Commentary

New Developments in the Epidemiology of Cancer Prognosis: Traditional and Molecular Predictors of Treatment Response and Survival

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Background

There have been numerous epidemiologic investigations to determine factors that may affect cancer risk. There is also a rich tradition of evaluating potential somatic changes in the cancer itself to predict recurrence and/or mortality after diagnosis. However, there has been relatively little epidemiologic research about inherited or environmental factors that may affect disease outcomes after cancer diagnosis. It is likely that multiple demographic, lifestyle, psychosocial, biological, and genetic factors interact to affect a patient’s prognosis after diagnosis with cancer and treatment. In this regard, attention has been given to the role of inherited genetic characteristics of the patient to evaluate variability in metabolism of chemotherapeutic agents, defenses against reactive oxygen species generated by radiation and some chemotherapeutic agents, and DNA repair on outcomes after treatment for cancer. Fewer data are available on steps that patients may take to decrease their chances of having a recurrence of cancer or to improve survival.

To address the multifactorial predictors of cancer prognosis, we recently convened an AACR-sponsored Special Conference “New Developments in the Epidemiology of Cancer Prognosis: Traditional and Molecular Predictors of Treatment Response and Survival.” The goal of the conference was to assemble a group of researchers representing a wide range of research disciplines and members of the advocacy community to discuss the current and future status of research about factors that could affect prognosis. These factors include diet, physical activity, adiposity, nutritional supplements, complementary and alternative medicines; the causes and effects of racial or ethnic disparities in cancer outcomes; pharmacogenetics and cancer treatment outcomes; biomarkers of response and outcomes; and complex statistical approaches needed to consider the role of multiple factors in cancer prognosis. Our aim was to adjourn the conference with a clear summary of strengths and limitations of approaches to research in cancer prognosis and to provide recommendations for progress in building comprehensive models to elucidate factors that affect cancer recurrence and mortality.

What Can Patients Do to Improve Their Prognosis?

Much remains unknown about the lifestyle steps that patients may take to decrease their chances of having a recurrence of cancer or to improve their survival. As noted by the American Cancer Society (1), “After receiving a diagnosis of cancer, survivors soon find there are few clear answers to even the simplest of questions, such as Should I change what I eat? Should I exercise? Should I lose weight? Should I take dietary supplements? How about herbal remedies?” Surprisingly, few data are available by which these questions can be addressed, although there are some studies under way, mostly in breast cancer, designed to determine factors that may affect prognosis among cancer survivors.

Calle et al. (2) have shown that obesity is associated with higher risk of cancer mortality for a number of cancer sites. However, it is often difficult to disentangle the biological effect of obesity on the cancer phenotype from its contribution to impaired detection (and hence later diagnosis) in obese individuals. There are many studies suggesting that adiposity before diagnosis is associated with poorer prognosis in women with breast cancer, and that this is unlikely to be explained by differential screening behavior. Among breast cancer patients, weight gain is a common side effect of chemotherapy. Results from available studies suggest that weight gain after diagnosis exerts an adverse effect on prognosis (3). Thus, elucidation of mechanisms of weight gain after diagnosis and its relationship to survival merits further attention. Additional research is needed to examine the relationship of adiposity to breast cancer prognosis by menopausal status, tumor characteristics, types of treatment, and smoking, as well as by location of fat deposition. Finally, studies need to be conducted to determine if intentional weight loss after diagnosis can change prognosis.

Several very recent studies suggest that obese men with prostate cancer are more likely to have aggressive disease that results in biochemical failure after radical prostatectomy (4, 5), but it remains unclear whether this observation is related to later detection or a different disease natural history than...
among men who are not obese. Very little is known about the effects of adiposity on prognosis among patients with cancers other than breast and prostate cancer.

As stressed by Leslie Bernstein, Julia Rowland, and other speakers, a diagnosis of cancer leads many patients to seek out ways that they can improve their quality of life and increase their likelihood of survival (6). Thus, cancer diagnosis is a “teachable moment” that can be used to guide patients to make lifestyle choices that can extend their lives. For example, data from the HEAL and CARE studies show that African American women who have overall higher breast cancer mortality are less physically active after diagnosis than European Americans. Many ongoing intervention studies are designed primarily to evaluate the effect of physical activity on quality of life after breast cancer. Few studies have assessed the role of physical activity in prognosis and survival for any cancers, and among the few that have, results have been mixed. For example, in the observational Nurses’ Health Study (7), it was shown that there was a marked decrease in breast cancer mortality associated with 3 to 5 hours per week of walking at an average pace, but the possibility of confounding by other health behaviors cannot be excluded.

