**PROSPECTIVE**

**Precision Prevention and Early Detection of Cancer: Fundamental Principles**

Timothy R. Rebbeck\(^1,2\), Karen Burns-White\(^1\), Andrew T. Chan\(^3,4,5\), Karen Emmons\(^2\), Matthew Freedman\(^1,4\), David J. Hunter\(^2\), Peter Kraft\(^2\), Francine Laden\(^2,5\), Lorelei Mucci\(^2\), Giovanni Parmigiani\(^1,2\), Deborah Schrag\(^1,4\), Sapna Syngal\(^1,4\), Rulla M. Tamimi\(^2,5\), Kasisomayajula Viswanath\(^1,2\), Matthew B. Yurgelun\(^1,4\), and Judy E. Garber\(^1,4\)

Summary: Prevention and early detection is critical for reducing the population burden of cancer. Two approaches have been used. Population approaches change social norms (e.g., smoking bans) or impose incentives (e.g., cigarette taxes); high-risk strategies intervene upon individuals with elevated cancer risk (e.g., smoking cessation). Knowledge about carcinogenesis mechanisms, extreme exposures, and inherited susceptibility provides opportunities to develop precision prevention and early-detection (PPED) strategies. PPED aims to understand the basis of risk, identify groups that optimally benefit from interventions, characterize heterogeneity in intervention responses, optimize intervention timing, and minimize toxicities. We propose a framework around which PPED strategies can be developed. Currently available cancer prevention and early-detection approaches have the potential to reduce a large proportion of the cancer burden in the population. However, even if fully implemented, existing methods cannot fully eliminate the cancer burden. New PPED approaches that exploit the growing knowledge of molecular and biological cancer mechanisms should be developed and implemented. *Cancer Discov; 8*(7); 803–11. © 2018 AACR.

An ounce of prevention is worth a pound of cure.
—Benjamin Franklin

**MOTIVATION FOR A “PRECISION” APPROACH TO CANCER PREVENTION AND EARLY DETECTION**

Prevention and early-detection strategies have great potential to reduce the population burden of cancer. It has been estimated that 50% to 60% of cancers could be prevented if known strategies were optimally used (1). This figure implies that improvements in the application of prevention and early detection can be optimized, but that additional prevention and early-detection strategies can still be developed. As framed by Geoffrey Rose and others in the 1980s (2), two successful and complementary strategies have been used to prevent cancer: the population strategy and the high-risk strategy (Fig. 1). The population strategy refers to a public health–oriented shift in the population distribution of a risk factor by changing societal, screening, and early-detection recommendations, norms, and behaviors. The population approach has been tremendously successful in terms of risk-factor mitigation that has led directly to decreases in cancer rates in the general population. Among the most salient of these successes is the dramatic decrease in tobacco use in the United States and the subsequent drop in smoking-related cancers. After a large increase in cigarette smoking after World Wars I and II, it was recognized that smoking was associated with lung cancer (3). The first Surgeon General’s Report to the Nation (4) led to implementation of cigarette taxes, broadcast ad bans, prohibitions in public smoking, and other population strategies that lowered smoking rates as well as lung cancer rates. Per capita cigarette consumption increased from 1900 to 4,345 cigarettes in 1963 and then decreased to 2,261 in 1998 (5). A subsequent decrease in lung, oral, and pharyngeal cancers as well as heart disease (6) is a testament to the power of the population prevention strategy to reduce cancer incidence. Accordingly, the number of lung cancer deaths in U.S. men peaked in 1993, and the lung cancer mortality rate has declined in the past decade by about 2.7% per year (7). Although there undoubtedly remains much room for improvement, implementation of laws and policies has had an impact on many cancer risk factors, including smoking, alcohol consumption, environmental and occupational exposures, and diet (1). Other notable examples include the implementation of human papillomavirus (HPV) vaccination to reduce cervical cancer incidence (8) and colonoscopy screening for the identification and removal of polyps and early detection of colorectal cancer (9).

Despite the success of some economic and social incentives to avoid cancer-causing exposures and behaviors, there has been controversy about the adequacy of the population approach. Rose himself noted the existence of a “prevention paradox,” namely, “a measure that brings large benefits to the community offers little to each participating individual.” Fineberg (10)
extended Rose’s “prevention paradox” concept to further explain barriers to prevention success, including the fact that the outcome of a successful prevention regimen is in lives saved for the overall target population, whereas the benefits to each individual within the group are often invisible. Those who receive the intervention may not individually see the rewards of their efforts.

