Guest Editorial: Progress in the Prevention and Management of Malignant Melanoma

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The incidence of malignant melanoma is increasing at a faster rate than that of any other cancer in the United States (Fig 1). It is estimated that for people born in the year 2000, one in 75 people will be diagnosed with the disease sometime during his or her lifetime. The number of people diagnosed with melanoma rose by approximately 4% per year from 1973 to 1992. The American Cancer Society estimates that 34,100 people will be diagnosed with melanoma in the United States in 1995, an approximate rate of one case every 15 minutes! This "undeclared epidemic" of melanoma is believed to be the consequence of the attitudes of the 1960s and 1970s, when people began to spend more time in the sun and wear less clothing. In addition, the thinning of the ozone layer, with the concomitant increase in ultraviolet radiation exposure to the skin, is also implicated. Despite increasing worldwide attention to melanoma as a result of campaigns for prevention and early detection of melanoma, the incidence in all parts of the world continues to increase.

Fig 1. - The epidemic of melanoma will continue into the next decade. This graph depicts the projected rate of malignant melanoma incidence for people born in these years. By the year 2000, an estimated 1 in 75 people will be diagnosed with malignant melanoma.

Melanoma, the deadliest of skin cancers, is now deadlier, especially in men over 50 years of age. The rate of deaths as a result of melanoma rose by 34% to nearly 2.2 per 100,000 people in 1992, compared with a rate of 1.6 per 100,000 in 1973 (Fig 2). Twice as many men die of melanoma as women. According to the Centers for Disease Control, a 48% increase in the rate of men who died of melanoma from 1973 to 1992 accounted for the largest increase among all cancers in men. In 1995, the number of melanoma deaths for both sexes in the United States is expected to reach 7200.

Cutaneous melanoma is not a subtle disease. Fig 3 illustrates a typical lesion that is hallmarked by the mnemonic "ABCD" for early diagnosis: asymmetry in its overall pattern, an irregular border, a variegated color pattern, and a diameter greater than 6 mm. An excisional biopsy of this lesion should be performed, and if a melanoma is diagnosed, the area should be widely excised. The diagnostic biopsy or appropriate referral should be obvious procedures for the primary care providers who are performing most of the physical examinations in the United States. Despite a relatively obvious diagnosis, however, melanoma incidence continues to increase and the death rate continues to climb. Until translational research can bring more benefits of basic science investigations to the bedside, advances in controlling the disease will depend on prevention, early detection, more accurate staging, and better adjuvant therapies.

This issue of Cancer Control explores the evolving care of the melanoma patient. Howard Koh, MD, MPH, and Alan C. Geller, RN, MPH, of the Boston University School of Medicine, have led the national effort with education and early detection programs. Since its beginning eight years ago, the American Academy of Dermatology under Dr. Koh's leadership has sponsored a demonstration project for the early detection of skin cancers and melanoma. Enrollment has expanded each year, which attests to the demand for the service. The project is staffed by dermatologists who screen individuals for melanomas at a "teachable" moment, at which time educational materials are offered for prevention and skin self-examination. A large percentage of melanomas diagnosed in the screen are "thin" and curable, thereby providing indirect evidence of...
efficacy. Yet, less than 1% of the population is served by this national program. To realize decreases in the incidence and mortality rates for melanoma, primary care providers need to be aware of the need for a complete skin examination and the differential diagnosis of pigmented lesions, and they should be motivated to include a skin examination as part of a routine physical examination. Health care professionals who are responsible for conducting the majority of the physical examinations in the United States—primary care providers, physician assistants, and nurse practitioners—need to be more involved in the early diagnosis of the disease. This is the only viable strategy from a public health viewpoint that will lead to a decreased incidence of malignant melanoma.

Yan-An Su, MD, PhD, and Jeffrey M. Trent, PhD, of the National Center for the Human Genome Project have been involved for several years in an investigation of a tumor suppressor gene for melanoma on chromosome 6. They review their work on the genetics of melanoma and the new data on the p16 gene. Approximately 8% to 12% of melanomas occur within family groups; an individual with one relative who is affected with the disease has a relative risk of 2.3 for developing melanoma compared with that of the general population. Excitement was generated in the fall of 1994 with the announcement of the isolation of the p16 gene, a tumor suppressor gene mapped to chromosome 9p21.1. The p16 protein binds to cyclin-dependent kinase and inhibits the ability of this enzyme to bind with cyclin D, thus blocking the passage of the cell through the cell cycle. Deletions or mutations of the p16 gene cause abnormal cell cycling and growth. Six different mutated genes have been found in 13 of 18 melanoma kindreds, with the mutation segregating with the melanoma development.[2] However, 31% of those with the mutation have not yet developed melanoma. Since the mutation is thought to have 80% penetrance, these individuals may be placed in intensive screening programs with suitable education for prevention (eg, hats, sunscreens) and skin self-examination.

