Commentary

Cancer Risk Assessment and Cancer Prevention: Promises and Challenges

Brian J. Reid

"*Acquired genetic lability permits stepwise selection of variant sublines and underlies tumor progression*" (1).

Despite intense efforts to cure cancers through advances in staging, surgery, chemo- and radiation therapy, treatment of most advanced, symptomatic epithelial malignancies continues to be challenging, and age-adjusted cancer mortality in the United States has decreased by only 5% since 1950 (2). The clinical course of treated cancer patients all too often culminates in relapse and death. Ironically, growing evidence also suggests that many patients with premalignancy or even malignancy follow benign courses and die far more often of non-cancer causes than of cancer (3–5). These paradoxical phenomena form the dilemma of early detection-underdetection of life-threatening early disease and overdetection of indolent early disease. Personalized medicine promises dramatic reductions in cancer mortality by identifying the patients at risk of cancer mortality and treating them before deep invasion, metastasis and death (6). The challenge for personalized medicine is to improve cancer risk assessment so that cancer prevention and early detection can focus on high- risk patients in whom interventions have the greatest probability of prolonging productive life expectancy.

Cancer risk assessment and cancer prevention are inevitably linked by their goals to accurately predict progression to cancer and intervene to decrease risk of death. Cancer genomics and epigenomics have the potential to target interventions on highest-risk patients most in need of prevention and thereby avoid unnecessary treatment-related harm to patients with indolent conditions unlikely to cause death. Many interventions are associated with adverse events, and the overdiagnosis of cancer can result in harm to a subset of patients who would not have suffered from cancer (7). Other potential harms of overdiagnosis are more subtle and include unnecessary fear of dying or suffering from cancer and the real loss of, limitations to, or increased premiums for health care insurance (8, 9). Accurate cancer risk biomarkers could provide evidence to reassure low-risk patients that they do not need an intervention, in addition to identifying high-risk patients for whom interventions can increase longevity. Interventions that act systemically to reduce all-cause mortality may be especially beneficial (10).

Cancer is an evolutionary process (11, 12). Morphology is the current standard for diagnosis of premalignant conditions and

cancer itself, but morphologic assessment may be limited in its ability to distinguish asymptomatic indolent conditions from those that will progress to advanced malignancies and death (3–5, 13). Examining cancer from an evolutionary perspective can open new approaches for cancer risk assessment, diagnosis, therapy and prevention. The evolution of multicellular organisms has been accompanied by constraint of cellular evolution, and cancer represents a breakdown of the mechanisms that suppress cellular evolution. Cairns hypothesized that the architecture of proliferating epithelial tissues would suppress tumor formation by restricting and sequestering stem cells in epithelial proliferative units, for example, at the base of intestinal crypts (14). Opportunities for competition between variants that might arise would be restrained by shedding differentiated cells from the epithelial surface (14). However, abnormalities involving some tumor suppressor genes such as *CDKN2A* predispose to clonal expansions in which self-renewing mutant cells with stem-cell-like qualities expand to encompass large numbers of epithelial proliferative units such as crypts in Barrett's esophagus (15). The number of such self-renewing cells is a critical factor that determines the effective population size of an evolving neoplasm (12). Several recent advances indicate that biomarkers that assess evolution of clones can improve cancer risk assessment (16–18) and provide insight into mechanisms of acquired therapeutic resistance, for example, to imatinib (19) and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors gefitinib and eroltinib (20, 21).

How can we predict who is likely to develop and die of cancer? Neoplastic evolution is governed by the generation of gene alterations (which can be genetic or epigenetic), selective advantages of these mutations (advantageous, disadvantageous and neutral), and clonal expansions of selected variants. Much of our understanding of neoplastic evolution comes from premalignant conditions that can be biopsied over time, such as Barrett's esophagus and oral leukoplakia, and most research has focused on selected gene mutations, including prominent mutations in tumor suppressor genes and oncogenes. Researchers in both oral leukoplakia and Barrett's esophagus have reported 10-year prospective studies of biomarkers that can be used to identify patients at a high risk of cancer (16, 18). In oral leukoplakia, the most important markers of cancer risk included histology, cancer history, chromosome polysomy, TP53 protein expression, and loss of heterozygosity (LOH) involving chromosomes 9p and 3p (18). In Barrett's esophagus, a chromosome instability panel of 9p LOH, 17p LOH, and DNA content tetraploidy and aneuploidy distinguished a high-risk population (79% five-year cumulative incidence of cancer) from a low-risk population (0% cumulative incidence of cancer over nearly 8 years; ref. 16). Adding the factors *TP53* and *CDKN2A* mutations and *CDKN2A* methylation did not improve the chromosome-instability risk model in Barrett's (Fig. 1). The panels for oral

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leukoplakia and Barrett's esophagus had several elements in common, including abnormalities associated with large clonal expansions (9p LOH), pleiotropic effects involving loss of G1/S control, evasion of apoptosis and genomic instability (*TP53*, 17p LOH), and generation of viable clones with large-scale chromosome abnormalities (polysomy, tetraploidy, aneuploidy).

