

# Melanoma and Nonmelanoma Skin Cancer: Epidemiology and Risk Factors

Mary C. Fraser, Patricia Hartge, and Margaret A. Tucker

**O**NE IN FOUR people in the United States will develop one or more primary skin cancers. The vast majority of these cancers are basal cell cancers that rarely metastasize or cause death. Also common are squamous cell carcinomas, which do occasionally metastasize and cause over 2,000 deaths each year. Least common and most lethal are skin melanomas.

## EPIDEMIOLOGY OF NONMELANOMA SKIN CANCERS AND MELANOMA

### *Incidence*

*Nonmelanoma skin cancer.* Nonmelanoma skin cancer (NMSC) is the most common malignant neoplasm in the US white population, and its incidence has been increasing for several decades. An estimated 600,000 cases will occur in 1990.<sup>1</sup> NMSCs generally are not reported to tumor registries, and statistics on skin cancer are not readily available from hospital sources. Because most patients are treated in outpatient settings, population-based estimates of NMSC incidence require special surveys to collect data. The National Cancer Institute (NCI) has conducted two such US surveys. The first was conducted as an adjunct of the Third National Cancer Survey<sup>2</sup> in 1971-1972 in four geographic areas with varying ultraviolet radiation (UVR) intensities. The second and more comprehensive survey identified 30,000 individu-

als with NMSC in eight geographic areas between 1977 and 1978.<sup>3</sup> The data from the 1977-1978 survey are widely reported as they represent the largest available data base on skin cancer incidence spanning a wide geographic area, thus permitting comparisons of ultraviolet B (UVB) measurements and skin cancer incidence.

*Cutaneous malignant melanoma.* Since cutaneous malignant melanomas (CMMs) are routinely reported to tumor registries, incidence data are available for many parts of the US and around the world.<sup>4,5</sup> The estimated total US incidence for 1990 is 27,600 cases;<sup>1</sup> however, this figure may be slightly underestimated<sup>5</sup> since not all melanomas removed in private physicians' offices are actually reported to tumor registries. Although CMM represents only about 3% of all skin cancers, its metastatic potential is great: it accounts for an estimated 6,000 deaths annually and for approximately three fourths of all deaths from skin cancer.<sup>1</sup>

The dramatic increase in incidence of CMM in the US and several other countries poses a major threat to public health.<sup>5,6</sup> For instance, in the US NCI Surveillance, Epidemiology, and End Results (SEER) program, the incidence for whites rose 4.4% each year over the period from 1973 to 1987, or 83.3% over the 15-year period (Fig 1).<sup>7</sup> This rate of increase leads all other cancers, including lung cancer in females. The highest rates in the US are found in southern Arizona, where the incidence among whites has increased at least fourfold.<sup>8</sup> If CMM incidence increases at the same rate it has over the past 50 years, by the year 2000 approximately 1 in 90 Americans will develop this disease during their lifetime.<sup>9</sup>

### *Demographic Patterns*

*NMSC.* Basal cell carcinoma (BCC) is the most common form of skin cancer, comprising 75% of skin cancers in the southern US and more than 90% in the northern US.<sup>1-3</sup> The ratio of BCC to squamous cell carcinoma (SCC) in the general population is approximately 1:4. Nonmelanoma skin cancers are much more common in whites

---

*From the Cancer Nursing Service, Warren Grant Magnuson Clinical Center, and the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, National Institutes of Health, Bethesda, MD.*

*Mary C. Fraser, MA, RN: Clinical Nurse Specialist, Cancer Nursing Service, and Epidemiology Research Nurse, Environmental Epidemiology Branch; Patricia Hartge, ScD: Epidemiologist, Environmental Epidemiology Branch; Margaret A. Tucker, MD: Chief, Family Studies Section of Environmental Epidemiology Branch, National Cancer Institute.*

*Address reprint requests to Mary C. Fraser, MA, RN, Family Studies Section, Environmental Epidemiology Branch, National Cancer Institute, NIH, EPN-439, Bethesda, MD 20892.*

*This is a US government work. There are no restrictions on its use.*

0749-2081/91/0701-0003\$0.00/0

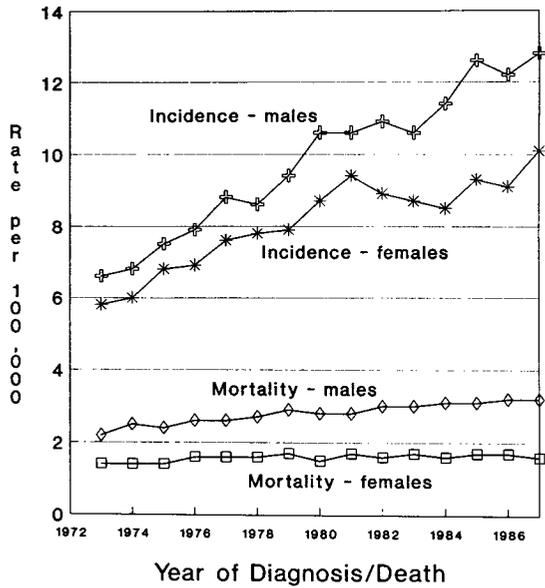


Fig 1. Melanoma of the skin: SEER incidence and US mortality in whites only from 1973 to 1987. Rates are age-adjusted to 1970.