Isaiah Fidler, DVM, PhD, from the M.D. Anderson Cancer Center discusses the mechanisms of melanoma metastases and his work on metastases to the central nervous system. He has demonstrated that the outcome of metastases involves the interaction of the metastatic cell with the host organ environment, with the discovery of these mechanisms leading to better methods of therapeutic interventions.

Investigators at our institution have been developing new assays for occult metastases for melanoma. These use molecular biology techniques to analyze for gene products of the tyrosinase gene. All cells of the body have the tyrosinase gene, but only cells that are actively producing pigment will express the mRNA for the gene. It is hypothesized that the presence of mRNA in a lymph node preparation, the peripheral blood, or a bone marrow specimen suggests that metastatic melanoma cells are present in that immune compartment. Combined with the new technologies of lymphatic mapping and selective lymphadenectomy for the primary surgical treatment of melanoma, the polymerase chain reaction (PCR) assay for “submicroscopic” metastases has the potential to provide staging information that can be orders of magnitude greater in sensitivity than routine histologic examination of the nodal basins.

Hilliard F. Seigler, MD, and associates from Duke University Medical Center have been investigating a gene therapy approach for treating stage IV melanoma. In this protocol, metastatic tumors are harvested, the gene for interferon gamma is inserted, and the irradiated but metabolically active tumor cells are returned to the patient. Timothy L. Darrow, PhD, Zeinab Abdel-Wahab, PhD, and Dr. Seigler discuss the various approaches to gene therapy and their phase I human trial.

Christopher A. Puleo, PA-C, of Moffitt Cancer Center and Marianne Luh of Venus Medical, Inc., discuss the management of extremity lymphedema. Lymphedema occurs in up to 40% of the lymph node dissections for malignant melanoma and causes the most morbidity for the patient after primary therapy. Nodal staging with sentinel node biopsy has the potential to limit this morbidity only to patients with solid evidence of metastases in the node drainage basin (those with positive sentinel nodes), but the problem remains in those patients requiring a complete node dissection. Lymphedema can cause time away from work and significant disability. A home care program consisting of massage, exercise, and sequential lymphatic compression pumps is outlined to minimize lost time and inconvenience for the patient.

The “Cancer Economics” section reviews Moffitt Cancer Center’s first attempt at cost/outcome measurements for melanoma care. Such analyses are becoming increasingly important in this era of health care reform and cost cutting. The reform rhetoric underemphasizes the question of who supports the research and education missions of the academic medical centers. The example given illustrates that a modest initial investment in new technology research can save millions of dollars in future health care costs. All groups—insurance companies, the government, community hospitals, and academic medical centers—must share in this added cost for medical research.

Claudia Berman, MD, has led the effort for the expanded role of nuclear medicine in melanoma care. Lymphoscintigraphy in the melanoma patient has helped surgeons plan colloid scans and allows nuclear medicine physicians to expand their practices. Adjuvant interferon is believed to benefit only 10% to 15% of the treated population. Certainly, this is neither the final result that investigators are hoping to achieve nor the only population that investigators are hoping to help. Research groups are actively involved in vaccine trials for treating patients with metastatic disease. Craig L. Slingluff, Jr, MD, of the University of Virginia Health Sciences Center describes his initial work with the development of a peptide vaccine. It has been found that an immune response can be generated against peptides on the melanoma cell surface. If this immune response can be augmented, it may be possible to vaccinate patients against disease or treat patients with active disease with a mass-produced quantities of peptide. This approach has obvious advantages over the process of taking the patient’s tumor and developing a vaccine, which would be applicable to only approximately 5% of the population.

This is an exciting time to be involved in the investigation and care of patients with melanoma. The progress that has taken place in the last five years holds tremendous promise for the future.

References