Strategies for Controlling Cancer through Genetics

Purpose of the Meeting

As is widely acknowledged (1–5), inheritance plays a role in the development of all human cancers—a large role in retinoblastoma, a moderate role in breast cancer, and a small role in esophageal cancer. If people who are at increased risk for cancer because of their genes can be identified, efforts toward prevention can be effectively targeted (6).

This 2-day workshop was held to evaluate current understanding of the genetics of human cancer with emphasis on prospects for controlling it. The Schlar who convened the meeting was Kare Berg of the University of Oslo, Oslo, Norway, in collaboration with John J. Mulvihill of the National Cancer Institute, Bethesda, MD. Participants included medical geneticists as well as an array of cancer biologists. It was hoped that the two groups would work together to adapt approaches developed to prevent nonneoplastic genetic conditions for use with persons at high risk of cancer.

Throughout the workshop, the term “cancer control” was used in the broadest sense, to embrace efforts in primary prevention (blocking initiation and promotion to a clinical cancer), clinical diagnosis and pretreatment evaluation (e.g., with karyotyping and genetically engineered monoclonal antibodies), and treatment and continuing care including genetic counseling (7).

Workshop Synopsis

Participants reviewed current knowledge of the demography and etiology of selected common and rare cancers, including breast and colon cancer, melanoma and other skin cancers, retinoblastoma, Wilms’ tumor and other childhood cancers, and cancers of endocrine organs with emphasis on those occurring in the multiple endocrine neoplasia syndromes. For several of these, discussants emphasized approaches to prevention that can be directed to the portion of cases attributed to genetic factors (e.g., 30–40% of all bilateral retinoblastomas, 10% or less of breast or colon cancer). In general, these measures included: (a) genetic counseling of individuals at increased risk for specific cancers because of a congenital or genetic disease in themselves or their relatives, or because of their familial pattern of cancer occurrence; (b) prenatal diagnosis for the, as yet, few genetic conditions that predispose to cancer and are amendable to prenatal testing, e.g., retinoblastoma, Fanconi anemia; (c) surveillance of high risk individuals to detect early manifestation of new or recurrent cancer (e.g., development of adenomatous colonic polyps in suspected carriers of the autosomal dominant gene for polyposis coli; development of dysplastic nevi in persons with the familial dysplastic nevus syndrome, etc.); (d) prophylactic surgery on the target organ or tissue in appropriate cases (the colon or dysplastic nevus, noted above; the testes in cryptorchism); and (e) limiting exposure of high risk individuals to known carcinogens (e.g., use of sunscreens and sun avoidance in patients with xeroderma pigmentosum or albinism). Approaches to cancer prevention that were suggested for future consideration included vaccination against cancer-causing viruses and the use of gene therapy for genetic immunodeficiencies amenable to cure through bone marrow manipulation (e.g., adenosine deaminase deficiency).

Following the discussion of specific tumors, participants reviewed cytogenetic studies that have greatly increased our understanding of carcinogenesis. Karyotyping of somatic and tumor tissue from rare patients with constitutional chromosome abnormalities has provided insight into changes that lead to tumor development, e.g., the loss of genetic heterozygosity for regions of chromosomes 13q and 11p in retinoblastoma and Wilms’ tumor, respectively (8). Even in patients with normal somatic karyotypes, tumor cells frequently have consistent cytogenetic changes. These abnormalities are well described for many hematological malignancies; in the acute leukemias, they now have a considerable impact on clinical decisions (9, 10). The recent use of tissue-disaggregating enzymes and selective growth factors has facilitated the finding of nonrandom cytogenetic defects in a variety of solid tumors and has contributed to the cloning of the retinoblastoma gene (11). Studies likely to yield insights into mechanisms of carcinogenesis in the future include karyotyping of benign and preneoplastic lesions and of tumors from persons with familial predisposition to malignancy or who share harmful exposure histories.

The medical geneticists then discussed approaches used to prevent genetic diseases that do not predispose to cancer. When applied to situations of high cancer risk, such strategies include collecting and interpreting family medical data, recognizing and delineating syndromes, assessing risk, providing genetic counseling, initiating medical surveillance and appropriate intervention to facilitate early detection and prevention of cancer, and evaluating the effectiveness of these efforts. Two pilot experiences with cancer prevention clinics modeled after the practice of clinical genetics have demonstrated this approach (12, 13).

Research continues to be the key to future clinical advances. Promising areas for study noted by workshop participants included (a) investigating oncogenes and antioncogenes and the interrelated roles of host and environmental factors in carcinogenesis (ecogenetics); (b) identifying cancer-prone clinical phenotypes as well as protein or DNA polymorphisms closely linked to a cancer-causing disease locus; and (c) using families ascertained through relatively unbiased methods for studies to
determine relative risks for specific types or patterns of cancer, the fraction of the cancer attributable to genetic causes, and the pattern of inheritance demonstrated by the genetic cases.

