Screening Strategies for Cancer

Implications and Results

In the fight against cancer we seem to have turned the corner. For the first time comprehensive surveys indicate a small but steady decline in cancer mortality rates over a 5-year period (1990 to 1995).[1] These improvements have resulted from advances in cancer prevention, early diagnosis, and treatment. The contribution of treatment is most easily quantified for children with cancer, most of whom are treated at cancer centers and on research protocols. For adults, improvements in survival suggest a significant impact of treatment in certain solid tumors, such as breast cancer, and in the hematologic malignancies.

Progress in prevention and screening is somewhat easier to document. Antismoking efforts have had some success among adult males, although women and teens seem less influenced by these interventions. In the field of cancer screening, Papanicolaou tests have dramatically lowered the incidence of cervical cancer in screened populations. Similarly, mammography is effective in detecting early and curable breast cancer and in lowering death rates.[2] The challenge now is to assure that all women, both insured and uninsured, have access to these measures. Yearly tests for occult blood in the stool lead to early detection of polyps and carcinomas and reduce death rates of colon cancer by 15% to 30%.[3] Colonoscopy may also have a limited screening role, particularly in individuals with a strong family history of colon cancer (2 affected first-degree relatives) and certainly in those carrying a proven genetic predisposition to this disease. However, this measure is expensive as a general screening device. Moreover, its effectiveness in decreasing death rates has not yet been established. Major questions are still unanswered as to who should have the procedure and how often. For lung cancer, screening measures, including chest x-ray and sputum cytologic examinations, have not been effective.

In this issue of THE JOURNAL, important articles address screening strategies in prostate cancer and malignant melanoma. In both diseases, incidence rates have risen sharply in the past decade, and in both, strategies exist for early detection. Prostate cancer incidence has tripled in the past 10 years, to an estimated 334 500 cases for 1997.[4] This increase comes as a direct result of the prostate-specific antigen (PSA) blood test. This highly sensitive test is elevated in 90% of men with 1 cm or greater prostate cancers. Only 30% of these tumors would be palpable on digital rectal examination (DRE).

We still have much to learn about the use of PSA in clinical practice. The value of detecting and treating early prostate cancer is clouded by the tumor's uncertain impact on survival and quality of life. Deaths due to prostate cancer have not increased, despite the rising incidence. Because many of the tumors detected by PSA would never become apparent clinically, it is not clear that the costs of detection and treatment, and the unpleasant adverse effects of treatment, are balanced by real benefit to the patient. Ongoing large-scale clinical studies of screening and treatment of prostate cancer sponsored by the National Cancer Institute and the US Department of Veterans Affairs should add to our understanding but will not be completed for at least a decade, owing in part to a lag in acquisition of cases.

Meanwhile, PSA testing will continue. In practice many physicians perform PSA and DRE annually, but clearly we need further guidance regarding the use of this test. In this issue of THE JOURNAL, the study by Carter et al[5] adds helpful information. They conclude that if an initial PSA level is less than 2 ng/mL, then the test need not be repeated again for 2 years. They also estimate there is less than a 4% chance that a patient with a low initial PSA level will have a subsequent PSA level out of the likely "curable" range (PSA level >5 ng/mL) 2 years later.

These conclusions should be accepted with caution. The authors make the important assumption that tumors pathologically confined to the prostate are "curable." They note that most tumors associated with a PSA level between 4 and 5 ng/mL are confined to the prostate and therefore curable. Thus, they define the range of 4 to 5 ng/mL as the target for detecting still-curable prostate cancer. This model and its conclusions need to be confirmed, using actual outcomes of treatment in larger patient populations.

Others have attempted to increase the sensitivity of the test by reducing the cutoff point of serum PSA levels from 4 to 2.6 ng/mL and by using the ratio of free to total PSA in serum to partially reduce the resulting increase in the number of biopsies.[6] The authors believe this would help identify high-risk patients with PSA levels of less than 4 ng/mL. In general, any of these refinements of testing strategy, including the biannual testing recommendations, would most clearly apply to the screening of men aged 50 to 70 years, 70% of whom will have a low initial PSA level. For subjects older than 70 years or for those with serious comorbid disease, the question remains as to whether any PSA testing is worthwhile, and whether any intervention, based on the PSA test result, would be justified.