Due to the long latency between most exposures and cancer occurrence, there may be a substantial delay in seeing the impact of prevention strategies on cancer incidence, and with improved therapies, an even longer deferral of a benefit for mortality, and it may not be clear whether the benefits are indeed attributable to the intervention. Compounding the lack of immediate benefit, some prevention strategies may require long-term commitments to a given intervention (e.g., smoking cessation or weight loss), which can be difficult to sustain. Because our understanding of disease etiology and preventive strategies changes with time, advice may also change and confuse or discourage those seeking prevention. Furthermore, promotion of prevention versus treatment is influenced by different forces, including commercial conflicts of interest, the prioritization of “sick care” rather than “health care,” as well as conflicts with personal or cultural beliefs. For example, HPV vaccination in children and young adults has been controversial among some groups due to the virus’s stigma as a sexually transmitted infection (11). Recent political and societal controversies have impeded population-level initiatives meant to affect individual exposures and behaviors. For instance, political pushback funded by the beverage industry in response to legislation aimed at limiting consumption of sugar-sweetened beverages has created unanticipated difficulties in implementing an obvious population prevention strategy (12). This scenario follows on many years of similar actions and counteractions between the tobacco industry and the anti-tobacco advocacy community.

A companion to the population strategy is the high-risk strategy (Fig. 1). Although some consider a high-risk strategy to be competitive with a population strategy, each has a place in the cancer prevention and control landscape. The high-risk strategy involves mitigation of risk by targeting individuals with a history of particular exposures or behaviors associated with cancer risk. For example, a high-risk approach would include use of low-dose CT screening for lung cancer in smokers, or breast cancer screening in Hodgkin disease survivors with prior radiation therapy. In both cases, mechanisms of risk may be understood or hypothesized, but the strategies and selection of screened individuals do not require mechanistic knowledge, measured genetic susceptibility, knowledge of screening efficacy in the high-risk population, or the presence of a preneoplastic lesion.

**PRECISION PREVENTION AND EARLY DETECTION**

To complement the population and high-risk strategies, a precision prevention and early-detection (PPED) strategy (Fig. 1; ref. 13) can be defined to consider the mechanistic underpinnings of the carcinogenesis process, as well as the corresponding inter-individual variation in risk and response to preventive interventions. PPED differs from precision oncology because of its focus on individuals who have not been diagnosed with cancer. Other related concepts include “stratified prevention,” “cancer interception,” “public health genetics/genomics,” “precision public health,” and others (14–18).

PPED has three central elements: (i) A mechanistic foundation for the definition of subgroups and preventive interventions; (ii) a means of identifying (e.g., via molecular, histologic, biochemical, syndromic, protein, or other biological characterization) individuals who are relatively homogeneous in terms of phenotype or risk; and (iii) application of interventions in these individuals that minimize harms associated with preventive strategies and maximize reduction of cancer incidence, morbidity, and mortality. A PPED approach should ideally involve all three of these features, but in some cases just one or two of these elements may be sufficient to define a PPED approach.

**MECHANISM-BASED RISK STRATIFICATION**

Cancer risk is not uniform across the population, but varies based on age, genetic susceptibility, exposures, existence...
of preneoplastic conditions, and unknown factors. However, many cancer prevention recommendations rely on a “one-size-fits-all” approach. For example, cervical cancer rates dropped substantially in the United States after it became standard practice to provide all adult women with a PAP smear every 3 to 5 years (19). However, many PAP tests were performed that were probably not needed, and some women who needed PAP tests did not receive them. A PPED strategy could, for example, refine standard cervical screening recommendations for some women who have high-risk HPV types associated with a more rapid course of disease development.

Inherent in the PPED approach is the concept that an individual’s unique biological features and history can be used to better define his or her cancer risk and specific preventive interventions applied. We can identify three major groups in which PPED may be relevant: carriers of high-risk mutations, individuals who have had extreme carcinogenic exposures, and those diagnosed with intraepithelial or preneoplastic traits or conditions (Supplementary Figure). In addition, other factors may be considered in order to define a narrower etiologic spectrum of risk, and thus more homogeneous groups of individuals, who should receive a particular intervention. These factors may include behavioral factors, characteristics of the individual including body habitus, polygenic risk scores that combine data from multiple genetic risk loci into a single risk metric, demographics, residence, and other nonbiological factors.