With these discussions as the background, two independent working groups developed recommendations for (a) disseminating the knowledge of strategies to control cancer through genetics into the relevant clinical and scientific communities and encouraging their utilization, and (b) guiding the direction of future research programs and educational and administrative activities concerned with human cancer genetics.

Recommendations
To Improve Clinical Practice

Many genetic and congenital conditions are known to increase the risk of cancer enormously. Individually, they are rare, but in the aggregate, they may be numerous. Guidelines seem necessary to enable physicians to identify patients who might benefit from referral to clinicians knowledgeable about cancer genetics. Such guidelines should be integral to the practice of clinical oncology. The following represent an attempt to propose such guidelines.

Guidelines for Identifying Individuals Who Merit Genetic Evaluation

The occurrence of cancer in an individual under any of the following circumstances may indicate an increased susceptibility to malignancy as a result of predisposing host factors:

1. cancer occurring in both of paired organs, not considered to be the result of metastases, e.g., in both breasts, both adrenal glands, both kidneys;
2. more than one focus of cancer in a single organ (multicentric tumors), e.g., multiple retinoblastomas in one eye, multiple foci of Wilms’ tumor in one kidney;
3. two or more distinct cancers (multiple primary malignancies), e.g., squamous cell carcinomas of the larynx and lung, adenocarcinoma of the endometrium and ovary, breast and ovarian cancers, endometrial and colon cancers;
4. cancer that has occurred: at an atypical age (e.g., breast or ovarian cancer in women under age 40 years, Wilms’ tumor or another embryonal tumor in an adolescent or adult), at an atypical site (e.g., osteosarcoma in the mid-humerus), or in the less usually affected sex (e.g., breast cancer in a man, lung cancer in a nonsmoking woman);
5. cancers associated with other conditions: birth defects (e.g., Wilms’ tumor in a patient with sporadic aniridia, urogenital malformations, mental retardation and growth abnormalities), one of the 200 single gene disorders known to be complicated by neoplasia (14) (e.g., neurofibrosarcoma or optic glioma in a person with neurofibromatosis; hepatocellular carcinoma in a person with hemochromatosis or tyrosinemia; basal cell carcinomas or medulloblastoma in a person with the nevoid basal cell carcinoma syndrome), precursor lesions (e.g., malignant melanoma in a person with dysplastic nevi or atypical moles, colon cancer in a person with multiple adenomatous polyps), and other diseases (e.g., lymphoma or other cancers in a person with a preexisting autoimmune disorder or immunodeficiency);
6. unusual or rare cancers, e.g., pheochromocytoma and sarcoma.

To aid in identifying such high risk patients, a few questions about past medical history should be routinely asked: e.g., Does the patient exhibit any birth defects, genetic disease, or precursor lesions? Other information that is often relevant includes the gross pathology and histopathology of the primary malignant neoplasm. Of course, any history of cancer or a preneoplastic syndrome in other family members should also be solicited.

Guidelines for Identifying a Family That Might Benefit from Genetic Evaluation

Even if a patient does not have cancer, he or she may be predisposed to cancer because of the family history. A family history of cancer may also be significant in evaluating a patient with cancer but who does not meet any of the criteria listed above. So, two additional guidelines for identifying high risk situations that incorporate knowledge of family history are proposed: (a) one first-degree relative (e.g., brother, sister, parent or offspring) with cancer, who meets any of the criteria listed under Guidelines 1-6; or, (b) two first-degree relatives (one may be the patient) with any cancer. If sibships in the family are large and the tumor types common for the ages at diagnosis and the patients’ sex, then further evaluation is not necessary. For example, one would not study in depth two sisters who developed breast cancer in their 70s, but one should seek expertise in evaluating and counseling two sisters with breast cancer under age 40.

An adequate family history can be collected for this purpose by asking patients “Who among your blood relatives has or had a cancer, tumor, or unusual growth?” (15). If the solicited family history appears significant by either of the above criteria, then all persons with cancer and their blood relatives merit evaluation.

Interpreting a family history is problematic. No firm definition of a “cancer family” is available. A working definition depends on the type and site of cancers, the ages at diagnosis, the patients’ sex, the number of tumors, and the absolute number of affected relatives. Guidance concerning the significance of a particular family history can be provided by a clinician with considerable experience in evaluating families with cancer.

