COMMENTARY

Evolution of Cancer Prevention and Control Program at The Arizona Cancer Center

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The opportunity to review the rapid evolution and history of our Cancer Prevention and Control (CPC) Program at The Arizona Cancer Center (ACC) was an invitation and challenge that could not be resisted.

This commentary is largely a weltanschauung and consequently personal interpretation of the history of the CPC Program at ACC. It is a mixture of descriptions and reflections on the development of this CPC Program, which I hope will be helpful to investigators who work in this area or who plan to do so.

Before I describe the elements of success of the program and the history leading to that success, let me focus on one perplexity that persists in the field of cancer prevention and control. Over the past decade, many of my colleagues who are in a variety of scientific disciplines have shaken their heads and questioned the involvement of "good scientists" in this area of research. This mindset has been disconcerting, and I continue to find it difficult to accept, especially when our group ventures into new, challenging, and "less traditional" aspects of this program.

Elements of Success

Several elements have been vital to the success of the CPC Program at ACC.

Benign and Nonthreatening Academic Environment

For a new program to successfully proliferate and differentiate without the formation of malignant or fatal teratogenic elements, it is important that the atmosphere be supportive or at least neutral. Since both the clinical and basic science programs of ACC were also undergoing rapid growth from 1976 to 1987, little internal competition existed; collegiality was generally superb, and the opportunity for synergistic scientific interactions across disciplines was extensive. The global encouragement and support of a well-disposed dean and a scientifically oriented and open-minded cancer center director have been essential components of an environment conducive to the spawning of the CPC Program at ACC.

Fundamental Belief That All Problem Solving Represents Science

Cancer prevention and control is not and may never be a distinct discipline. Its proponents and opponents need to accept this fundamental fact if CPC programs are to evolve in the multidisciplinary milieu of cancer centers and universities. On the other hand, sniping between those engaged in the "hard" and "soft" sciences about the relative "value" or "science" of each discipline creates a no-win situation for those who are attempting to develop a CPC program. Cancer prevention and control, by its very nature, is interdisciplinary. For successful evolution of a CPC program at a cancer center, emphasis must be placed not on the fundamental differences between the hard and soft sciences, but on their common ground—the approach to problem solving via the scientific method.

Dedicated Faculty and Staff

The funding of our CPC Program has increased from zero in 1980 to about $8 million in 1987. Several areas of expertise have been essential to this progress.

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Biostatistical and clinical trials support. A biostatistician who is committed to clinical trials and has a good understanding of epidemiology and, if possible, biology is essential to any CPC program.

Clinical pharmacology expertise. Adequate performance of clinical trials with normal subjects or near-normal patients who do not have cancer requires detailed understanding of the pharmacology of intervention agents. Our program at ACC has attracted investigators who have extensive experience with cytotoxic drugs and who are dedicated to the complex challenge of chemoprevention pharmacology.

Involvement of biologists with diverse specialties. An understanding of the process of carcinogenesis requires input from biologists in a broad range of fields. For example, in the future, major contributions to the prevention of cancer can be expected in such arenas as genetic risk assessment and intermediate markers of cancer risk.

Diet and nutrition perspective. Many prevention trials involve dietary manipulation or require assessment of dietary intake as a confounding variable. In addition, the different viewpoints of epidemiologists and nutritionists about dietary variables is often striking, and the overall quality of a CPC program is enhanced by combination of the two approaches.

Input from behavioral scientists. The proper conduct and evaluation of studies in such areas as smoking cessation, risk assessment, rehabilitation, and continuing care require extensive use of behavioral approaches. Additionally, in contrast to most therapeutic trials, the execution of prevention studies requires great attention to compliance and/or adherence.

Integration of efforts. To ensure that interactions among all of the specialists are continuing, dedicated staff support and strong program and administrative direction have been essential.

Successful Extramural Grant Support

No new program can flourish unless extramural support is garnered. Multiple sources of support must be diligently sought: federal, state, and private sources, including foundations and pharmaceutical companies. The multidisciplinary nature of research in cancer prevention and control makes the preparation of grant applications a formidable task and the external review process more complex and variable than that for other fields of study. On the other hand, the funding options are considerably more extensive than those for any one discipline. Creative integration of the diverse mandates of a CPC program and organization and synthesis of the information into a meaningful presentation is difficult, but this is the key to success.