than blacks or other dark-skinned populations, a pattern that reflects a more general protective effect of skin pigmentation on skin cancer risk. Males develop BCC and SCC two to three times more often than do females, a finding that is thought to be related to occupational exposures.<sup>2,10-13</sup>

All types of skin cancers are rare in children and increase in incidence with each decade of life. Figure 2 shows the age-specific incidence rates for BCC and SCC for white males and females in the 1977-1978 US survey.<sup>3</sup> Over the 6-year period from 1971-1972 to 1977-1978, an increased incidence of 15% to 20% was observed, predomi-

nantly for BCC. Males and females have similar rates of BCC at younger ages, but males show twice the rate at older ages. The disparity between males and females appears earlier in life in southern areas. In contrast, male incidence of SCC at any age is always greater than the incidence in females.

In 1989, Glass and Hoover<sup>5</sup> found increasing incidence of SCC in a continuous population-based registry in a large, prepaid health plan over a 27-year period. This unique long-range study showed that the incidence of SCC increased 2.6 times in males and 3.1 times in females (Table 1). The incidence increased 6% to 8% per year from the 1960s to the 1970s, and 4% per year from the 1970s to the early and mid-1980s.

**CMM.** White males have a slightly higher age-adjusted incidence rate than white females (12.8 versus 10.1/100,000, respectively, for 1987).<sup>7</sup> Males and females show a different age-specific incidence pattern. For the period from 1983 to 1987, white females under the age of 40 had higher rates than white males. Around age 40 to 44, the age-specific incidence curves crossed, and male incidence exceeded female incidence at ages 45 years and over. By age 65, white male rates were approximately double female rates.<sup>7</sup>

The increase in incidence has been greater in men than women (Fig 1). White males have increased 5.1% each year, 93.3% overall, while females have increased only 3.8% per year, 67.7% overall. This increase has been especially pronounced for older white males. The rates for blacks have not increased significantly. Whites are at a much greater risk of CMM than blacks, as reflected by their respective age-adjusted incidence rates: 11.2 versus 1.0/100,000 for 1987.<sup>7</sup>

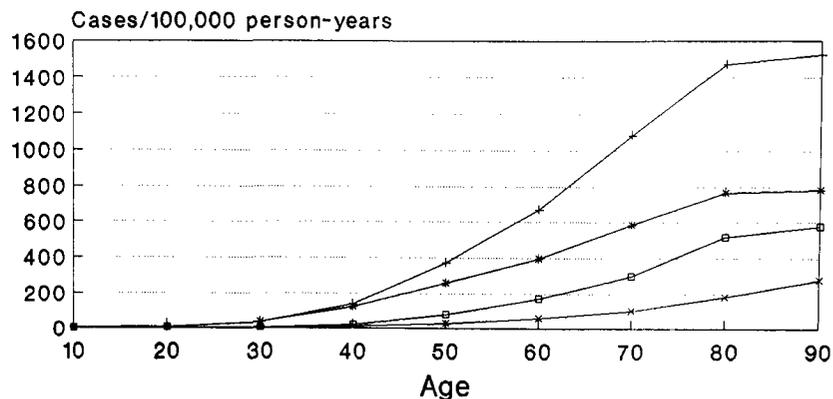


Fig 2. Incidence of SCC among white males (□) and white females (\*), and BCC among white males (+) and white females (x) in the 1977 to 1978 US survey.

**Table 1. Incidence of Skin Cancer by Type of Cancer, Gender, and Calendar Period**

Type	Age-Adjusted Rates/100,000 SE (no. of cases)	
	Females	Males
Squamous cell		
1960-1969	9.7 ± 2.05 (33)	41.6 ± 4.18 (124)
1970-1979	21.0 ± 1.71 (154)	76.9 ± 3.78 (452)
1980-1986	29.8 ± 1.71 (308)	106.1 ± 3.79 (803)
Melanoma		
1960-1969	4.9 ± 1.11 (20)	4.4 ± 1.56 (13)
1970-1979	10.6 ± 1.10 (97)	10.2 ± 1.21 (77)
1980-1986	17.0 ± 1.32 (178)	20.1 ± 1.55 (176)

Abbreviation: SE, standard error.

Data from Kaiser Permanente Health Plan in the Portland, OR/Vancouver, WA, area. Reprinted with permission from *JAMA*, 1989, 262:2097-2100.<sup>5</sup> Copyright 1989, American Medical Association.