Genetic Evaluation

The evaluation of an individual with an unusual personal and/or family history of cancer by an expert in cancer genetics should include: (a) a review of the patient’s family history for evidence of a preneoplastic syndrome or constellation of cancers that is considered to have a genetic etiology. Retrieval of medical records on family members, especially pathology reports confirming cancer diagnoses, may be an essential part of this review; (b) a review of the patient’s medical history for evidence of a genetic condition predisposing to malignancy, and a clinical examination searching for dysmorphic features, congenital anomalies, abnormal cutaneous manifestations, or other abnormal findings which might form the basis for a syndromic diagnosis; (c) a review of the patient's environmental history for evidence of any unusual occupational, demographic or medical exposures which might lead to cancer in a genetically susceptible person; (d) the ordering of studies whose results may provide key data confirming or ruling out specific diagnoses, e.g., a peripheral blood karyotype seeking structural or numerical chromosome changes, a slit lamp examination seeking Lisch nodules (e.g., von Recklinghausen neurofibromatosis).

The consultant will then meet with the patient to present the conclusions of this evaluation. If a single gene disorder or
deletion syndrome predisposing to cancer has been diagnosed, the consultant can provide information on prognosis, offer appropriate genetic counseling, and recommend medical surveillance for the patient and at-risk family members intended to detect early any deleterious manifestations of the underlying condition, including cancer. In addition, for an increasing number of genetic disorders with neoplastic manifestations, it will soon be possible to provide information on studies to identify affected fetuses or asymptomatic gene carriers in the family through the use of DNA or protein markers closely linked to the chromosomal locus determining the relevant disease.

In some instances, it will not be possible to diagnose a specific genetic disorder. However, to a clinician experienced in evaluating cancer families, features of the medical history may suggest that genetic factors are relevant to cancer occurrence. For some conditions (e.g., familial breast cancer) empiric risk estimates for future disease occurrence, modified by the patient’s own circumstances, can be calculated and recommendations can be made for appropriate medical surveillance of family members considered to have an elevated risk of cancer.

Finally, in a few instances, the circumstances surrounding the presentation of cancer in an individual or a family may lack any features suggesting a genetic predisposition to neoplasia. The consultant may then reassure the patient that, based on current knowledge, the development of cancer was most likely a chance event, and that the risk of developing additional cancers is no greater than that of the population at large. The caveat might be added that if future developments in the patient’s or family’s medical history alter the patient’s perception of this prognosis, they should be brought to the consultant’s attention.

**Educational and Administrative Measures**

The following administrative and educational measures would promote practical application of the above guidelines:

1. Physicians caring for cancer patients should be encouraged to evaluate each patient's personal and family medical history with respect to the guidelines to recognize high risk situations.

2. Medical geneticists are among the appropriate specialists to evaluate referrals from cancer clinicians, but to do so they may need more knowledge of cancer genetics than they now have. Communication among medical geneticists, oncologists, and other relevant practitioners should be encouraged at their respective national society meetings, in their respective journals, in cancer and medical genetics centers, and at continuing education courses. To facilitate interdisciplinary education, oncology fellows should be able to rotate through medical genetics services and vice versa. Geneticists should also attend tumor board presentations and participate in etiologically oriented oncology rounds. Examinations by subspecialty boards for certification in oncology or medical genetics should include questions on cancer genetics. In addition, medical genetics and oncology should be part of training in cancer epidemiology.

3. Genetics-associate programs offer master's degree level training in medical genetics and genetic counseling; knowledge of cancer genetics should be incorporated into their curricula.

4. Schools of medicine and public health should develop graduate-level programs that offer interdisciplinary exposure to the principles and practical aspects of medical genetics, epidemiology, biostatistics, molecular biology, and clinical medicine including oncology.

5. The public needs to be educated about the relevance to cancer of etiologic factors (genetic, familial, and environmental) in a way that they will assimilate, e.g., through popular media. The content of cancer information hotlines in these areas should be assessed and augmented if it is found to be scanty. As an extension of this approach, efforts should be made to provide appropriate information on cancer risk to persons with predisposing conditions. This could be facilitated through diseasespecific foundations and societies, e.g., the National Neurofibromatosis Foundation.

6. A directory should be compiled of research and clinical groups with expertise in the genetics of certain oncolgical diseases that would serve as referral centers and resources. These groups would be particularly helpful for rare hereditary cancers (or conditions predisposing to cancer) such as xeroderma pigmentosum, the multiple endocrine neoplasia syndromes and retinoblastoma. A limited number of cancer-prevention clinics for persons in high risk categories should be established as demonstration projects. Such clinics must include some means of evaluating the impact of this approach; they should also incorporate strategies for procuring valuable research specimens, e.g., lymphocytes, fibroblasts or tumor for cytogenetic studies and isolation of DNA, serum for storage.

