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Cancer Epidemiology, Biomarkers & Prevention

Editorial

Precision Prevention of Cancer

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"Prevention is better than cure."
Desiderius Erasmus (1466–1536)

Most tumors are incurable once they reach an advanced (e.g., metastatic) stage. Even for those cancers with effective treatment options, prevention has the greatest potential to reduce the burden of cancer in the general population. The *2014 AACR Cancer Progress Report* states that a large proportion of cancers could be prevented by modifying factors such as tobacco use (33%), obesity (20%), and cancer-causing pathogens (16%). The American Cancer Society estimates that three quarters of women over age 50 have undergone mammography screening for breast cancer, which saves approximately 10,000 lives each year in the United States. Death rates from cervical cancer can be reduced by more than 80% among women who undergo routine Pap smears.

Prevention can be implemented at a number of levels: Primary prevention of tumor occurrence includes risk assessment, modification of carcinogenic exposures, vaccination, risk-reducing surgeries, and chemoprevention; secondary prevention includes screening, early detection, and treatment of precancerous lesions; tertiary prevention includes survivorship approaches that minimize unfavorable outcomes. Each of these levels has challenges and limitations, and mortality for any given cancer may be preventable at more than one of these levels.

Despite the need and potential to prevent cancer, not all individuals benefit equally from current cancer prevention strategies. For example, prostate cancer screening by prostate-specific antigen and digital rectal examination can detect tumors at an early stage. However, the test characteristics of PSA screening are poor when applied to all men equally, and the risks associated with unnecessary postscreening procedures may outweigh the decrease in cancer mortality in some men. Early detection of colorectal cancer by fecal occult blood tests, flexible sigmoidoscopy, and colonoscopy is highly effective: screening can produce an 80% reduction in colon cancer–related deaths, yet more than two third of people over age 50 do not follow recommended screening protocols. Finally, screening for some tumors is inadequate or nonexistent. These include cancers that account for a relatively large proportion of cancer mortality such as ovarian and pancreatic cancers. Thus, cancer prevention strategies have yet to impact cancer incidence, morbidity, and mortality in all individuals who may benefit from them.

Furthermore, any given prevention strategy may not be equally effective in all individuals because of biologic differences in risk and response to the preventive modality. Vogelstein and colleagues (1) recently discussed the extreme complexity and heterogeneity in tumor phenotype as a critical barrier in the treatment of many cancers. They state that cancers result from sequential mutations in 2 to 8 key "driver" genes occurring over 20 to 30 years, and there are somatic mutations in >140 genes that contribute to cancer. Epigenomic changes and other biologic events also increase phenotypic heterogeneity of tumors. The result of these events means that every individual's tumor may ultimately be found to be phenotypically unique. This heterogeneity extends to intratumor and intermetastasis heterogeneity in addition to interindividual heterogeneity. Cancer, even at a single organ site, should therefore be thought of as not one disease but many rare diseases. Similarly, Lupski (2) describes germline mosaicism as a potentially common source of intraindividual genomic variability: genotypes may vary across an individual's tissues or organs even before somatic mutations arise. If this is the case, it is possible that genetic susceptibility, as measured in studies using peripheral blood DNA, may not reflect the genotype in the tissue in which a tumor arises. Vogelstein and colleagues (1) conclude that although effective treatments will always be needed, the extreme intra- and interindividual heterogeneity in cancer suggests that prevention may have a greater impact on reducing the population cancer burden than treatment. These observations also imply that prevention strategies may require precision approaches that consider an individual's unique cancer risk profile and the unique biologic features of an individual's tumor.

Unlike precision medicine, which has traditionally focused on molecular data to target specific treatments to an individual or tumor, precision prevention requires a broader conceptual framework. Precision prevention involves use of biologic, behavioral, socioeconomic, and epidemiologic data to devise and implement strategies tailored to reducing cancer incidence and mortality in a specific individual or group of individuals.