### Sites

**NMSC.** Approximately 80% of BCC and 70% of SCC arise on the face, head, and neck.<sup>2,3,10-12</sup> The trunk and upper extremities are the next most common sites. In Fig 3, data from the 1977-1978 US survey show the percentage of cases with NMSC by anatomical site.<sup>3</sup> Between the 1971-1972 and 1977-1978 surveys, BCC increased, especially on the trunk in males, on the lips in females, and on the upper extremities of both genders. The incidence of SCCs on the upper extremities of females appeared to be increasing.<sup>3</sup>

**CMM.** CMMs can occur on any cutaneous surface, but a clear excess occurs on the trunk in men, on the lower extremities in women, and on the head and neck regions in both genders (Fig 4).<sup>4,7,14</sup>

### Survival/Mortality

**NMSC.** Generally, the prognosis for NMSC is excellent, with the cure rates being about 96% to 99%.<sup>2,10-12</sup> The tendency to metastasize reportedly differs according to etiology, location on the body, and morphologic characteristics. Only a small percentage of NMSCs, usually SCC, metastasize or result in death; this occurs more commonly in immunosuppressed patients. The number of deaths due to NMSC is estimated at 2,200 per year in the US mainly attributed to SCC.<sup>1</sup>

**CMM.** Survival rates have been increasing, largely due to earlier stage at diagnosis (Table 2).<sup>1,4,7,14</sup> The overall relative 5-year survival rate for whites is shown in Fig 5. Despite a larger sur-

vival percentage, the mortality rate continues to increase because of the dramatic increase in incidence. During the 15-year period between 1973-1987, the age-adjusted cancer mortality rates for whites reported by the NCI SEER program rose 32.3%.<sup>7</sup> For white males in the 15- to 34-year age group, skin cancer, mainly CMM, was the second leading cause of cancer mortality.<sup>1</sup>

### Geographic Patterns

Epidemiologic studies have shown higher incidence of NMSC and CMM in whites living in latitudes closer to the equator. The highest rates in the world have been recorded in southern Arizona, South Africa, and Australia, followed by Ireland, where there is comparatively less intense UVR exposure but a large fair-skinned population.<sup>2-7,10-12,14</sup>

Scotto et al<sup>3</sup> reported in the 1977-1978 skin cancer survey that the age-adjusted incidence of NMSC for New Orleans, LA, 30.0°N latitude, was 384.2/100,000; the rate for Detroit, MI, 42.2°N latitude, was 135.6/100,000. The latitudinal gradient is steepest for SCC, intermediate for BCC, and least but still marked for CMM.

### RISK FACTORS/ETIOLOGY FOR NONMELANOMA SKIN CANCER

#### Environmental Factors

**Ultraviolet radiation.** The distribution of SCC and BCC on the body, the pattern of incidence by latitude, and the male:female ratio reflect the direct role the ultraviolet part of the solar spectrum plays in human skin cancer. Epidemiologic studies indicate that more than 90% of BCC and SCC can be attributed to exposure to UVB.<sup>15</sup> Experimental studies indicate that the UVB 290-320 nanometers (nm) portion of the solar spectrum is primarily responsible for the carcinogenic properties of sunlight.<sup>16</sup> It is mainly responsible for sunburns, suntans, skin cancer, and changes associated with aging of the skin. Ultraviolet A (UVA) radiation (320-400 nm) is 10- to 100-fold more common than the UVB that reaches the earth's surface, and penetrates more deeply into the skin. UVA plays a far more important role in contributing to the harmful effects of sun exposure than previously suspected. UVA has very weak tanning and carcinogenic activities, and contributes to aging of the skin.<sup>16</sup>