A second article in this issue, by Partin et al,[7] describes a model for predicting extent of disease and curability, based on DRE, PSA, and Gleason grade of the prostate biopsy specimen. The combination of a low Gleason grade, PSA level of less than 10 ng/mL, and nonpalpable disease predicts a 60% chance that the disease is confined to the prostate and is

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therefore likely curable with surgery (or irradiation); while a PSA level over 20 ng/mL, with palpable disease and a Gleason score showing poor to moderate differentiation, predicts a less than a 10% chance of resectability and cure. Patient age, general health, and willingness to accept the adverse effects of treatment must also enter into the consideration of the appropriate course of action. Patients who choose not to be treated initially should be informed of the absence of effective therapy, beyond the 1- to 2-year response to hormonal therapy, for advanced disease.

Another important article in this issue of THE JOURNAL[8] addresses the role of screening for cutaneous melanoma, a malignancy that is rising rapidly in incidence (40 000 cases in the United States in 1996[4]). The increase is not due to earlier detection but represents a true doubling of cases each decade, likely owing to increased sun exposure. The lesions being detected are fully capable of local progression and metastasis as indicated by the rising mortality rate. Early detection of lesions carries a special urgency, as cure is directly related to the size and depth of the primary lesion.

In this case-control study, patients with melanoma were likelier to have more than 25 small nevi, more than 10 large nevi (>5 mm in diameter), or dysplastic nevi. Even a single dysplastic nevus increased the risk of melanoma 2-fold. These findings are consistent with the well-accepted view that both nevi and dysplastic nevi are potential precursors of cutaneous melanoma.

Dysplastic nevi can be difficult to recognize clinically. They are characterized by their flatness and their asymmetry, border irregularity, color variability, and large diameter (together known as "ABCD"), the same features that alert clinicians to melanoma. However, even experts often have difficulty in determining the difference between benign, dysplastic, and malignant lesions by visual inspection. Thus, referring a patient to an expert for evaluation and potential biopsy must be foremost in the mind of the primary care physician confronted with a suspicious lesion.

Both the benign and malignant lesions result from sun exposure and, in about 10% of patients, from an inherited predisposition to develop dysplastic nevi and melanoma. We are just beginning to understand the genetics of inherited melanoma. Familial dysplastic nevus syndrome is associated with a high rate of melanoma but has not been ascribed to a specific molecular defect. In other families, melanoma is associated with mutations in either of 2 genes (*p16/CDKN2* and *CDK4*) that are components of the retinoblastoma pathway, which regulates cell proliferation.[9] However, these defects likely account for fewer than 50% of the cases of familial melanoma and have not been implicated in the familial dysplastic nevus syndrome. We hope that in the near future genetic testing will allow us to identify high-risk patients and target them for screening.

Thus, the articles in this issue of THE JOURNAL reflect the spectrum of advances, from basic genetics to applied measures in the field of prevention, diagnosis, and treatment, that should lead to the eventual control of cancer. The effective application of these advances and continued progress against cancer will require the participation of primary care physicians who have a comprehensive understanding of this all too common disease.

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Genetics Is Coming to Oncology

Picture the mechanisms that govern the behavior of a cell as an enormous puzzle. Each piece represents a critical function responsible for some aspect(s) of cellular behavior. In normal cells, all of the pieces fit perfectly. Those that touch one another represent communicating functions that carry vital chemical signals from one point to another in the cell. This function-to-function communication or signaling contributes to the normal control of growth and differentiation and the failure of a cell to develop neoplastic characteristics.

In a cancer cell, some of the pieces do not fit, because of distortions of shape, size, or both. Others are lost altogether. Yet others are abnormally replicated, sometimes many times over. By comparison with that of a normal cell, the picture that emerges from a cancer cell puzzle is disorderly. However, it is still a picture of limited size and shape, and discoveries of the last 20 years have made it possible to deconvolute significant parts of it with the tools of genetics and molecular biology. At the current pace of technological discovery and development, figuring out which key pieces do not fit and why will not be a limiting step in characterizing the cancer cells of our patients in a decade or so.