Precision prevention of cancer, of course, already exists. Pharmacogenetic trials have demonstrated that inherited genetic signatures can be used to identify individuals who will benefit from targeted smoking cessation modalities

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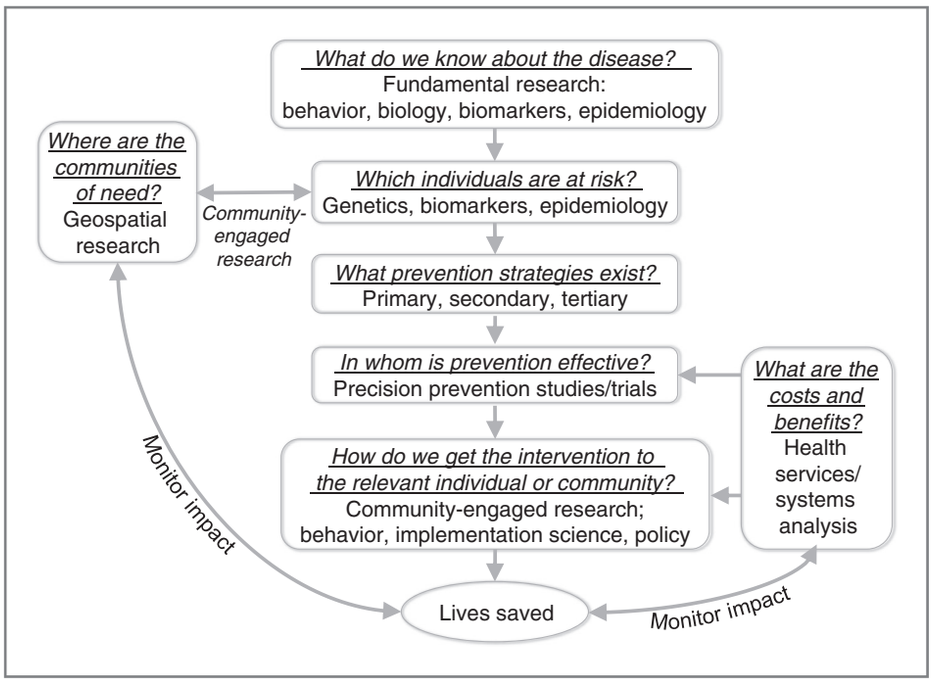

Figure 1. Framework for precision prevention of cancer.

(3). A woman who has inherited a *BRCA1* or *BRCA2* mutation can lower her cancer risk and mortality through the appropriate use of risk-reducing surgeries (4), whereas these interventions would not be recommended in the general population. However, most prevention strategies are not developed or implemented based on biologic or other individual-specific factors.

The development of precision prevention strategies requires coordination of numerous activities and disciplines. Figure 1 presents a framework for precision prevention of cancer, which includes the following activities:

- Generate knowledge about cancer causation, including carcinogenic mechanisms. This information can be used to identify risk factors, genotypes, and biomarkers that can be applied in primary prevention, early detection of cancer, and prediction of those individuals who are most likely to have unfavorable cancer outcomes.
- Understand social and behavioral factors that influence use of screening.
- Identify "communities of need" that may benefit from targeted interventions, and engaging these communities in the conceptualization, development, testing, implementation, and dissemination of precision prevention strategies.
- Develop primary, secondary, and tertiary prevention strategies that are optimized to specific individuals or groups of individuals based on their specific risk and phenotypic profiles.
- Undertake observational studies or interventional trials in relevant individuals to assess the efficacy of prevention strategies.
- Obtain information about the impact of precision prevention strategies on health services and systems.
- Disseminate and implement prevention approaches to relevant individuals or groups, including interactions with policy makers.
- Evaluate the effectiveness of precision prevention strategies and monitor their impact in populations.

The integration of a broad range of research domains is required to achieve these goals. These include cancer biology, epidemiology, biomedical informatics, bioinformatics, biostatistics, risk estimation, genetics, biomarkers, disparities, health services research, clinical trials, geospatial analysis, and dissemination and implementation research. These domains should be integrated under a community engagement framework. In the past, these disciplines have generally not been unified into an integrated team committed to promoting cancer prevention. Furthermore, many academic pursuits that do involve these domains end at the publication stage and do not translate findings into activities that may have public health impact. Thus, a multidisciplinary, translational "team science" approach is required to achieve precision prevention of cancer.

Precision prevention activities should also consider the unique needs for a particular cancer site. For some cancers, the need is to increase the equitable provision of prevention modalities to all populations (e.g., colorectal and breast cancer screening; human papillomavirus vaccination). For others, the need is to improve existing prevention modalities (e.g., PSA screening for prostate cancer). For a number of cancer sites, the need is to develop new prevention modalities where options are

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currently limited or nonexistent (e.g., ovarian and pancreatic cancer). To ensure that cancer prevention is available to all individuals who may benefit (and to maximize the chances that disparities in cancer prevention can be eliminated), diverse populations need to be included in precision prevention research and translation.

The incredible progress in molecularly targeted cancer therapeutics in recent years testifies to the impact precision medicine approaches can have. Just as development of novel therapeutics is a major goal of basic and translational scientists, development and implementation of precision prevention strategies should be a major focus of population scientists.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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