PREVENTIVE INTERVENTIONS

PPED strategies can also guide the choice of interventions that maximize benefits and minimize harms based on knowledge of underlying carcinogenic events and level of risk. A series of examples demonstrate the utility of the PPED strategy in cancer prevention. First, inherited genotypes involved in the metabolism of chemopreventive agents may predict which individuals are more likely to benefit from the agent and experience fewer toxicities. For agents may predict which individuals are more likely to benefit from the prevention or early-detection strategies. Individuals with high polygenic risk remains to be determined.

Finally, pharmacogenetic determinants of response to specific agents used to reduce smoking have been reported, and clinical trials assessing the efficacy of these pharmacogenomics approaches suggest they could have value in increasing the effectiveness of smoking cessation therapy (25).

PPED PRINCIPLES

In order to develop and implement effective cancer PPED strategies, we define a series of principles around which PPED approaches can be built (Table 1).

Risk Quantification

PPED requires the identification of individuals who will benefit from the prevention or early-detection strategies. Individuals can be defined as at risk based on genetic inheritance, existence of preneoplastic conditions, or exposure. Consideration of individuals with one or more of these features serves a number of purposes. First, a mechanistic understanding of the events that determine an individual’s cancer risk may provide a stronger inference about his/her cancer causation. However, not all measures of elevated risk will inform the biological basis of disease, yet they may still have value in predicting those who may benefit from a preventive strategy.

Second, groups with a specific mutation in a specific gene may have homogeneous features that increase the chances that they will have similar and predictable response to preventive interventions. Third, implementing preventive strategies in relatively homogeneous groups at elevated risk could be more cost effective, and have more favorable risk-benefit ratios, than approaches that target a wider, more heterogeneous population. As an individual’s risk increases, the person may be more willing to accept more extreme cancer prevention interventions with higher levels of toxicity than would individuals at lower risk.

Case in Point

Lynch syndrome (LS) represents an early PPED success story. Carriers of mutations in a number of genes (e.g., MLH1, MSH2, MSH6, PMS2, and EPCAM) are associated with elevated colorectal, endometrial, and other cancers that...
require effective prevention strategies. Genetic screening followed by appropriate interventions (e.g., early and frequent colonoscopic surveillance) is associated with reduction in mortality (26). Microsatellite instability testing, with concurrent \( BRAF \) testing for individuals with characteristic features, has been demonstrated to be cost-effective (27), which has led to public health recommendations for general screening for \( LS \) mutations in all individuals with colorectal cancer (28) to help guide surgical strategies that would reduce the risk of additional primary tumors. Cascade testing of relatives of patients who test positive for \( LS \) mutations can also be applied. Further, based on the mechanistic knowledge of elevated cancer risk in a targetable population, multiple authors have identified high-dose aspirin as an effective chemopreventive agent in obese, but not in nonobese, \( LS \) mutation carriers (29). Similarly, combined erlotinib/sulindac

