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Authors
Meyskens, Frank L, Jr
Tully, Patricia

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OBJECTIVE:
To summarize the scientific principles underlying cancer prevention.

DATA SOURCES:
Articles, textbooks, personal communications, and experience.

CONCLUSION:
The scientific basis of cancer prevention is complex and involves experimental and epidemiologic approaches and clinical trials.

IMPLICATIONS FOR NURSING PRACTICE:
As more information becomes available regarding proven and potential cancer-prevention strategies, oncology nurses are regularly called upon to guide patients and others in making choices regarding preventative options. It is important for oncology nurses to stay abreast of this growing body of knowledge.

PRINCIPLES OF CANCER PREVENTION

FRANK L. MEYSKENS, JR AND PATRICIA TULLY

Cancer prevention has classically encompassed three large areas of clinical practice: prevention, screening, and early detection. Several excellent reviews and book chapters have been published involving these topics.1-3 The importance of biological and molecular markers as potential surrogates have been emphasized in the past several years,4,5 and more recently precancers or intraepithelial neoplasia (IEN) have become a target.6,7 The integration of the well-established approaches of prevention, screening, and early detection with biological measures of disease risk, progression, and prognosis has become the hallmark of modern cancer prevention (see Fig 1). In this article we will review the principles of cancer prevention and will emphasize the scientific underpinnings of this emerging discipline. The principles of cancer prevention have evolved from three separate scientific disciplines: carcinogenesis, epidemiology, and clinical trials. Many other areas of science and medicine, including genetics and the behavioral sciences, are contributing to this evolving and complex field.

SCIENTIFIC PRINCIPLES

Carcinogenesis

Carcinogenesis is the study of factors that contribute to the pathogenesis of cancer formation, the processes that regulate normal differentiation and maturation of cells, and the genetic and epigenetic factors that enhance or exhibit tumor formation. The overall relationship of the process of carcinogenesis to cancer prevention, screening, and early detection is depicted schematically in Fig 1 and should be referred to liberally throughout this article. This figure represents an integrated systematic biological and clinical approach in which the process of cancer formation is related to underlying biologic changes and the influence of the environment and the preclinical detection of clinical outcomes by screening and early detection strategies or the interruption or suppression of the malignant process by chemoprevention.
Classically, carcinogenesis has been separated into three distinct phases: initiation, promotion, and progression.\(^8\) Initiation is the first step of carcinogenesis and results in irreversible damage to DNA by a physical, chemical, or viral agent (ie, a carcinogen). The events of initiation occur rapidly. In some cases damage to DNA may be repaired before it is “fixed” as a mutation. In such situations, initiation does not happen and the cell returns to its baseline state. In general, any intervention that slows cellular proliferation should provide more time for DNA repair and lessen DNA damage and mutation. Alternatively, initiated cells are damaged and, if recognized as such, undergo apoptosis (“cell death”) and are removed before they can evolve into a malignancy.

Progression occurs over a prolonged period of time (many years in humans) and results in expansion of an initiated clone of cells without further or minimal genetic change. Exogenous or endogenous factors that enhance the cell cycle or endocrine responsiveness of the cell play a major role in this stage of cancer formation. The fault line between promotion and progression is generally regarded as the appearance of a clinically detectable lesion, frequently referred to as a pre-cancer, premalignancy, or in solid tumors, an IEN. The systematic characterization of IEN and the biologic factors that determine risk and evolution have been a major issue in the past few years.\(^5\) Colorectal adenomas, cervical IEN, oral leukopla-kia, and actinic keratoses of the skin are representative examples of IEN that can be detected by visual or endoscopic means. During progression, additional genetic damage occurs, mutations result, and the cell gradually acquires the properties of a fully transformed phenotype including invasive and metastatic properties.