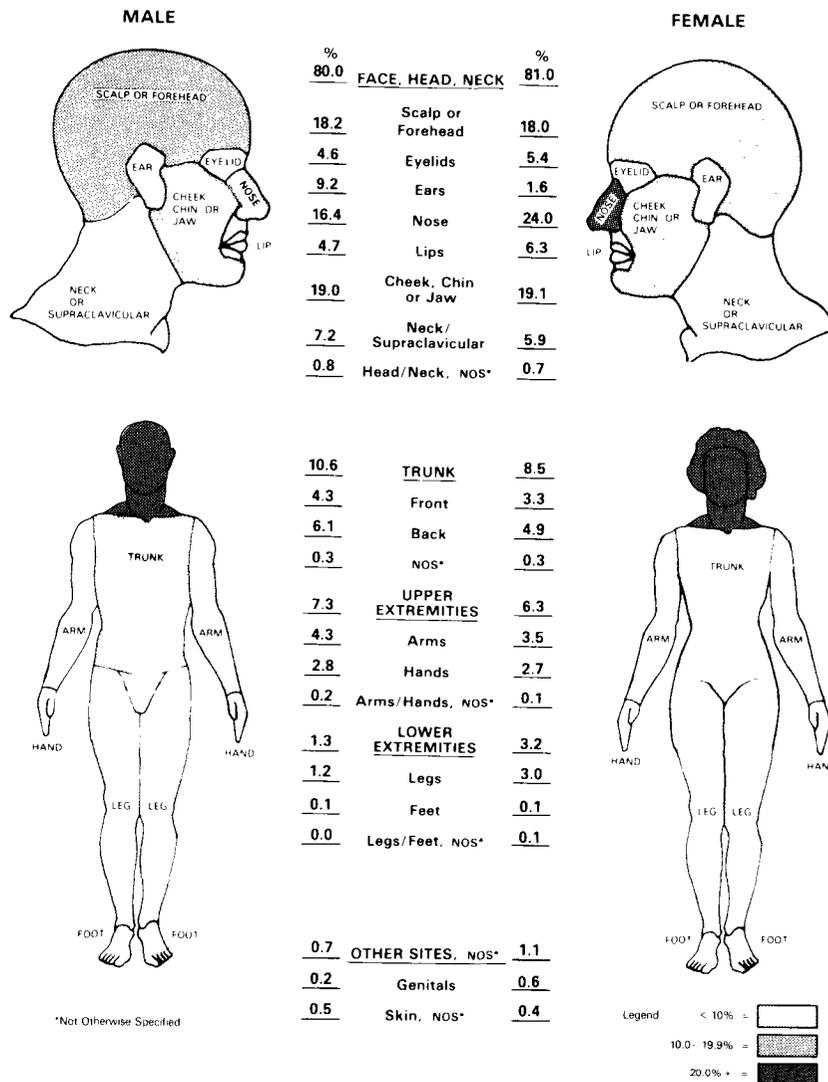


Fig 3. Percentage of cases of NMSC by anatomical site among white males and females in the US (1977-1978). Reprinted from Scotto et al.<sup>3</sup>

Two distinct biologic effects of UVR on the skin that are likely to be responsible for the carcinogenic effects are photochemical alteration of DNA and partial suppression of immunity.<sup>10,16-19</sup> UVR modifies local and systemic immune responses, functionally alters Langerhans cells, and activates the T-cell suppressor pathway. Soluble factors released from UV-irradiated epidermal cells also may be responsible for this altered immune response. Kripke<sup>18,19</sup> and others<sup>16</sup> have reported an association between the ability of UVR to suppress the immune response and the development of skin cancer in experimental animals. Skin cancers induced in mice by UVR are highly antigenic. If transplanted to genetically identical mice, they are destroyed by the immune system. If the host ani-

mals are UV-irradiated before transplantation, the tumor graft is accepted. Much remains unknown about the role of UVR in the immunobiology of human skin cancer.

Human exposure to UVR varies widely depending on clothing, occupation, lifestyle, age, and environmental and geographic factors.<sup>17</sup> UVR exposure rises with decreasing latitude and increasing altitude. For every 1,000 feet above sea level, there is a compounded 4% increase in UVR exposure.<sup>16</sup> Other factors that influence exposure to UVR include heat, wind, humidity, pollutants, cloud cover, snow, season, and time of day.

In recent years, serious concern has arisen about depletion of stratospheric ozone by man-made chlorofluorocarbons (CFC).<sup>16</sup> In a recent risk as-

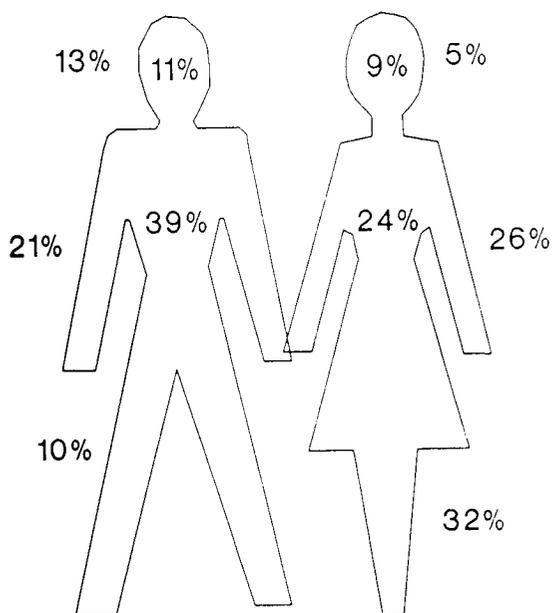


Fig 4. Melanoma of the skin: site distribution by gender in whites only in 1987. Data from NCI SEER program.<sup>7</sup> Other sites, not otherwise specified: males, 6%; females, 4%.

assessment document, the US Environmental Protection Agency (EPA) predicted that, without controls on CFC production, there would be a 40% depletion of ozone by the year 2075. The EPA also concluded that for every 1% decrease in ozone, there will be a compounded 2% increase in UVB wavelengths reaching the earth's surface. Such an increase is predicted to result in an additional 1% to 3% increase per year in the incidence of NMSC.<sup>16</sup>

Because of this continued threat of stratospheric ozone depletion, a network of ground-level stations was begun in 1974 to use photosensitive meters (Robertson-Berger [R-B] meters) in several different latitudes in the US to measure UVB.<sup>20</sup> The fact that no increases of UVB have been detected at ground levels from 1974 to 1985 suggests

that meteorological, climatic, and environmental factors in the troposphere may play a greater role in attenuating UVB radiation than was previously suspected.

**Chemicals.** In addition to UVR, certain chemical agents also cause skin cancer or enhance the carcinogenic effects of sunlight.<sup>2,10-12,21</sup> Indeed, skin cancer was the first cancer shown to be caused by chemicals, in Percivall Pott's 1775 description of SCC of the scrotum induced by chimney soot. Several decades ago, polycyclic aromatic hydrocarbons were shown to induce skin cancers in animals. Mixtures of these agents are found in coal tars, pitch, asphalt, soot, creosotes, anthracenes, paraffin waxes, and lubricating and cutting oils. Exposures to mineral oils have been linked to NMSCs among shale oil workers, jute processors, tool setters operating automatic lathes, and mule spinners.