Most biomarker studies have focused on frequent genetic or epigenetic events in a given neoplasm, but these events in one tissue may vary from those in another. Some supportive preliminary data support another approach-studying evolutionary measures such as clone size, mutation rate, generation time and natural selective advantages that may be common across tissues and neoplasms. For example, neutral mutations increase diversity in a neoplasm, and some neutral mutations can undergo large clonal expansions as hitchhikers (aka "passengers") on an expansion driven by a selected mutation ("driver"; refs. 17, 22). Measures of clonal diversity derived from evolutionary biology and ecology and including neutral mutations have been reported to predict progression from Barrett's esophagus to esophageal adenocarcinoma (Fig. 1), even when adjusting for *TP53* and aneuploid status (23). Size of genetically unstable clones also predicts progression in Barrett's esophagus (24).

What are the evolutionary causes of acquired resistance, and can we monitor for them? An intervention to treat or prevent cancer can dramatically change selective pressure in a neoplasm, decreasing progression to cancer but also possibly selecting for resistant variants. It is not yet clear

how many pathways will be discovered for therapeutic resistance. Therapeutic resistance has been well documented in chronic myelogenous leukemia (CML), where mutations in BCR-ABL confer resistance to imatinib (19). Molecular therapy surveillance has become integral to clinical management of CML, and second-generation inhibitors of BCR-ABL have been developed for treating imatinib-resistant disease. At least two pathways of acquired resistance have been reported for the EGFR tyrosine kinase inhibitors gefitinib and eroltinib in lung cancer, including a secondary mutation in *EGFR* and amplification of the *MET* oncogene (20). These examples illustrate that molecular surveillance is likely to be important for monitoring interventions so that mechanisms of resistance can be understood and new targeted interventions developed. Our current understanding of premalignant conditions suggests that they have fewer somatic genetic abnormalities and less clonal diversity than does cancer, which might translate to less acquired therapeutic resistance, but our understanding is incomplete. Whether or not evolutionary measures such as cellular or clonal genetic diversity can provide an estimate of the chance of developing acquired resistance to chemoprevention or chemotherapy remains an open question.

So how might we use cancer screening, risk assessment, and prevention to lower the mortality of cancer? Screening may identify some patients early in progression but also potentially biases toward detection of indolent conditions that persist
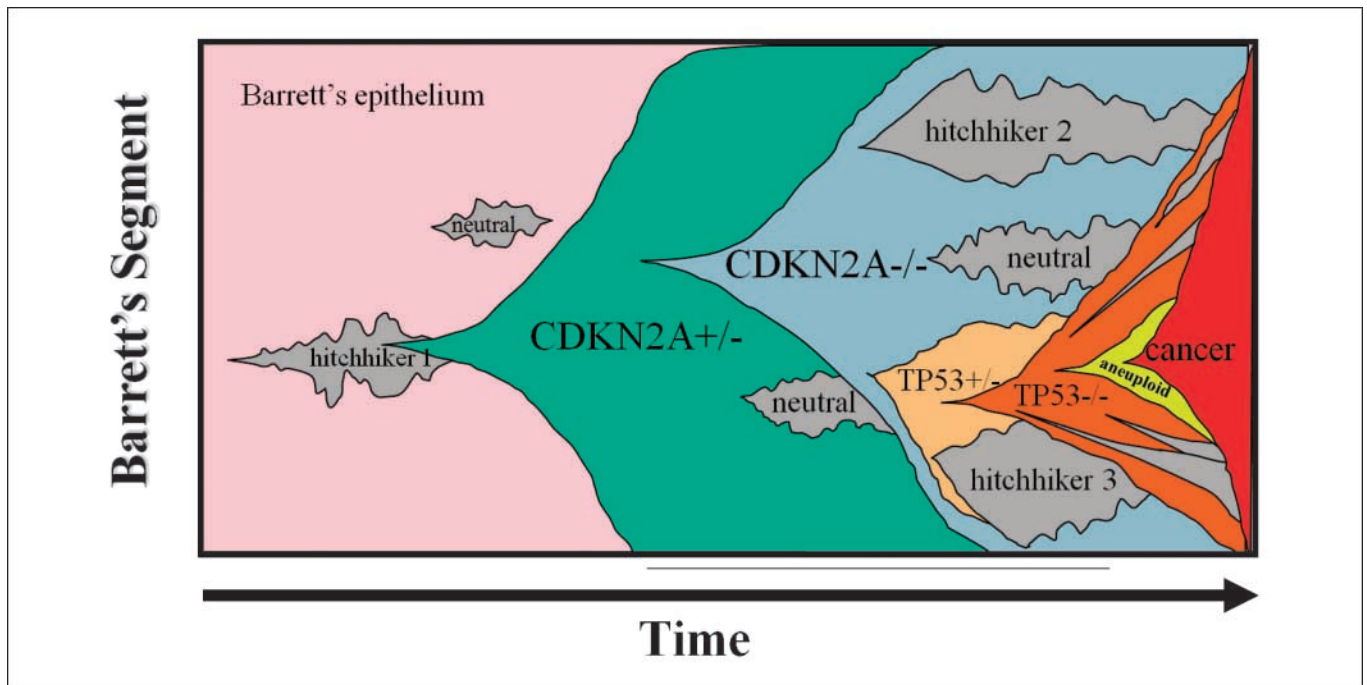