Of great interest to patients is whether or not diet and use of vitamin supplements after the diagnosis of cancer may prevent or modify toxicities experienced during treatment as well as recurrence and survival after treatment ends. The potential role of antioxidant supplement use in cancer therapy outcomes has been investigated for a number of years in studies using cell lines, animal models, and small samples of patient populations. As reviewed by Ladas et al. (8), the data resulting from these studies are, for the most part, conflicting, and supplement use during treatment remains a controversial area (9). Because of the potential for antioxidants to block the cytotoxic reactive oxygen species generated by therapy, there is a need for studies that evaluate supplement use throughout the therapeutic period. Cheryl Rock reviewed available studies that have evaluated diet before cancer diagnosis in relation to cancer survival; there are few studies that have assessed diet following cancer, particularly during treatment. Results from ongoing intervention trials in cancer patients, such as the WHEL Study (10), will hopefully yield informative results. As discussed by Neli Ulrich, some nutritional supplements may also cause harm in cancer patients. Folate is such an example because biological links to nucleotide synthesis can be important for primary cancer prevention, yet potentially increase the risk of recurrence and death among cancer patients (11, 12). It should not be assumed that dietary and other factors affect cancer etiology in the same way as cancer prognosis, and thus the question of prognostic relationships needs to be addressed in specific studies with an assessment of postdiagnostic exposures. This is of critical importance, in that supplement use among cancer patients is very high.

It must be recognized that cancer does not occur in a closed biological system, but rather in a whole person. There are numerous psychosocial factors that may have an effect on health-related behaviors, and may exert both direct and indirect influences on treatment outcomes as well. As reviewed by Dana Bovbjerg, biopsychosocial influences on cancer prognosis are largely understudied and often represented by studies with small sample size and/or poor study design. Factors such as stress associated with cancer diagnosis and treatment, methods of coping, social support, and emotional expression may all ultimately contribute to prognosis, either through effects on compliance with treatment or through biologically mediated pathways, such as effects on the immune system. However, to date, there are no strong data to support these notions. This area represents a major opportunity for interdisciplinary research that involves epidemiologists, basic scientists, and behavioral scientists to address this multifactorial issue.

What Is the Role of Race and Socioeconomic Status in Determining Cancer Outcomes?

For many cancers, African Americans have different mortality rates from European Americans. As noted by Kathy Albain, differences in outcomes after selected cancer diagnoses seem to be affected by self-reported racial designations within Cooperative Group trials, even after controlling for other factors that could influence mortality (13, 14). The reasons for these disparities are unclear. There are substantial data showing that breast cancer characteristics in African American women have more aggressive features than those in European Americans (15). For prostate cancer, Isaac Powell presented data indicating that differences in clinical characteristics and disease outcomes between African American and European American men diverge from the earliest preclinical phase of prostate tumor initiation, where differences are minimal to increasingly large as the disease progresses (16). This divergence increases with age and indicates that although African American men may have more biologically aggressive disease, the effect of race on outcome disparities may be decreased if men are diagnosed and treated early.

In addition to potential differences in tumor biology, it is possible that some survival differences could be due to differential delivery of treatment by race, based on either socioeconomic or biological factors. Dawn Hershman presented data indicating that African American women had lower baseline WBC counts than European Americans. This apparent neuropsychiatric could lead to reduced or delayed chemotherapy dosing. This phenomenon has also been observed in a large analysis (17) and correlated with higher cancer recurrence. Additional sociocultural factors, morbidity, and access to care may also differentially affect outcomes. Clearly, there is a need for comprehensive studies that can take all of these multifaceted variables into account simultaneously when evaluating racial differences in cancer mortality.

There has been continuing controversy in the research community about the use of “race” as a biological construct, with discussions of the relative contribution of poverty and poor access to care as important determinants of health disparities (18). The need for a broader concept of race and its possible genetic correlates was presented by Mark Shriver, who provided data to support the existence of a metapopulation, with interactions between ethnic heredity and biological ancestry. Dr. Shriver distinguished the concepts of self-reported designations of race from genetic analysis of area of geographic origin, emphasizing that both may be important. Race was discussed as having both cultural and biological components, reflecting contributions from ancestry as well as genetics. The use of Ancestry Informative Markers in admixture mapping can be used to control for heterogeneity within populations (19), particularly between cases and controls, and it was suggested that future studies assess genetic indications of ancestry (genomic marker panels), rather than self-reported racial designation, when evaluating health disparities.

How Can Therapy Be Tailored Based on Genetics and Phenotypic Assays?