Recognition of CPC Program as Community, Academic, and Scientific Partnership

In these early years, the CPC Program at ACC has been an environmentally driven (sunshine and skin cancer) program depending on both the academic milieu and the community for its success. We were fortunate to start with the problem of skin cancer, since the issue was familiar to the community. Our mistakes were made in a supportive arena, and they were interpreted by the community as "growing pains" rather than as a fundamental town-gown problem. The importance of appreciation for the interdependence of the academic and community constituencies and the necessity for their interaction to achieve the success of a CPC program should not be underestimated.

History

The success of the program has been an evolutionary process. In June 1977, I arrived at the University of Arizona in Tucson. I was immediately struck by two factors about my new professional setting: the practice of medical oncology was enormously different from that in my only previous experience, and cutaneous malignant melanoma was very common and not under active investigation by any of my new colleagues. A review of the literature on malignant melanoma quickly underscored two important issues: the incidence of the malignancy was increasing rapidly, and except for early diagnosis and surgery, there was no effective treatment. (Only recently has the broader oncology community really appreciated the former observation.) This realization prompted an interest in both the prevention and treatment of the disease, which led to growth of the CPC Program in two distinct directions, chemoprevention and cancer control.

In the scientific community at this time, there was a great deal of interest in retinoids for two reasons. First, these compounds inhibited carcinogenesis, and second, in certain systems, they were strong effectors of the differentiated phenotype. The second property was particularly noteworthy for cells from murine melanoma and to a lesser extent for cells from human melanoma. These observations prompted development of a program project grant with the purpose of achieving an understanding of the function and role of retinoids in oncology from the molecular to the clinical level. Funding of this application in 1980 led to excellent local interactions between basic scientists and clinicians, provided an initial important identification for a new and different area of research activity, and established a focus for future development. Additionally, I was promptly identified as the local guru of vitamins, which resulted in many crazy early morning phone calls.

In about 1979, in a parallel effort, our group became interested in the chemoprevention of cervical cancer. As we wished to avoid the systemic side effects of retinoids, we embarked on a long detour to demonstrate that retinoids could be delivered locally to the cervix in a safe and efficient manner. These studies were initially funded locally through small grants and as a developmental project of our program project. In 1982, we successfully competed for a contract to expand this work. On the basis of highly encouraging responses, we then proposed a randomized phase III trial of local β-*trans*-retinoic acid for cervical dysplasia and were awarded a 4-year grant (1985-1989).

A second major new area emanating from the program project was interest in the chemoprevention of nonmelanoma skin cancer. In our first recompetition for the grant, we shifted the emphasis to include chemoprevention and focused on a phase III trial of patients at high risk for skin cancer. Unfortunately, our spotlight was misdirected, and we were

unsuccessful in the first recompetition. This experience was salutary in that we learned several important lessons:

(*a*) Not everyone was enthusiastic about chemoprevention.

(*b*) Not everyone was enthusiastic about retinoids.

(*c*) There was a wide gulf between the public health approach and the medical oncology approach. The public health approach sought use of the highest dose that had no toxic effects, whereas the aim of the medical oncology approach was to ensure evidence of biological responsiveness by using a dose sufficient to produce some toxic effects.

These lessons were learned and mulled over; the problems were recognized, the questions were reframed, and recompetition for the grant was successful. Furthermore, these newly acquired perspectives allowed our group to develop a strong application to conduct a randomized (retinol vs. placebo) phase III trial of subjects at low risk for nonmelanoma skin cancer, and a 4-year renewal request was subsequently successful as well.

Implementation of these three chemoprevention trials has led us to a fuller appreciation of the difficulties encountered in performing chemoprevention studies in a free-living population. The three major lessons we have learned from these studies are important to the successful implementation of similar trials.

First, prevention trials have a level of visibility considerably higher than that of therapeutic clinical studies. Patience is essential, and there must be a willingness to deal repeatedly with federal and state authorities, private institutions, and regulatory bodies. In our first three trials and in subsequent trials, the actual entry of subjects began an average of 12 months after the scheduled date. The reasons for such delays are numerous, and they range from the ridiculous (previous occupant of off-site leased space refused to move out) to the sublime (no side effects allowed in a prevention trial).