**The Role of Genetics and Genes**

An increased understanding of the malignant process in the last 15 to 20 years has established, beyond a reasonable doubt, that hereditary and acquired genetic changes play a role in all cancers (Fig 2). The process is complex and the specifics vary from cancer to cancer, but the essential elements are probably quite similar.\(^8\) Vis-à-vis the malignant process, two major changes occur to genes: a loss or gain in function. Genes that suppress proliferation or enhance apoptosis are known as tumor suppressor genes.\(^9,10\) Genes that enhance proliferation or inhibit apoptosis are known as oncogenes.\(^11\) One useful way to think of these two major types of genes is as the brake and gas pedal of the genome.

When a key gene is altered at a constitutive or hereditable level, a malignant outcome is nearly inevitable early in life (eg, loss of the Rb gene and development of a retinoblastoma) or is highly likely in adult life and occurs earlier (eg, loss or mutation of the adenomatosis polyposis gene, leading to thousands of colorectal polyps early in life and colon cancer at a young age). In both these cases a key gene that represses growth has been lost; this element is called a tumor suppressor...
gene. Other genes can be altered in a less severe fashion, for example, the BRCA1 and BRCA2 genes that, if altered, lead to breast cancer at an earlier age and at a higher frequency. A large number of genes have now been identified that contribute to a high risk of human cancer. Taken together, however, they contribute perhaps at most 15% to 20% of the major risk for human cancers.

So what might the contribution of other genetic factors be? Changes in genes can be lumped into a general category called polymorphisms, which account for variation in genes. The study of single nucleotide polymorphisms, or changes in the single base of a gene and their possible role in cancer risk or outcome, has exploded in the last few years. A wide variety of genes may be affected such as those that regulate hormone and carcinogen metabolism, each an important property that contributes to risk that is dependent on the particular property of the protein coded for by the gene in question.

Almost all human cancers seem to evolve to their malignant state over a long period of time, at least in immunologically competent individuals. Influencing the fate of this genetic background are a wide range of potential direct and indirect carcinogens. Among the more potent direct carcinogens to which human populations are exposed include viruses, chemicals, and radiation. Potent indirect influences include products of inflammation and infection, endogenous and exogenous hormones, and dietary constituents.

The nature of the defined genetic changes in many of the major malignancies has now been characterized with a substantial understanding of the changes in colon and head and neck malignancies. Molecular classifications have emerged that will profoundly influence the prognostic classification of tumors; for example, recent work using chromosomal genomic hybridization has led to a new understanding of melanoma and its precursor that has etiologic and prognostic implications. Although treatment decisions have been driven less by specific genetic alterations, the recent recognition that the same specific genetic alteration in diseases as histologically and clinically diverse as chronic myelogenous leukemia and gastrointestinal malignancies predict responsiveness to the tyrosine kinase inhibitor imatinib mesylate was eye opening. Although the genetic changes in most solid tumors are considerably more complex than in this unique case, even early in the life history of tumors, this type of observation suggests that the development of prevention strategies based on an understanding of the basis of these molecular changes will be worthwhile. A little explored notion is, “why are specific genetic changes acquired and what is the role of the
environment exterior to the cell in producing these mutations?" This area of research, gene-environment interactions, is burgeoning and has become a focus of many recent investigations. The potential in the future of this approach for developing useful agents should be significant.

Epidemiology

The second major discipline that underpins prevention is epidemiology, which classically has been the study of diseases in populations. With the advent of powerful molecular techniques that can assess the role of individual genetic variation at risk, there has been an increased interest in assessing individual risk for diseases, including cancers, although the idea is not a new one. The basic principle of epidemiology is that evidence for causality can be identified by studying one group with a condition or disease and by comparing the test group to an appropriate control group, factor(s) can be assessed for their presence in the two groups. The relative involvement in the two groups leads to determination of a relative risk profile for a particular item(s) in the test group.