Through presentations by leaders in the field of pharmacogenetics, including William Evans, Howard McLeod, Gareth Morgan, Mary Relling, Heinz-Joseph Lenz, and Federico Innocenti, it became clear that there have been great advances over the last several years in our understanding of how inherited genetic factors influence treatment response. Using examples from treatment of leukemia with mercaptopurine and of colon cancer with irinotecan and 5-fluorouracil, the usefulness of pharmacogenetics in the clinic is now apparent. The importance of these findings is...
reflected in the fact that Food and Drug Administration packet inserts now note the potential effects of variability in drug metabolism pathways for both chemotherapeutic agents and some other potential drug/gene interactions. Although there is still use for genotyping for functional single nucleotide polymorphisms in known pathways to determine effects on drug outcomes, gene expression arrays, proteomic patterns, and whole genome scans may more accurately discriminate patients who will respond from those who will not benefit from specific drug regimens. Importantly, it was noted that biomarker-driven studies might be used to eventually quantitate risk of toxicity so that the balance between drug toxicity and efficacy can be better assessed.

In addition to traditional prognostic factors, germ-line genetic variability in immune pathways may be associated with survival among individuals with numerous cancers, including non-Hodgkin’s lymphoma, as reviewed by James Cerhan. This type of immunogenetic evaluation may provide a promising approach to prognostic assessment and tailoring of individual therapies.

Antineoplastic therapies are associated with substantial and highly publicized toxicities. However, their use may be life-saving. Thus, research has been focused on individualization of cancer therapies based on analysis of somatic tumor-related changes. For example, estrogen and progesterone receptor content have been used for years to decide whether to use endocrine treatments for breast cancer (20). More recently, again in breast cancer, HER2 evaluation has been found to be critical for selection of patients most likely to benefit from anti-HER2 monoclonal antibody therapy (trastuzumab). However, the field of tumor marker research has been chaotic and poorly disciplined. Daniel Hayes stressed the importance of rigorous study design to address specific questions, with appropriate patient populations and control groups. He stressed that “bigger is not better”: if the study design is not rigorous, a bigger population does not result in better results; rather, it results in bigger bias. He provided a recent example in which a new assay has moved very quickly to apparent clinical use: the 21-gene prognostic index (Oncotype DX Assay) for node-negative, ER+ breast cancer (21). Several other speakers in this session emphasized current and nearly completed studies of other markers in different diseases; for instance, p53 analysis in bladder cancer (Richard Cote) and various markers in head and neck cancers (Gregory Wolf). John Semmes discussed the promises and technical pitfalls of the emerging field of proteomics.

Tom Budd reviewed the exciting field of detection of circulating cancer cells in breast cancer, which has recently taken a step forward with the availability of a highly accurate and precise assay. Soon Paik presented his experience with investigations of novel prognostic and predictive factors using data sets from prospective randomized clinical trials of breast cancer conducted by the National Surgical Adjuvant Breast and Bowel Project.

How Do We Move the Field Forward?

As shown in Fig. 1, it is likely that numerous factors have the capacity to affect outcomes after treatment for cancer, and there is a need to develop statistical approaches to model the contributions and potential interactions of all of these factors. Chris Amos noted the importance of comprehensive statistical models to evaluate complex determinants of outcome. In addition, these studies require validation for the information to be translatable into clinical practice. With input from epidemiologists, clinicians, pharmacologists, basic scientists, biostatisticians, and behavioral and social scientists, we can take steps toward understanding the complex interplay of factors that will determine prognosis after a diagnosis of cancer.

A variety of approaches may be considered in undertaking these studies. Predictors of treatment outcomes can be assessed by taking advantage of existing case-control and cohort studies, by using therapeutic clinical trials for correlative studies, and by initiating new prospective follow-up studies among newly diagnosed patients. Each of these approaches has strengths and limitations.

Using existing studies of cancer etiology to follow up cases for recurrence and survival can be cost-efficient. Furthermore, such studies can provide information on pre-diagnosis habits and, sometimes, assays for markers before disease onset. At the same time, it is critical that post-diagnostic health behaviors be assessed, if conclusions are to be drawn about the effect on prognosis. Existing studies may be limited if the research requires good assessment of habits during cancer therapy or biomarkers that may modify the effects of treatment. Collection of clinical data also requires appropriate care, as emphasized by Geoffrey Liu.

![Figure 1. The molecular epidemiology of cancer outcomes.](source_url)
data on toxicities and treatment, including dose and scheduling, are important. This may be difficult to collect, particularly if treatments were given in different clinical settings. Even if data are present in medical records, there may be severe constraints on access to patient information due to Health Insurance Portability and Accountability Act and health care provider regulations. Cohort studies may also suffer from time lags in case ascertainment, which may result in inability to obtain information and specimens at relevant time points. Important questions to be addressed in prognostic studies that build on existing resources include "What are the most important critical prognostic variables that need to be included in every study?" "What level of detail is absolutely necessary (e.g., about treatments) in using these data?" and "How critical is uniformity of data across centers?"