Chronic exposure to arsenic is another cause of both BCC and SCC.<sup>10-12,21,22</sup> This link has been confirmed in epidemiological studies of patients exposed to arsenic in medicinals (such as Fowler's solution) used in the treatment of psoriasis and asthma, and in environmental exposure by applying agricultural insecticide and drinking well-water contaminated with arsenic.

Psoralens, used in combination with UVA for the treatment of psoriasis, have been linked to skin cancer, primarily SCC at sites not ordinarily exposed to the sun.<sup>10,11,21</sup> Stern et al<sup>23</sup> reported that the risk of skin cancer in patients treated with oral 8-methoxypsoralen phototherapy (PUVA regimen) was 2.6 times higher than expected for a matched control group.

**Ionizing radiation.** Skin cancers were the first neoplasms related to ionizing radiation, with reports in 1902 among workers using roentgen x-ray machines.<sup>2,10-12</sup> An excess risk of skin cancer has been described among radiologists, uranium min-

Table 2. CMM: 5-Year Relative Survival Rates for All Stages

	Year of Diagnosis				
	1960-1963*	1970-1973*	1974-1976†	1977-1980†	1981-1986†
Females	68	75	84.3	86.3	86.6‡
Males	51	62	74.4	76.4	76.2‡

Values are percentages.

\* Rates are based on End Results Group data from a series of hospital registries and one population-based registry.

† Rates are from the NCI SEER program and are based on data from population-based registries in CT, NM, UT, IA, HI, Atlanta, GA, Detroit, MI, Seattle-Puget Sound, WA, and San Francisco-Oakland, CA. Rates are based on follow-up of patients through 1986.

‡ The difference in rates between 1974-1976 and 1981-1986 is statistically significant ( $P < .05$ ).

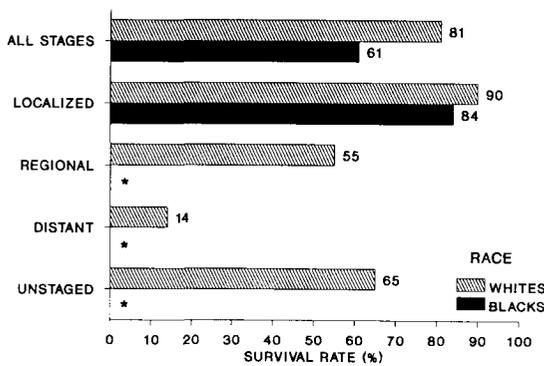


Fig 5. Melanoma of the skin: 5-year survival rates. Data from NCI SEER program, 1981-1986.<sup>7</sup>

ers, and in individuals treated with x-ray therapy for tinea capitis and enlarged thymus glands. Although epidemiologic data are insufficient for examining dose-response relationships and quantifying risk estimates with accuracy, the risk from exposures under 1,000 rem appears to be very small. The findings in humans are generally consistent with the capacity of ionizing radiation to induce skin cancers in laboratory animals. Today, ionizing radiation is rarely used to treat benign skin disease, and industrial and occupational exposure are well controlled; thus, ionizing radiation makes minimal contribution to the burden of skin cancer.<sup>2,10-12</sup>

*Immunologic Factors*

Immunologic surveillance may affect the occurrence of SCC, since the incidence of malignancies in patients who are immunosuppressed, whether or not they have had organ transplants, is greater than in the general population.<sup>10,11</sup> The prolonged immunosuppression among organ transplant recipi-

ents has been associated with a dramatically increased risk of SCC. These reports suggest that preexisting keratoses may become SCCs more readily in the immunosuppressed patient.

*Host Factors*

*Pigmentation/phenotype.* Skin pigmentation is clearly important in the etiology of both melanoma and NMSCs.<sup>2,4,10-16,24,25</sup> The genetically regulated amount of melanin pigment produced by melanocytes determines an individual's skin coloring and protects the skin from the cumulative damage produced by UVR. Thus, dark-skinned individuals (eg, blacks and Asians) are more resistant to all forms of UV-induced skin cancer, while light-skinned (eg, Irish, Scottish, Scandinavian, and English) individuals are significantly predisposed.

The correlation of skin, eye, and hair color with susceptibility to skin cancer has been studied. Pathak et al<sup>26</sup> have formulated a working classification for sun-reactive types that assigns individuals with white skin by skin types. The categories, shown in Table 3, permit an estimate of the relative risk (RR) of the development of the acute and chronic changes related to UVR exposure. Individuals with Type I or II skin are at increased risk of CMM and NMSC because they have poor tolerance to sunlight.

*Precursor lesions.* There are several precancerous skin lesions that may evolve into invasive SCC.<sup>10,11,27</sup> There is no premalignant stage for BCC equivalent to the lesions described for SCC. Actinic keratosis, also known as solar keratosis or senile keratosis, is a premalignant stage of SCC. It is the most common epithelial precancerous lesion among whites, affecting nearly 100% of the el-

Table 3. Skin Types

Skin Type and Reactions	Individual Characteristics
I. Always burns easily and severely (painful burn); tans little or none and peels.	Fair skin; blue, green, or even brown eyes; freckles; unexposed skin is white.
II. Usually burns easily and severely (painful burn); tans minimally or lightly, also peels.	Fair skin; blond or brown hair; blue, hazel, brown eyes; unexposed skin is white.
III. Burns moderately; tans about average.	Average Caucasian; unexposed skin is white.
IV. Burns minimally; tans easily and above average with each exposure.	White or light brown skin; dark brown hair; dark eyes; unexposed skin is white or light brown.
V. Rarely burns, tans easily and substantially.	Brown skin; unexposed skin is brown.
VI. Never burns and tans profusely.	Blacks; unexposed skin is black.