7. All cancer centers should have ready access to medical genetics services either through their own staff or through collaboration with medical genetics centers. They should have genetics associates specifically trained in cancer genetics.

8. Insurance companies should be educated about the advantageous long-term cost-benefit ratios of supporting services oriented to preventing cancer. If such services were reimbursed through third-party payments, physicians could practice preventive medicine freed from current concerns of increasing a family's financial burden.

9. Geneticists should be involved in the cancer clinical trials organized by Cancer and Leukemia Group B, Southwest Oncology Group, Children’s Cancer Study Group, and Pediatric Oncology Group. Family history or other types of genetic data should be incorporated into the patient information gained during these studies.

10. There should be cancer geneticists on study sections and on site-visit teams for cancer core grants and on other relevant review boards for research projects related to cancer.

**Ethical Issues**

There was agreement that there should be strict confidentiality concerning clinical information on patients as well as results of predictive tests. The latter may require new rules to protect insurability of family members and to prevent the use of predictive test results to a person’s disadvantage (16).

In contrast to the nondirective approach to counseling encouraged in the practice of clinical genetics, it was agreed that, in certain circumstances, clinicians counseling patients with or at high risk for genetic cancers should be directive and urge implementation of the medical options most conducive to preserving a patient’s health, e.g., recommending colectomy in the presence of premalignant colonic polyps.

**Research Needs**

Although the emphasis of the preceding recommendations is on the application of present knowledge of genetics to control cancer, participants shared enormous enthusiasm about the potential contributions current and future research into the genetics of human cancers might make to cancer prevention. In a sense, these activities have such momentum that additional comments might seem gratuitous. Still, participants enumerated several areas that appear to hold special merit and promise toward enhancing cancer control through genetics:
1. Establishment of programs to foster interdisciplinary cancer research encompassing genetic epidemiology, molecular biology, and oncology. A program project grant is likely to be the best mechanism.

2. Establishment of regional and/or national repositories for storage of DNA from population-based samples as well as from families, perhaps with links to existing cancer registries. The population-based studies would be of unrelated individuals, collected prospectively in defined populations. DNA from families would be collected retrospectively on individuals with cancers apparently caused by single genes and on their unaffected spouses and first degree relatives.

3. Collection of population-based data on the incidence of genetic and familial cancers. A recent example of this approach is the population-based study to determine risk of breast cancer to relatives of young breast cancer patients (17).

4. Investigation of the mechanisms of DNA damage and repair and evaluation of the utility of screening for cancer susceptibility by testing for heterozygosity for the rare disorders with deficient DNA repair.

5. Elucidation of the relevance to tumor development of chromosomal rearrangements, the loss of heterozygosity and oncogenes.


7. Development of studies to identify and quantitate genetic risk factors for cancer; data from twins would be particularly useful in this regard.

8. Development of screening tests to detect cancer susceptibility in high risk individuals. This could include genetic linkage studies of protein and DNA polymorphisms to identify markers useful as preclinical indicators of risk status in studies of families.

9. Development of studies to identify genetic components of environmentally induced cancers, and to determine the mechanism of susceptibility. Examples include the role of debrisoquine-4-hydroxylation activity and the inducibility of aryl hydrocarbon hydroxylase in the development of lung cancer, and the relationship between acetyl transferase and bladder cancer.

10. Evaluation of the relationship between pharmacogenetics and the adverse responses of certain patients to drug or radiation therapy.

11. Evaluation of the use of risk factors to promote life-style changes.

12. Establishment of quality control procedures for existing and new laboratory procedures that will be used in screening for or evaluating cancer risk (e.g., cytogenetics, somatic cell procedures, recombinant DNA techniques, etc.).

13. Development of user-friendly, multiple-access supercomputers for the biomedical sciences.

Critical Comments

The workshop participants did not address the practical ramifications of the proposed clinical recommendations. Thus, while some of the benefits and costs that an individual or family may experience following the identification of a genetic predisposition to cancer can be defined, the overall balance of benefits to costs of identifying a significant population with different genetic risks for a variety of common and rare cancers has not been considered. The ratio likely differs for each condition and depends on many variables including the frequency of the genetic disease or risk factors in the population, average age at cancer diagnosis, the impact on morbidity and mortality of early intervention to prevent or treat the cancer or preneoplastic condition, and the medical resources needed for adequate surveillance. Indeed, we do not presently know whether sufficient numbers of persons with expertise in cancer genetics are available to address the initial needs of persons that the proposed clinical guidelines would direct be referred to them. Clearly, this workshop was the initial step in what we hope will be a continuing effort to target preventative medical care for a select group of patients with an elevated cancer risk.3

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3 With the knowledge and consents of the Editors of both journals, a similar article has appeared in Am. J. Hum Genet. 41:63–69, 1987.
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