Second, recruitment of subjects was initially more difficult than we expected, and the best methods for recruitment varied markedly for the three trials. The necessity for help with accrual led to major interactions with our Biomedical Communications Department. Successful general recruitment strategies for these three trials also were very different, ranging from media advertisements to individual physician contacts. We have learned some important things that are seemingly obvious. For example: (*a*) the content and design of an advertisement for subjects in a trial are critical and crucial, and (*b*) the placement of an ad is critical because communication is a very sophisticated and exact science. If the ad appears next to a story about the trial, the phone rings off the hook. If the ad is placed next to the X-rated movie section, the phone remains silent.

Third, careers in cancer control and prevention are not made overnight. The task of interesting trainees or junior faculty in prevention research has been difficult. Furthermore, because the trials are long, appropriate publication of new methods and/or interim observations that do not compromise the trial are very important to maintain morale and a sense of success.

In November 1983, at one of our periodic scientific retreats, our group made the conscious decision to develop a multidisciplinary colon cancer prevention program project. Essential features included two clinical chemoprevention trials using measurement of intermediate markers of risk as well as dietary and behavioral science cores with service and research functions. These trials required many long, but fruitful, discussions to achieve an interdisciplinary understanding and respect for colleagues from different disciplines, in addition to extensive interaction with the lay community. A subsequent supplementary grant (Minority Investigator grant) expanded activities to include research issues related to Hispanics and colon cancer. A happy accident that evolved from our community interactions was development of a strong association with the Sun City retirement community and the associated Boswell Hospital. This large retirement community has been very responsive to the study, and a large study focusing on long-term epidemiologic evaluation (Arizona Health Study) led by Thomas Moon has begun. In the development of our community cancer prevention program, we have established formal cancer prevention units in Tucson, Sun City, central Phoenix, and Mesa. Interactions between the CPC and clinical oncology programs have led to establishment of nine satellites in the Arizona community for epidemiology, prevention, and clinical trials research.

The other major area of the CPC Program evolved from our concern about the prevention and early detection of skin cancer in Arizona. An educational and outreach program was jointly initiated in 1980 with Michael Schreiber of the Tucson dermatologic community and was designated the Arizona Sun Awareness Program (ASAP). Using a number of strategies, this program has provided education regarding the basic principles of prevention and early detection of skin cancer to both lay and professional communities. This effort has been internationally recognized, and each week we receive requests from around the world to help in starting similar programs. The success of this program was important and has led to a fine working relationship between ACC and the broader medical and lay communities. Additionally, ASAP established a good rapport with community dermatologists, a necessity for performance of chemoprevention trials in patients at risk for skin cancer. We soon realized the importance of documenting the incidence of nonmelanoma and melanoma skin cancer within our geographic region, and the epidemiology program at ACC has set up a site-specific tumor registry in southern Arizona. For future cancer control phase IV and V trials, establishment of a statewide tumor registry will be important, and this is a goal we hope to achieve soon.

An important effort to refocus our prevention program during the past year has been the integration of biologic and molecular investigations into the chemoprevention arena. Our goal is simple yet difficult: to determine the biologic basis of specific cancers and to intervene using chemoprevention strategies based on this acquired knowledge. An ultimate goal is to develop risk profiles for subjects at high risk for cancer by using modern molecular and biochemical techniques. Intervention with chemoprevention agents could then be more rationally based on true individual risk rather than population estimates. We have recently established a

preventive oncology clinic to provide a centralized locus to register subjects at high genetic or familial risk for selected cancers. This resource will provide a focus for research activities in clinical oncology, screening and early detection, genetic epidemiology, and biologic studies.

Future Plans

We have many plans for the future. These include progression of current prevention studies to more advanced phases; new chemoprevention initiatives, including phase II trials in patients with Barrett's esophagus and oral leukoplakia; and a multi-institutional phase III trial of cutaneous malignant melanoma. Extensive phase I and II testing of candidate chemoprevention agents in normal subjects or patients with preneoplastic lesions is also under way.

Conclusions

The best treatment of cancer is its prevention. The CPC Program that has evolved at ACC over the past decade not only provides service to the community, but also uses the community as a laboratory to conduct cancer prevention investigations. Our research activities have increased public awareness of cancer prevention in Arizona so that it will be easier to recruit subjects for additional investigations involving other cancers. This community-based research program demonstrates the feasibility and possibilities for effective research in the community. The academic, research, lay, and professional communities can now cooperate in the study, prevention, and control of cancer.

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