Based on first exposure of unexposed skin to approximately 45 minutes (3 minimal erythema dose [MED]) solar radiation (noon, June-July). Developed by M.A. Pathak, T.B. Fitzpatrick, J.A. Parrish, and D.B. Mosher, Harvard Medical School, Massachusetts General Hospital, Boston, MA; and F.J. Greiter, Vienna, Austria.

derly white population. Actinic keratoses present on sun-exposed body regions. In approximately one fourth of patients with actinic keratoses, the lesions progress to in situ SCC. Further progression of actinic keratoses to invasive SCC occurs in only 12 to 13% of untreated lesions, which tend to be locally aggressive only, and very rarely metastasize.<sup>10,11,27</sup>

Arsenical keratoses develop at sites of friction and trauma, especially on the palms and soles. Most arsenical keratoses persist for years without evolving into invasive SCC.<sup>27</sup>

Bowen's disease is a variant of in situ SCC.<sup>10,11,27,28</sup> It is predominantly a disease of the elderly, with a mean age at diagnosis in the sixth decade and an age range beginning in the late 20s. The male:female ratio shows a slight preponderance (1.2:1) in some studies, while in the largest study to date, the ratio is reversed (0.8:1, male:female).<sup>28</sup>

Chronic radiation keratoses are premalignant cutaneous dysplasias excluding those induced by the UV spectrum (actinic keratoses) or the infrared spectrum (thermal keratoses). Chronic radiation keratoses are of great concern since they may evolve into invasive SCC, which has a high metastatic potential, especially when x-ray-induced.<sup>27</sup>

A variety of dermatologic conditions may give rise to SCC, including cutaneous horns, burns, scars, erythema ab igne from thermal damage, thermal keratoses, chronic inflammatory conditions, chronic sinuses and ulcers, and other dermatoses.<sup>27</sup>

Keratoacanthoma is fairly common, but, since it is a benign cutaneous tumor, accurate information regarding its true incidence is not available.<sup>10,27,29</sup> These lesions never metastasize, but often present a dilemma because clinically they can mimic SCC. Keratoacanthomas are rare in blacks, and occur almost twice as frequently in males as in females, usually around age 60.

Several rare hereditary diseases predispose to skin cancer, primarily by increasing susceptibility to the effects of UVR.<sup>2,10-12</sup> The nevoid basal cell carcinoma syndrome, inherited in an autosomal dominant manner, consists of multiple BCCs and various developmental defects. The basal cell tumors usually begin in childhood, but continue to appear throughout adult years. Some patients have had more than 1,000 primary BCCs. In children treated with radiation for their medulloblastomas,

BCCs are particularly prevalent in the radiation ports.

Xeroderma pigmentosum (XP), inherited in an autosomal recessive manner, is a progressive sun-sensitive disease that is recognized in early childhood.<sup>2,10-12</sup> Nearly all XP cases exposed to sunlight develop various forms of skin cancer, including BCC, SCC, and CMM. The carcinogenic mechanism in XP appears to be related to several variants of an enzyme responsible for repairing DNA damage induced by UV light.

Other recessively inherited diseases are associated with an increased risk of skin cancer. Albinism predisposes to skin neoplasms, especially SCC, in sun-exposed body regions.<sup>2</sup> In the genetic immunodeficiency disease epidermolytic hyperkeratosis, multiple virus-induced warty lesions develop in early childhood.<sup>10</sup> For many years, a close relationship between benign papillomas induced by human papillomavirus (HPV; types 5, 6, 8, 11, 16, 18, and others) and subsequent cutaneous SCC infection has suggested that HPV might play a role in the development of these tumors.<sup>30</sup> Dyskeratosis congenita, a rare sex-linked recessive trait, carries a high risk of SCC.<sup>2</sup>

#### RISK FACTORS/ETIOLOGY FOR CMM

Sunlight exposure, fair skin, and mole patterns are the three main known risk factors for CMM.<sup>4,14,24,25,31-54</sup> The descriptive data leave no doubt that UVR affects risk, yet analytic data have not isolated a measure of sun exposure that identifies more than a two- to threefold difference in risk.<sup>31,49</sup> Recent studies have found significantly increased risks of melanoma associated with sun exposure during recreational activities, especially those with intense exposure, which has led to the hypothesis that intermittent sun exposure is an important risk factor for CMM. A history of sunburning has been linked to risk in most studies,<sup>34,37,39,49</sup> but not all.<sup>40,55</sup> One study delineated a strong effect of sunburn before age 15 but not at later ages,<sup>39</sup> and childhood sunburn was associated with the development of nevi in another study.<sup>56</sup> People who migrate to sunnier climates at an early age increase their risk markedly; those who migrate at a later age increase their risk only slightly.<sup>24,54</sup> Inconsistent associations have been reported with regard to the influence of constant long-term exposure to sun.