**Table 1. Precision prevention and early-detection principles**

<table>
<thead>
<tr>
<th>Principle</th>
<th>Key concepts</th>
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<tr>
<td>Risk quantification</td>
<td>Identification of individuals who will maximally benefit from prevention or early-detection strategies based on genetic, molecular, and other biomarker information. Risk may be conferred by inheritance, existence of preneoplastic conditions, or exposure.</td>
</tr>
<tr>
<td>Mechanistic foundation</td>
<td>An understanding of the basic biology of early carcinogenesis events, including genomic susceptibility, metabolic reprogramming, drivers of preneoplasia, the tumor microenvironment, immune modulation, and biomarkers that may define etiologic and risk heterogeneity.</td>
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<tr>
<td>Heterogeneity in phenotype and response</td>
<td>Preventive interventions or early-detection strategies may have different efficacy and toxicities in certain individuals based on their biological characteristics (Fig. 2).</td>
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<tr>
<td>Timing</td>
<td>A prevention “sweet spot” may exist in terms of the timing of the preventive intervention or detection method. Optimal timing of preventive interventions or early-detection strategies requires a clear understanding of the etiologic window in which carcinogenic events are working.</td>
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<tr>
<td>Effective prevention modalities</td>
<td>Effective interventions including risk-reducing surgery to remove tissue at risk, exposure modification, vaccination including immunoprevention, chemoprevention, treatment or removal of premalignant lesions, screening and early-detection methods based on molecular events. The optimal application of these interventions may depend on an individual’s underlying risk profile.</td>
</tr>
<tr>
<td>Consideration of unintended effects</td>
<td>Favorable risk–benefit ratios for patients and/or cost–benefit ratios to governments or insurers may exist. Some very high-risk individuals may accept more intensive/invasive extreme preventive strategies (that may confer higher levels of toxicity) that would not be acceptable to the general population.</td>
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Figure 2. Population heterogeneity in efficacy and toxicity.
chemoprevention is effective in reducing duodenal polyposis burden among patients with familial adenomatous polyposis (FAP; ref. 30), but this intervention has been considered inappropriate in lower-risk groups in whom the risk-benefit ratio is less favorable. Thus, PPED strategies can be identified for prevention and early-detection of cancers that have a clinically meaningful effect on cancer risk and mortality.

**Mechanistic Foundation**

The complex, multifactorial nature of most cancers implies the existence of substantial etiologic and tumor heterogeneity. Even cancers occurring in the same organ site may be thought of not as a single disease but as many disease subtypes when defined by molecular phenotype and potential for prevention. Similarly, individuals with germline mutations in the same gene may have very different cancer risks or treatment responses.

An understanding of the basic biology of early carcinogenesis events, including genomic susceptibility, metabolic reprogramming, drivers of preneoplasia, the tumor microenvironment, immune modulation, and biomarkers that may define etiologic and risk heterogeneity, should facilitate successful PPED activities. This mechanistic knowledge should focus around early events in preneoplasia and biological events occurring in the preneoplastic state that could be reversed before the occurrence of cancer. The proposed creation of a precancer genome atlas, analogous to The Cancer Genome Atlas, is expected to be of great value to this effort. This atlas will consist of somatic changes in intraepithelial or preneoplastic traits or conditions. PPED approaches could therefore use this mechanistic foundation to identify appropriate targets, agents, and endpoints for the prevention or early-detection of cancer. Similarly, the availability of new technologies that facilitate the implementation of PPED will also advance this field.

**Case in Point**

Approaches to cancer prevention that have been applied to all individuals without regard to etiologic heterogeneity may be more likely to fail. For example, the Alpha-Tocopherol Beta Carotene (ATBC) study and the Carotene and Retinol Efficacy Trial (CARET) were motivated by reasonable observational data that led to large-scale interventional randomized trials (31). In both cases, however, the intervention not only failed to reduce cancer risk, but was actually associated with increased cancer rates compared with the placebo arm. Although various explanations for these findings have been proposed, limited mechanistic understanding and underlying heterogeneity in risk and response to the interventions were in part responsible for these unexpected results (32). The failure of these and other chemoprevention studies argues for a strong mechanistic foundation before the application of the preventive strategy.

**Heterogeneity in Phenotype and Response**

All individuals may not respond to or benefit from prevention strategies in the same way (33). The unique set of biological events that comprise every individual’s cancer risk trajectory may enable more, or less, from PPED. As depicted in Fig. 2, a preventive or early-detection strategy may have moderate efficacy and toxicities in the population as a whole (G4), yet certain individuals may experience no net benefit and/or toxicities, or excellent benefit and reduced toxicities. Thus, the total population can likely be characterized broadly in the following subsets: those who will experience high levels of toxicity with minimal benefit based on their underlying genomic or biological profile (G6); those with propensity to experience similar toxicity to the population overall but experience lower benefit (G2); or those with higher toxicity than the population overall, but similar benefit (G3). In contrast, there may be subgroups that will experience similar benefit to the population overall, but lower toxicity (G4); lower toxicity and higher benefit (G3); and similar toxicity to the population overall but higher benefit (G1). The goal of PPED is to avoid application of strategies in individuals who will experience no benefit or those in whom toxicities outweigh benefits (i.e., G4, G6, and G3) and apply strategies in individuals who will experience maximal benefit and minimal toxicity (i.e., G6, G5, and G6). There may be substantial variability in application of the intervention. For example, in some disease contexts, only G4 would be an acceptable group in which the intervention may be applied. In other settings, some level of toxicity may be acceptable for extremely high-risk individuals if the intervention is highly effective (i.e., G6).