There are many types of epidemiologic studies used, and they can be divided into two major types; observational and experimental. In order of increasing power to accurately predict the observational studies include case-control, cohort, and secondary analysis of a randomized clinical trial. The reader is referred to Jepson et al for a more detailed discussion. Many case-control studies are performed because they are relatively easy to do, can be done rapidly (the cases are available), and are not expensive. In these types of studies, cases of a particular disease or entity are identified and matched with controls (usually 2 to 3 times the number of cases). The presence of a large number of particular factors (e.g., age, gender, pill consumption) is enumerated and the frequency determined in both cases and controls and the ratios of the factors in cases and in controls determined. A ratio of 1.0 implies no effect. Less than 1.0 suggests a protective effort of the factor in the cases while a ratio of greater than 1.0 suggests an adverse effect for the condition being measured. The significance of the association is then tested. The power of case-control studies is relatively weak so, unless a marked association is seen (e.g., odds ratio <0.5 or >2.0) and/or multiple case control studies of the same entity are consistent, making definitive conclusions is risky. While the results of a case-control study usually do not provide definitive evidence of causation, they may suggest that a more rigorous design is worth exploring. In some cases in which other types of epidemiologic studies are not possible, a larger study (many cases) may clarify the risk.

In a cohort study the approach is somewhat different. In general, the characteristics of a target group is defined at the beginning of the study and after enough primary events (e.g., a disease) have accumulated a comparison of the presence of risk factors can be made between those participants in the cohort who have experienced an event and those who have not, and a relative risk calculated. Blood and tissue samples are frequently collected at the beginning of the study and at times thereafter and the contribution of a variety of biochemical and molecular measurements to risk can also be assessed. Cohort studies require following a large group of individuals over time, frequently a long time, and requires extensive planning and a long-term commitment. A great deal about cancer and other diseases has been learned from cohort studies, such as the Physicians Health Study, the Nursing Health Studies, and others.

Analysis of secondary events in completed randomized trials has provided a valuable opportunity to identify risk factors because the randomized design provides a critical control population that has been matched for key parameters. For example, results from a randomized trial of selenium supplementation and skin cancer identified that selenium appeared to protect against prostate and other cancers. Largely based on this observation, a large number of randomized clinical trials are being undertaken using selenium as the treatment drug. All of these observational studies have strengths and weaknesses, but they have been important in identifying possible risk (e.g., smoking, many cancers) and protective factors (e.g., oral contraceptive pills, ovarian cancer). With sufficiently consistent observational results, public health recommendations are frequently made and modifications in clinical practice undertaken even without the results of randomized trials being available. However, in those situations in which a randomized trial can be launched, it is frequently needed to sort out conflicting results from observational studies. Two important examples include the value of mammography to screen for breast cancer and the effect of hormone replacement therapy on breast cancer inci-
Clinical Trials

The clinical trial represents the third major discipline that is essential for moving the prevention agenda forward. Although the nosology for prevention studies is similar to that for treatment trials, there are substantial differences, the most important overall being that the risk/benefit ratio in prevention trials must be low if a technique or drug is to be eventually adapted by well or nearly well individuals. There are also several different sources of intervention agents that add complexity to clinical prevention trials: these include nutriceuticals, dietary compounds used in a pharmacologic manner, drugs approved for another indication and being tested for a cancer prevention purpose, and compounds specifically developed as drugs for cancer chemoprevention.

In general, clinical chemoprevention trials have adhered to US Food and Drug Administration guidelines, but nutriceuticals (and to an extent dietary compounds) have not undergone rigorous clinical testing before widespread adoption. This cavalier approach has presented a real problem because the claims made for many of these compounds has exceeded the evidence, in some cases rather markedly so.

The nuances of clinical chemoprevention trials are numerous and evolving. Four major points will be made here. First, a critical first step is to show, whenever possible, that a candidate drug affects a relevant biomarker in the human organ of interest at a dose that is achievable and likely to have minimal to no side effects at the chosen dose. This objective is no easy task and is the major goal of phase II trials. Most commonly, a relatively short-term trial (2 to 4 weeks for presurgical models; 4 to 12 weeks for IEN interventions) is initially performed in which the effects of several doses of a drug (and placebo whenever possible) on a relevant biomarker are assessed. The lowest dose at which a consistent alteration in the marker is produced is advanced to the longer phase IIb trial, in which both the effect on the biomarker and a clinical endpoint is determined. Phase IIb trials last from 6 months to about 3 years and in addition carefully monitor for side effects in a rigorous fashion. In some cases a randomized phase IIb trial may be a pivotal study and could lead to the approval of a drug for a new indication.