Fair skin and associated light eyes and hair are consistently related to risk, with typical twofold risk gradient.<sup>24,49</sup> Mole patterns are the other main host factor. Indeed, the major advance in the recognition of individuals at very high risk of CMM was the identification of distinctive precursor lesions, dysplastic nevi (originally called B-K moles), in members of melanoma-prone families.<sup>31,33,57</sup> Lynch et al<sup>58</sup> subsequently described a syndrome of unusual nevi in some melanoma-prone families and called it the familial atypical multiple mole and melanoma syndrome (FAMMMS). Although some variation in definition persists, dysplastic nevi have now been clinically and histologically well defined.<sup>31</sup> In the melanoma-prone families followed in a collaborative study between NCI and University of Pennsylvania Pigmented Lesion Clinic,<sup>57,59</sup> the age-adjusted incidence of CMM was 1.4% per year. Those individuals with at least one prior melanoma have a 500-fold risk of developing another primary melanoma. Approximately 5.4% of those individuals affected with melanoma each year will develop another melanoma.<sup>31,59</sup> The cumulative risk of CMM in family members with dysplastic nevi was 56% between the ages of 20 and 59. Table 4 shows the risk of CMM in identified high-risk groups. Family history of CMM without dysplastic nevi is also a risk factor for CMM. From several studies to date, 6% to 18% of individuals with CMM reported that one or more relatives have had melanoma.<sup>31,57,60</sup>

Dysplastic nevi also occur in people who are not members of melanoma-prone families. Surveys of the general population, prison inmates, and dermatology patients suggest a prevalence of 2% to

**Table 4. Risk of CMM in Identified High-Risk Groups**

Group	RR
Member of melanoma-prone family with prior melanoma	500
Member of melanoma-prone family with dysplastic nevi	148
Individual with prior melanoma	8.5
Individual with dysplastic nevi, not from melanoma-prone family	7
Individual with increased number of nevi	6-25
Renal transplant	4-5
Hodgkin's disease	8
Brain cancer	3-6
Breast cancer	1.5

Reprinted with permission.<sup>31</sup>

9%.<sup>31,61-63</sup> Kraemer et al<sup>64</sup> proposed a classification of kindreds with and without CMM and dysplastic nevi. He estimated that individuals with dysplastic nevi but without a family history of melanoma have a sevenfold increased risk.

Studies to date have been too small to differentiate clearly the effects of dysplastic and common acquired nevi. The common finding in all the studies that have counted nevi is that the RR of CMM in the category of the greatest number of nevi is 6- to 25-fold increased.<sup>31,35,36,38,45</sup> Future studies will need to further clarify the relationship of number of dysplastic nevi and sun exposure to melanoma risk. Giant congenital nevi are a risk factor for CMM, but the risk of CMM associated with small congenital nevi is more controversial.<sup>4,16</sup>

Individuals who have already had one CMM also have increased risk, probably 6- to 10-fold.<sup>31,65</sup> In addition, significantly elevated risks of CMM are seen after brain and breast cancer.<sup>31,65</sup> The increase of CMM after breast cancer may relate to shared hormonal or reproductive risk factors. The increased risk after brain cancers may reflect an underlying abnormality of neural crest cells because both tumors are derived from that tissue. Various immunosuppressed conditions also lead to increased risk, eg, renal transplant and Hodgkin's disease.<sup>4,14,31</sup>

In 1988, Evans et al<sup>49</sup> reviewed the case-control studies of CMM published between 1970 and 1987. Table 5 summarizes the risk factors associ-

**Table 5. Significant Risk Factors Frequently Reported for CMM**

Risk Factor	Estimated RR
Phenotypic factors	
Blue eyes	1.6-3.1
Blond/light hair	1.6-9.7
Red hair	2.3-5.5
Fair/pale complexion	1.7-18.4
Tendency to sunburn	1.4-4.6
Inability to tan	1.5-4.5
Freckles	2.6-20.1
History of cutaneous cancer/precancer	
Higher socioeconomic status	2.8-5.0
Increased numbers of nevi	1.8-5.8
Intermittent sun exposure	2.0-20.1
	1.6-2.5

Adapted and reprinted by permission of the publisher from "Risk Factors for the Development of Malignant Melanoma—I: Review of Case Control Studies," by Evans et al, *Journal of Dermatologic Surgery and Oncology*, 14:393-408.<sup>49</sup> Copyright 1988 by Elsevier Science Publishing Co., Inc.

ated with a significantly increased RR in more than half of the studies reviewed, plus more recently published case-control studies.