PPED strategies should leverage an understanding of phenotypic heterogeneity in normal and preneoplastic tissues that may be targets for PPED. This heterogeneity may result from inter-individual differences in susceptibility or phenotype; tissue-specific differences in development of intraepithelial or preneoplastic traits or conditions; response to preventive interventions that may be driven by these tissue phenotypes; or susceptibility to experience unintended (toxic) effects of preventive strategies. Limiting phenotypic heterogeneity not only could have benefits in terms of efficacy and toxicity, but could simplify implementation and dissemination strategies in target groups at risk.

**Case in Point**

Numerous hereditary cancer susceptibility syndromes are known to exist for which susceptibility genes are known. For many of these, mutation-specific risks have been reported, such that an individual’s cancer risk is dependent on the specific mutation. For example, there are known correlations between APC mutation location and disease severity in FAP. Specifically, mutations in the 5’ and 3’ regions of the APC gene tend to confer attenuated FAP, mutations in bp 1250 to 1464 confer risk of severe FAP, and mutations 5’ of this region confer risk of desmoid tumors (34). RET mutations confer risk of multiple endocrine neoplasia type 2 (MEN2) and familial medullary thyroid cancer (MTC). At least three groups of MTC have been defined based on the levels of cancer risk that are conferred by different mutations. For example, level 2 RET mutations in codons 611, 618, 620, and 634 confer risk of aggressive MTC, and for which thyroidectomy is recommended before age 5 (35). Finally, BRCA1/BRCA2 mutations in hereditary breast/ovarian cancer syndrome also appear to exhibit mutation-specific risks of breast and ovarian cancers, with the existence of breast cancer/ovarian cancer cluster regions conferring elevated risks of specific cancers depending on mutation (36).
Timing
A major challenge in prevention and early-detection strategies is identifying the optimal timing of effective interventions. PPED approaches have the potential to identify a prevention “sweet spot” in terms of the timing of the preventive intervention and can provide a clear understanding of the etiologic window in which a cancer-predisposing exposure acts or a cancer-initiating or cancer-promoting mutation arises. If the relevant biological events are identified too early in carcinogenesis, those events may occur in too many cells and may not be a good target for prevention. Similarly, if the events in carcinogenesis are targeted too late in the development of preneoplastic lesions, heterogeneity of tissue genomes found in the preneoplastic lesion may limit efficacy of prevention. PPED strategies can be developed to target events timed around specific biological events, including inhibition or repair of early DNA damage during cancer initiation, anti-inflammatory activity or anti-hormonal events that occur during tumor promotion, targeting abnormal cellular proliferation or differentiation, inducing apoptosis, or leveraging similar events occurring in preneoplastic traits or conditions. A key to meeting the goal of identifying key events early in the carcinogenesis process is the need for biological sensors or other detection tools that rely on only a few abnormal cells. Methods have been proposed or developed that have the capacity for extremely early-detection of a small number of events in near-normal cellular populations, such as single-cell sequencing and droplet-digital PCR (37).

Case in Point
Carriers of CDH1 mutations are often advised to undergo risk-reducing gastrectomy to avoid gastric cancer mortality (38). This surgery often occurs in 20- to 30-year-olds, although the timing of this surgery cannot be generalized to all patients and may depend on individual decisions related to quality of life (39). Women who have inherited a BRCA1 or BRCA2 mutation are recommended to undergo a risk-reducing salpingo-oophorectomy (RRSO) around ages 35 to 40 or at the completion of childbearing to reduce their substantial ovarian cancer risk (40). This extreme surgical intervention is appropriate because no other preventive or early-detection approaches are available for ovarian cancer. However, the use of RRSO is accompanied by premature surgical menopause that itself may confer unwanted health effects. These include the potential for adverse consequences on bone and cardiovascular health as well as vasomotor symptoms and sexual dysfunction. Recent studies suggest that not all BRCA1 or BRCA2 mutations confer the same cancer risks (36), so that some women may experience cancer at a later age than others, depending on their specific mutation. If this heterogeneity in age of average risk is confirmed, then some women may be able to delay RRSO, and thus minimize the effects of surgical menopause. Knowledge of underlying mechanisms of risk that influence timing of cancer development can therefore be relevant to understand the timing of preventive strategies. The ongoing Women Choosing Surgical Prevention (WISP) Trial is one such intervention that bases preventive interventions for ovarian cancer on either an approach using oophorectomy or a stepped approach using salpingectomy followed by oophorectomy.