Secondly, the issue of biomarkers is a difficult and complex one. This term is thrown around fairly casually. A biomarker can be any biochemical, molecular, histologic, or imaging alteration that may or may not predict or be on the progression pathway to cancer. In contrast, a surrogate endpoint biomarker is on the pathway to cancer and, most critically, accurately predicts that a drug will modulate the true endpoint (in most cases cancer). A validated US Food and Drug Administration is one that has undergone independent confirmation. There are an infinite number of potential biomarkers but to date no validated surrogate endpoint biomarker for cancer exists. The issues and limitations of developing biomarkers has been debated and discussed at length, although far too many investigators are unaware or choose to ignore the problems and launch into conducting trials that are seriously flawed or, even worse, uninformative.

Thirdly, the risk/benefit ratio needs to be carefully assessed. In a predisposing situation where the risk for cancer is low, then the side effects must be low. In a high-risk situation more side effects may be acceptable. Both 13-cis retinoic acid and tamoxifen have not been adopted in practice despite randomized trials that showed a marked decrease in second malignancies in those with a prior aerodigestive malignancy or a decrease in first breast cancer in women at high risk based on an epidemiologic profile of high risk, respectively. Largely because of real risks that were measured in well-conducted trials and/or perceived by the target population as too risky.

Fourth, the criteria for US Food and Drug Administration approval for chemoprevention agents is not firmly established. Although there are several approved drugs for prevention, these confirmations have to date occurred almost incidentally. There has also been convened a large task force to explore this area, but opinions remain fluid.

Types of Prevention

There have been various classifications proposed to categorize the activities that represent prevention used. One that has been widely adapted is the idea of primary, secondary, and tertiary prevention which is modeled
on, but different from, the public health designations. Primary prevention addresses the initiation phase of cancer and has the overall goal to decrease the appearance of cancer. This approach includes such strategies as “sun sense,” anti-smoking education, smoking cessation, dietary and physical activity changes, and condom usage, among others. Primary prevention also includes counseling of genetically-at-high-risk individuals and intervention with dietary or pharmacologic compounds in individuals at high risk for cancer. This approach also includes screening in which no symptomatology is evident, but in which precancers or cancers are found. Some well-accepted screening modalities include mammography, colonoscopy, and Papanicolaou cytology.

Secondary prevention addresses the promotional phase of carcinogenesis. Once the initial genotypic change has occurred, there is a likelihood that the malignant process will eventually evolve to a cancer. Secondary prevention includes management of precancers (IEN) either by ablative (surgery, laser) or non-ablative (eg, drugs) means. The goal is to abrogate or reverse the precancer or IEN. This area has been a major focus of the pharmaceutical approach to prevention, also called chemoprevention. Nearly 15 years ago one of us (F.M.) wrote that the field of chemoprevention of cancer was “coming of age,” the process has indeed been a slow one. The systematic development of strategies by organ site is an important one; a particularly organized effort is that of the Arizona group and skin cancer.

Tertiary prevention represents an attempt to detect cancers early. Early detection in which cancers are found secondary to follow-up of symptoms is classified as tertiary prevention and has become increasingly incorporated into the mainstream practice of clinical oncology. Chemoprevention of a secondary malignancy in an individual who has already had a malignancy also represents tertiary prevention. The techniques used for screening also used early detection and include radiologic imaging techniques.

**CONCLUSION**

The disease is not cancer, but carcinogenesis—the process by which tumors and malignancies develop. Modern cancer prevention integrates our understanding of the biological and molecular features associated with cancer formation. Application of the principles of screening and early detection has contributed to the decline of morbidity and mortality from several cancers and we can anticipate success in others. The field of chemoprevention is strongly supported by findings from epidemiology and preclinical experimental models, and “proof of principle” has been established in several cancers including breast, colon, and prostate. Developing risk profiles and less toxic agents will allow the eventual adoption of chemoprevention as a standard practice similar to the use of antihypertensives for high blood pressure and statins for elevated lipids.

**REFERENCES**


