed by low-dose lenalidomide alone. Progression to clinically active myeloma occurred in 8% (5 of 60) of lenalidomide-treated patients versus 46% (28 of 61) of no-treatment/control patients after 22 months of median follow-up; median time to progression was 25 months (no treatment) versus not reached (treatment; HR = 8.0, $P < 0.0001$; ref. 25). Recent study of agents targeting interleukin 6 is showing great promise in this setting.

The breast provides another promising reverse migration in the form of synthetic lethality, an emerging approach of personalized, targeted therapy and, also, interception. PARP inhibitors induced therapeutic synthetic lethality in *BRCA* mutation carriers with advanced breast (26) and ovarian cancer and have since moved into early clinical testing for breast cancer interception (27). The development of this approach includes a phase II therapy trial of the PARP inhibitor olaparib (competitive inhibitor of PARP1 and PARP2), which produced a response rate of 41% in advanced breast cancer patients with germ line *BRCA1* or *BRCA2* mutations. Synthetic lethality with other agents [TNF-related apoptosis-inducing ligand (TRAIL) plus a Smac/DIABLO mimic] has moved into preclinical testing for the interception of colorectal and lung neoplasia (28, 29). This synthetic lethality approach targets *APC* and *KRAS* mutations, which occur in invasive and preinvasive disease, respectively (30).

Reverse migration is also exemplified very well by the biology of hedgehog signaling in basal cell cancer. Basal cell skin cancer, the most common cancer in humans, results largely from mutations in hedgehog pathway genes, including the protein patched homolog 1 (*PTCH1*) gene, which constitutively activates smoothened (SMO) during progression to basal cell cancer. The oral, highly specific small-molecule SMO inhibitor GDC-0449 first produced remarkable clinical responses (response rate of 50%) in advanced metastatic basal cell carcinoma (31) and then nearly completely suppressed basal cell lesions ($P < 0.001$) in a very recent double-blind, placebo-controlled randomized prevention trial in 41 very high-risk Gorlin syndrome patients, who have a germ line *PTCH1* mutation; patients were randomly assigned in a drug-to-placebo ratio of 2 to 1 (32). GDC-0449 also reduced the downstream hedgehog signaling target Gli1 mRNA levels by 200-fold. Despite the small number of patients, this trial was very robust because of its extremely high-risk setting; it also is an excellent example of taking personalized cancer therapy back into interception (33). Even in this robust, positive trial, most lesions recurred after stopping therapy, underscoring the importance of understanding drug resistance mechanisms. Recent study suggesting cross-talk between hedgehog and insulin-like growth factor pathways potentially will advance our understanding of resistance in this setting and will contribute to the identification of targeted agents for overcoming it (34).

Last, like so much in cancer biology, telomere maintenance or dysfunction (which is caused by inadequate maintenance of telomeres, causing them to shorten) is a double-edged sword with distinct, context-specific effects (35, 36). For example, telomere maintenance in normal cells protects against genomic instability that can lead to cancer or other aging-related diseases; whereas, once the full hallmarks of cancer develop (9), telomere maintenance can enable the advanced malignant cells to keep replicating. Telomere shortness in normal cells (with its concomitant potential for loss of genome protection) is a measurable risk factor for the clinical development of cancer (37). That rare inherited genetic mutations in genes causing telomere shortness are clearly linked to cancer has been known for a while (38, 39). It was not known until recently, however, whether common single-nucleotide polymorphisms (SNP) associated with cancer also are associated with telomere changes. Very recent work was first in showing that the association between a common SNP in the general population and bladder cancer is statistically significantly mediated in part by telomere shortening (40); other factors contribute to the risk of bladder cancer as well. The influence of telomere maintenance or dysfunction in premalignant or normal-appearing but molecularly altered precancerous cells is less clear. In a normal cell, telomere dysfunction causes cells to senesce (i.e., stop proliferating), thus intercepting any potential trajectory toward cancer development. But, such

senescent cells secrete tumor-promoting factors and thus may promote cancer progression in neighboring cells (41). In a cell with molecular damage (even a normal-appearing cell), telomere dysfunction can launch the cell toward carcinogenesis. The predisposing damage may come from cellular stress related to obesity, inflammation, smoking, and psychosocial factors (42), all of which are associated with telomere shortness and dysfunction. A recent study of psychosocial factors has shown that psychological stress increases cancer progression in the breast and ovaries, but it is unclear if it also increases cancer risk (43). A study of the influence of psychosocial stress on molecular changes in metastasis identified molecular targets that could lead to the interception of metastasis development; for example, such a target was suggested by recent work showing the mechanistic link between adrenergic stress and focal adhesion kinase (FAK) activation (which protects cells from anoikis), supporting the potential of β-2 adrenergic receptor blockers to intercept metastasis (44). Although clinical therapy trials in advanced cancers are only just beginning to target telomerase activity, there are many other genes involved in regulation of telomere function and many cellular pathways that can indirectly affect it (e.g., DNA repair pathways). There are a number of telomere maintenance genes encoding telomerase components (e.g., *hTERT* and *hTERC*) and telomere-protective proteins (e.g., *TIN2*, *TRF1*, and *TRF2*) which may lead to the discovery of targets for cancer interception (45).

Advances over the next few years in cancer research that will continue to feed into cancer interception, for example, for profiling premalignant cells, will arise largely from rapidly emerging next-generation sequencing platforms (Fig. 2). Elsewhere in this issue of the journal, Beane and colleagues show the potential impact of transcriptome sequencing (RNA-seq) on developing novel insights into the early molecular events in airway epithelial cells that may lead to the development of lung cancer among smokers (46). This group previously used microarray technology to globally profile the mRNA changes associated with tobacco smoke exposure (47, 48) and to identify a gene expression signature in the bronchial airway that can serve as a sensitive and specific biomarker for the early detection of lung cancer (49). These alterations in airway gene expression may precede the development of lung cancer and can potentially be reversed by preventive strategies (50). Using the next-generation sequencing platform RNA-seq, this group has now uncovered novel coding and noncoding RNAs, whose expression is altered in the airway in response to smoking and lung cancer and which microarrays did not interrogate or find to be significantly altered (46). In addition to their potential for providing novel insights into the molecular field of injury associated with tobacco smoke exposure, coding and noncoding transcripts uncovered by RNA-seq may function as biomarkers of lung cancer risk and as novel targets for prevention.

Although treating or even curing cancer is often, understandably, at the forefront of people's minds, cancer will never be brought under control unless the other side of the equation is addressed: intercepting, or preventing, it (Fig. 1). This is not impossible. Just from smoking control efforts alone, countless cancers have been prevented, and interception can be accomplished with diet and exercise (51) interventions as well, with effects of exercise possibly mediated in part by effects on telomere maintenance (52). Prevention is clearly more cost-effective—counting at least human costs—than treatment. The ability to intercept cancers at earlier and earlier stages, which is arising from the rapidly increasing armamentarium of emerging technologies and therapies, is predicted to further reduce the burden of cancer on the health and well being of the public.

Disclosure of Potential Conflicts of Interest

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