Fig. 1. Clonal evolution. *X* axis, time; *Y* axis, the extent of a neoplasm, in this case Barrett's segment length. Barrett's esophagus arises in a subset of patients in response to the harsh environment of gastroesophageal reflux. Loss of one or both alleles of *CDKN2A* provides a selective advantage leading to clonal expansion. Neutral mutations also arise during clonal evolution. If they arise in a clone that has a selected mutation such as those affecting *CDKN2A*. the neutral mutation can expand as a hitchhiker on the selected mutation. Otherwise, neutral mutations expand or contract through a random process of genetic drift. *TP53* mutations and LOH are selected as later events in neoplastic evolution, but *TP53* variants seem to be selected almost exclusively in the genetic background of *CDKN2A* variants. *TP53* variants have pleiotropic effects including loss of cell cycle checkpoint control, evasion of apoptosis and genomic instability that increase genetic diversity within the neoplasm, and they are permissive for subsequent evolution of tetraploid and aneuploid clones. The sizes of genetically unstable clones with *TP53* abnormalities and aneuploidy are predictive of future progression to esophageal adenocarcinoma. A panel of chromosomal instability biomarkers (9p, 17p LOH, tetraploidy, aneuploidy) provides independent cancer risk prediction in Barrett's esophagus, but mutations in *CDKN2A* and *TP53* and methylation of the *CDKN2A* promoter do not.

for years and require no intervention (7). This may be the case for Barrett's esophagus, where the rate of progression to esophageal adenocarcinoma is low (7 per 1,000 person-years of follow-up) and endoscopic screening can miss rapidly progressing neoplasms (25–28). Improved population-based cancer risk models (employing clinical/classical epidemiologic factors) that could help guide screening with tissue-based molecular-biomarker risk models in the premalignant neoplasm could lead to identifying high-risk patients for cancer prevention (29). In the absence of robust cancer risk models, screening and surveillance may become inefficient as has been the case with Barrett's esophagus. Endoscopic clinics are filled with Barrett's patients with a low or no risk of developing esophageal adenocarcinoma, and prior recommendations for population-based screening have recently been withdrawn (30). A strategy to treat all cases of Barrett's esophagus (31) without accurate risk stratification would be cost prohibitive, expose low- or no-risk patients to harm from serious adverse events (including esophageal perforation and stricture; ref. 30), and have a negligible impact on the mortality of esophageal adenocarcinoma (26–28). Any strategy for cancer control in Barrett's esophagus must consider the indolent state of most cases, especially in light of recent evidence that Barrett's epithelium appears to be a successful protective adaptation to the harsh environment of gastroesophageal reflux that may be beneficial to the patient in many cases (32–36). Whether or not other indolent premalignant conditions represent an adaptation to injury or an evolution to a fitness peak, from which it is difficult to progress to cancer, or simply lack critical abnormalities required for progression to cancer remains an unknown and challenging question. Indolent cancers, such as some prostate cancers, that fulfill the morphologic criteria for malignancy and yet follow a benign course are especially perplexing challenges for clinical management; a better understanding of the evolutionary differences between indolent and aggressive cancers might lead to improved strategies for cancer control. These differences might be properties of the tumors themselves; for example, indolent cancers may have evolved to a fitness peak from which it is difficult to acquire the properties that confer an aggressive, metastatic phenotype. Alternatively, the differences might reside in host or microenvironmental factors that suppress critical steps in neoplastic evolution (37).

Cancer risk biomarkers could become entry criteria for randomized cancer prevention trials in high-risk patients and thus most likely to reduce cancer incidence and mortality. A randomized trial of photodynamic therapy with sodium porfimer reduced the incidence of cancer, but not mortality, in patients with high-grade dysplasia in Barrett's esophagus (38, 39). Aspirin might reduce other causes of mortality for Barrett's patients, and another tailored chemoprevention approach would be to use high-risk biomarkers in selecting Barrett's patients for a randomized trial of aspirin (16, 40). Similar cancer prevention strategies have been proposed for high-risk oral leukoplakia patients.

Remarkable advances in cancer risk modeling are identifying high-risk patients for whom cancer prevention would significantly reduce cancer morbidity and mortality. These advances are paralleled by an increased understanding of the mechanisms of acquired resistance to therapy, especially when the neoplasm can be evaluated before and after treatment. We still lack essential information about clonal and cellular diversity that may be critical in managing premalignant conditions, but serial sampling of neoplasms in randomized clinical trials of high-risk patients offers a great opportunity to delay or prevent cancer; to identify mechanisms of acquired resistance; and to develop preventive combination therapies to reduce cancer mortality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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