Effective Prevention Modalities
As implied elsewhere, effective PPED strategies include risk-reducing surgery to remove tissue at risk, exposure modification, vaccination, chemoprevention, treatment or removal of premalignant lesions, and screening and early-detection methods based on molecular biomarkers. In the PPED setting, these strategies may involve biomarkers, possibly in conjunction with an imaging modality.

You and colleagues (41) proposed guidelines for surgical prevention of cancer which could be modified for the PPED setting. These criteria include application of prevention strategies in those with a very high cancer risk; existence of a reliable and accurate metric that can clearly establish risks, such as a genetic test or pathologic confirmation of preneoplasia; for surgical strategies, expendability of the organ at risk where organ removal can be accomplished with minimal morbidity and mortality; and appropriate strategies to monitor the success of the intervention. These guidelines provide a reasonable framework around which preventive surgeries can be achieved in individuals at increased risk of cancer due to genetic inheritance or preneoplasia.

Case in Point
Examples of treatment of intraepithelial or preneoplastic traits or conditions include implementation of treatment using agents (e.g., combination lenalidomide, elotuzumab, and dexamethasone) in some patients with high-risk smoldering myeloma prior to the development of malignant myeloma (42) and use of chemopreventive agents such as sulindac to treat polyps in hereditary colorectal cancer syndromes or combination erlotinib/sulindac treatment of FAP-related duodenal polyps (30).

Consideration of Unintended Effects
In order to be successful, prevention strategies may require favorable risk–benefit ratios for patients and/or cost–benefit ratios to governments or insurers. Thus, high-risk individuals may accept more intensive/invasive extreme preventive strategies that would not be acceptable to the general population. For example, RRSO reduces cancer risk in women who have inherited a BRCA1 mutation (22), but would not be appropriately applied to the general population because of the multiple potential costs of early menopause to bone, cardiovascular risk, and possibly cognitive function. Nonetheless, because ovarian cancer risk in BRCA1 mutation carriers is approximately 40% by age 80, a substantial proportion of high-risk women who carry BRCA1 mutations may undergo this preventive strategy unnecessarily.

As in other areas of disease prevention, it is critical that cancer PPED strategies avoid, anticipate, minimize, or treat toxicities that may arise from the intervention itself. For example, experience with COX2 inhibitor chemoprevention among individuals at high risk for colorectal cancer that led to elevated cardiovascular risk is a cautionary tale of unintended effects of a prevention intervention (43). The success of tamoxifen in preventing at least some breast cancers in moderately high-risk women was accompanied by a small increase in endometrial cancers (44) and pulmonary embolism and stroke (45). Tamoxifen is metabolized to
endoxifen (4-hydroxy-N-desmethyl tamoxifen) by cytochrome P450 2D6 (encoded by CYP2D6). This metabolite has endometrial cancer–inducing properties (46). Thus, genetic variation may identify a subset of women at increased endometrial cancer risk when exposed to tamoxifen. Therefore, the biological knowledge used to motivate the PPED strategy will also afford the opportunity to predict and limit side effects. It is critical to minimize unintended effects so that the intervention will allow for maximal patient acceptability and adherence. It is particularly important for individuals who do not yet have disease that the intervention is less harmful than the potential cancer, and that they be aware of this. However, some toxicities, including patient-reported events, may be acceptable if the group undergoing the preventive strategy is at sufficiently high risk. As in the example cited above, combination erlotinib/sulindac treatment of FAP-related duodenal polyposis is more toxic than most chemopreventive strategies, but individuals may consider their risks sufficiently high to warrant higher toxicities as long as the overall risk–benefit ratio is favorable (30).