Randomized clinical trials, particularly those being undertaken in the context of large cooperative groups, can be an outstanding resource for studies of prognosis. Patients who are enrolled on specific studies may have homogeneous disease characteristics and are treated with similar drugs and dosing regimens. Detailed data on toxicities and outcomes are collected, and this is one arena in which excellent data on toxicities may be obtained. A number of therapeutic trials are now including collection of biospecimens, although the use of these samples is somewhat limited due to the logistics of processing and shipment of blood specimens from sites throughout the United States. This results in variable time between blood draw and storage and consequent exposure of the specimen to varying temperature conditions, which can affect some biomarkers. One limitation of most clinical trials is the lack of data on lifestyle factors. In one exception to this general pattern noted by Christine Ambrosone, Southwest Oncology Group is supporting the incorporation of a questionnaire on lifestyle factors within one of their clinical treatment trials. In this study, patients are being queried about habits before, and at the completion of, therapy and annually thereafter, so that modifiable factors can be evaluated in relation to treatment toxicities and outcomes. Through the participation of epidemiologists and behavioral scientists in cooperative group studies, it is likely that there will be more collaborations with clinicians, enhancing and maximizing results of therapeutic trials to obtain comprehensive predictors of treatment outcomes.

The Children's Oncology Group may be used as a model for other Cooperative Groups, given their history of success in conducting research among survivors of childhood cancers. As reviewed by Julie Ross, remarkable achievements have been made in the treatment of childhood cancers over the past three decades. The pediatric oncology community, however, realized that early cure may have costs. To better understand these costs, childhood cancer investigators have been meeting the challenge of conducting systematic follow-up studies (particularly the large Childhood Cancer Survivors Study) in these survivors, many of whom are at risk for second cancers, heart disease, obesity, and cognitive disorders. To facilitate their current and future studies, Children's Oncology Group is in the process of incorporating a check-off box on consent forms for Children's Oncology Group therapeutic trials to allow future contact for permission to participate in these ancillary and follow-up studies. This approach will alleviate many of the logistical deterrents to conducting long-term, multi-institutional research.

Common data elements that may be considered in studies of cancer prognosis include:

- Blood specimens drawn within the same time frame as diagnosis or treatment for all patients, with rigorous standards applied for consistency for time between blood draw and freezing;
- Common data elements on tumor characteristics (e.g., in breast cancer, common collection of information about ER, PR, HER2, and tumor stage and grade);
- Detailed treatment information, including dose and field exposure for radiation, drugs and dose for chemotherapy, follow-up for hormone therapy, and timing of these therapies;
- Comorbidities;
- Detailed collection of toxicities with treatment;
- Follow-up information particularly on recurrence and survival;
- Questionnaire for psychosocial factors including behavior and quality of life;
- Comprehensive data on socioeconomic status;
- Ancestry informative markers for optimal characterization of race or ethnicity.

Clearly, prospective studies designed to collect rigorous data addressing the above points require an extensive infrastructure. As noted by Larry Kushi, for assessment of the effects of use of complementary and alternative medicines on treatment outcomes, observational studies may be much more efficient than clinical trials designed to test the effect of specific complementary and alternative medicine agents. Ideally, the research community should share survey instruments so that data can be pooled when necessary. Most current research on prognosis is related to breast cancer patients; meeting participants noted that the research community needs to pool data and work together in consortia to achieve sufficient power to study less common cancers.

Participants from the advocacy community noted that advocates should work together, focusing on cancer survivorship issues common to all cancer patients, in addition to cancer site-specific activities. A critical long-term benefit of such research would be greater information for patients on which to base choices, not just about treatment but also about lifestyle changes that could improve quality of life and long-term survival.

In summary, transdisciplinary research on the multifactorial nature of cancer prognosis is in its infancy, and there is a critical need to provide data that patients and clinicians can use for guidance during and following cancer treatment. However, as Julia Rowland noted, cancer prevention interventions should be undertaken in cancer survivors now, particularly because we know that they are looking for factors that could improve quality of life and perhaps enhance survival; most notably, there is a need for programs to promote physical activity and smoking cessation. It is estimated that more than 10 million cancer patients live in the United States (22). With such a large and growing population of individuals living with cancer, the research community needs to begin to address issues of survivorship using more comprehensive approaches to the factors that may lead to optimal outcomes.

References


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