As the science of cancer biology progresses, opportunities for taking clinical advantage of the disorderly picture puzzles of cancer cells are emerging rapidly. Pictorial distortion means dysfunctional signaling, the kind that makes cells grow when and where they should not. Intimate knowledge of the abnormal communications of a given tumor cell should provide opportunities for therapeutic intervention which, in part, rely on the fact that normal cells do not suffer from such abnormalities. Moreover, if the right distorted piece performs a known biochemical function and contributes to neoplastic

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behavior, this information alone can lead to the design of specific therapy. Complete remission induction in acute promyelocytic leukemia with retinoic acid is an example.

Puzzle architecture is genetically controlled. Each piece of the puzzle is a product of the action of one or more genes. Within the next decade, the DNA sequences of all human genes will be known and available to us all. Better still, it will be possible to adapt this invaluable information to analysis of the structures of all of the potentially important cancer-producing genes in a patient's tumor quickly. Knowing the structures of the cancer genes at work in a tumor cell should reveal major elements of its signaling puzzle, including some of those responsible for its clinical behavior.

Consider the prospect of an infiltrating ductal carcinoma of the breast in patient X being the product of abnormalities in multiple cancer genes (which give rise to multiple abnormalities in its puzzle). Add to these observations knowledge of the structure of numerous normal genes of patient X. As these combined images become linked to incisive clinical research, detailed understandings will emerge of the clinical behavior of patient X's tumor before and after treatment. This kind of information can provide an oncologist with advance knowledge of how a tumor will behave and, in time, how to treat it. There is already evidence linking tumor genotype to predictions of response to certain existing therapies. As knowledge of how tumor and host genotype translates into sound predictions of tumor cell behavior, the choice of effective antitumor therapy can be guided by genetic information.

We still call our patients' tumors as we see them—in the microscope, at the operating table, in the radiology department, and from other clinical observations. If knowing the detailed genotype of a tumor can predict its gross behavior before and after therapeutic intervention and govern choice of therapy, oncologic practice will change to accommodate the new opportunities for improved clinical care. The traditional methods of tumor diagnosis and classification will not disappear. Rather, they likely will be joined by more precise genetic methods.

Coming to grips with the clinical opportunities afforded by discoveries in human cancer genetics will not be easy. There are several nonscientific hurdles to jump. Among them are the innate fear of the knowledge of abnormal genotype by many people and the need to ensure absolute patient confidentiality to those undergoing genetic analysis, including genotype analysis of their tumors. And then there is the roadblock that arises when people are offered cancer genetic screening without a simultaneous offer of entry into a suitable cancer prevention trial. Moreover, right now, there are sound reasons for advocating the limitation of cancer genetic screening to research populations.

These problems notwithstanding, are we ready for the avalanche of genetic information that will soon be available to physicians responsible for cancer care? Is the oncologic community prepared to think and speak genetically? It will need to master a language that has retreated to the recesses of memory since leaving medical school or residency. On the other hand, is learning a language so difficult for a profession that is rapidly becoming expert at information management and has long been comfortable with its biochemical, pharmacological, physiological, and technological roots? History says no. Since American physicians embraced Flexner's ideas, we have risen to every major technical challenge that has faced us. Indeed, we may be the most scientifically and technically adventurous doctors in the world.

Our facility with cancer genetics cannot come too soon, because the rate of discovery in this field is already high and growing. As a result, we will soon be offered the opportunity to diagnose, prognosticate, and make simple therapeutic decisions based on tumor and host genotype. Hence, mounting effective programs in genetic education cannot be a casual affair. Many medical schools are doing their part in educating the young, but they can and should not bear the sole responsibility for teaching cancer genetics to the practicing community and to other health care professionals. The American Society of Clinical Oncologists is taking a leading role in efforts to enhance genetic education among oncologists. So is the National Cancer Institute, which is planning to support a network of cancer genetics research centers, each with a professional education capability. Yet other efforts are now afoot. All are welcome additions to the scene.

However, more effort will be needed to achieve uniform, national postgraduate training. Dedicated cancer centers, teaching hospitals, biology departments, research institutes, professional societies, certain specialty boards, medical journals, pharmaceutical and biotechnology companies, and health insurers all have a role to play here. Considering the opportunities for making major clinical progress that lie ahead, these institutions should be urged to join those institutions and groups already engaged in professional cancer genetic education to form genetic educational consortia which, in the aggregate, can reach a national audience in a coordinated manner. If successful, they would have performed major public service, while benefiting themselves considerably. Anything less than meeting our needs in cancer genetic education runs the risk in the future of leaving American oncologic medicine at the starting gate.

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