Case in Point

Early cancer diagnosis is a common paradigm for cancer mortality reduction and has driven many prevention initiatives. However, the ongoing controversy about PSA screening (47) has led to the realization that early-detection is not always beneficial. Some small and localized prostate tumors may have already micrometastasized at the time of detection by PSA; others may never spread. Lead time and length bias may result in apparent benefits that are not real, and overdiagnosis may result in morbidity associated with unnecessary treatments. Nonetheless, some cancer experts have concluded that improved early-detection offers the only hope for cancer control for some types of cancers. For example, there is intense interest in the use of “liquid biopsies” for the detection of tumor DNA in blood as one means of identifying persons who harbor an early and undiagnosed cancer (48). Although these techniques hold promise, unless the specificity of a screening test is very high, very large numbers of people may be subjected to follow-up tests to evaluate likely predominantly false-positive molecular screens. In the case of cancer, this may require workups to identify a primary lesion through imaging and surgery. The PPED approach of targeting screening to those most likely to harbor an undiagnosed but treatable malignancy at least means the risk–benefit equation will be weighted toward benefit, and the probability that a test positive is a true positive improves.

EQUITY IN APPLICATION OF PPED APPROACHES

The development and application of novel technologies for improved human health can affect some populations more than others. This has been the case even in standard preventive strategies, including mammography and colorectal cancer screening, where access to effective preventive strategies may be inadequate in some low socioeconomic or minority populations. The principles of health equity and social determinants of health established by the National Academy of Medicine and other groups are relevant to cancer prevention and early-detection broadly as well as PPED (49). Thus, a key principle of PPED is that the strategies should be developed with the goal of equitable access by members of any group that has the relevant genomic or biological characteristics being used to target a PPED approach. The declining cost of genomic technologies and potential for their insurance coverage may help facilitate this goal. However, education among health-care professionals will be critical to the success of access to precision prevention methods. The inherent complexity of PPED approaches implies that inter-individual variation across groups defined by gender, race/ethnicity, or other key demographic features will require qualitative or mixed-methods research in diverse groups to achieve acceptability of these approaches. This will require that large numbers of diverse study participants be included in the research leading to these preventive strategies and that the strategies themselves be disseminated, implemented, and evaluated broadly.

CONCLUSION: THE CASE FOR PPED

PPED represents a strategy for cancer control that complements (rather than supplants) prevention strategies at the population and high-risk levels (1). As described above, the population and high-risk prevention strategies as well as improved cancer therapeutics have demonstrated important successes in limiting cancer incidence and mortality. These strategies should be continued and expanded for those situations in which they are likely to succeed. Similarly, development of cancer therapeutics will continue to hold a central place in cancer control. We argue that PPED presents a complementary activity for cancer control that includes building interventions and identifying populations on a strong biological/mechanistic foundation to maximize efficacy and minimize unintended effects. To achieve these goals, it will be necessary to understand where PPED may be optimally applied. Implementation of precision strategies should be favored only where they demonstrate a clear net benefit and/or reduced harm compared with other prevention or early-detection methods. PPED strategies should exploit mechanisms for quantifying risk at a sufficiently precise level that the preventive strategy can be reasonably applied. At increasing levels of risk, greater toxicities may be tolerated. However, these toxicities need to be balanced against adherence to and acceptability of the intervention in those who may benefit. The prioritization of cancers that may maximally benefit from a precision approach should be carefully considered by weighing the potential for the precision approach to show promise relative to standard approaches or effective treatment. Ideally, PPED will both benefit from and contribute to an improved fundamental understanding of cancer etiology and mechanism through scientific discovery. Finally, precision approaches must be developed and implemented in ways that will make them accessible to all who may benefit from them. This will include implementation of cost-effective prevention strategies in targeted populations who are most likely to benefit. Careful consideration of access to PPED approaches should be considered by both public and private insurance mechanisms.
Disclosure of Potential Conflicts of Interest

S. Syngal is a consultant/advisory board member for Myriad Genetics. M.B. Yurgelun reports receiving a commercial research grant from Myriad Genetic Laboratories, Inc. No potential conflicts of interest were disclosed by the other authors.

Acknowledgments

This work was supported by institutional support from the Dana-Farber Cancer Institute and the Dana-Farber Harvard Cancer Center (P30-CA06516). The authors thank Miguel Hernan for his contribution of key concepts that were incorporated into this article.

Received December 15, 2017; revised March 18, 2018; accepted May 2, 2018; published first June 15, 2018.

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