Oral contraceptives were proposed as a risk factor in 1977, but most subsequent studies have found no association.<sup>31,49,66,67</sup> Other factors that have been studied and generally found to be unrelated to risk include alcohol, caffeine, tobacco, hair dyes, pesticides, marital status, and parity.<sup>49,68</sup>

Fluorescent lighting has been proposed as a risk factor, but has not been extensively studied.<sup>35,49,69</sup> The effects of sunscreen on risk are uncertain because their widespread use is so recent. Stern et al<sup>15</sup> projected that regular use of a sunscreen with a sun protection factor (SPF) of 15 during the first

18 years of life would reduce the lifetime incidence of NMSCs by 78%, and possibly reduce CMM risk as well. Dietary constituents may play a role, but no consistent associations have emerged to date.<sup>49,68,70</sup> Similarly, no occupational hazards, apart from UVR exposures, have been identified.<sup>71</sup>

There is considerable uncertainty about some of the risk factors for CMM and other skin cancers. These topics will receive increased scrutiny as the epidemic of skin cancers continues into the next century.<sup>72</sup>

#### ACKNOWLEDGMENT

The authors gratefully acknowledge the contribution of Joseph Scotto, MS.

#### REFERENCES

1. Silverberg E, Boring CC, Squires TS: Cancer statistics, 1990. *CA* 40:9-26, 1990
2. Scotto J, Fraumeni JF Jr: Skin (other than melanoma), in Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*. Philadelphia, PA, Saunders, 1982, pp 996-1011
3. Scotto J, Fears TR, Fraumeni JF Jr: Incidence of Non-melanoma Skin Cancer in the United States. Bethesda, MD: NIH, 1983 (Publication No. 83-2433)
4. Lee JAH: Melanoma, in Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*. Philadelphia, PA, Saunders, 1982, pp 984-995
5. Glass AG, Hoover RN: The emerging epidemic of melanoma and squamous cell skin cancer. *JAMA* 262:2097-2100, 1989
6. Lee JAH: Trend with time of the incidence of malignant melanoma of skin in white populations, in MacKie RM (ed): *Pigment Cell*, vol 9. Basel, Switzerland, Karger, 1988, pp 1-7
7. Ries LAG, Hankey BF, Edwards BK (eds): *Cancer Statistics Review 1973-87*. Bethesda, MD, NIH, 1990 (Publication No. 90-2789)
8. Schreiber MM, Bozzo PD, Moon TE: Malignant melanoma in southern Arizona: Increasing incidence and sunlight as an etiologic factor. *Arch Dermatol* 117:6-11, 1981
9. Rigel DS, Kopf AW, Friedman RJ: The rate of malignant melanoma in the United States: Are we making an impact? *J Am Acad Dermatol* 17:1050-1053, 1987
10. Haynes HA, Mead KW, Goldwyn RM: Cancers of the skin, in DeVita VT, Hellman S, Rosenberg S (eds): *Cancer: Principles and Practice of Oncology*. Philadelphia, PA, Lippincott, 1985, pp 1343-1368
11. Stoll HL, Schwartz RA: Squamous cell carcinoma, in Fitzpatrick T, Eisen A, Wolff K, Freedberg I, Austen KF (eds): *Dermatology in General Medicine* (ed 3). New York, NY, McGraw-Hill, 1987, pp 746-758
12. Carter DM: Basal cell carcinoma, in Fitzpatrick T, Eisen A, Wolff K, Freedberg I, Austen KF (eds): *Dermatology in General Medicine* (ed 3). New York, NY, McGraw-Hill, 1987, pp 759-765
13. Strickland PT, Vitasa BC, West SK, et al: Quantitative carcinogenesis in man: Solar ultraviolet B dose dependence of skin cancer in Maryland watermen. *J Natl Cancer Inst* 81:1910-1913, 1989
14. Mastrangelo MJ, Baker AR, Katz HR: Cutaneous melanoma, in DeVita VT, Hellman S, Rosenberg SA (eds): *Cancer: Principles and Practice of Oncology* (ed 2). Philadelphia, PA, Lippincott, 1985, pp 1371-1422
15. Stern RS, Weinstock MC, Baker SG: Risk reduction for nonmelanoma skin cancer with childhood sunscreen use. *Arch Dermatol* 122:537-545, 1986
16. National Institutes of Health Consensus Development Conference Statement: Sunlight, ultraviolet radiation, and the skin. *J Am Acad Dermatol* (in press)
17. Scotto J, Fears TR, Fraumeni JF Jr: Solar radiation, in Schottenfeld D, Fraumeni JF Jr (eds): *Cancer Epidemiology and Prevention*. Philadelphia, PA, Saunders, 1982, pp 254-276
18. Kripke ML: Antigenicity of murine skin tumors induced by UV light. *J Natl Cancer Inst* 53:1333-1336, 1974
19. Kripke ML: Immunoregulation of carcinogenesis: Past, present, and future. *J Natl Cancer Inst* 80:722-727, 1988
20. Scotto J, Cotton G, Urbach F, et al: Biologically effective ultraviolet radiation: Surface measurements in the United States, 1974 to 1985. *Science* 239:762-764, 1988
21. Yuspa SH: Carcinogenesis: Chemical, in Fitzpatrick T, Eisen A, Wolff K, Freedberg I, Austen KF (eds): *Dermatology in General Medicine* (ed 3). New York, NY, McGraw-Hill, 1987, pp 722-729
22. International Agency for Research on Cancer: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Proceedings of a meeting of an IARC ad hoc Working Group on the Evaluation of Carcinogenic Risks to Humans, Lyon, France, March 10-18, 1987. World Health Organization, 1987, pp 100-106 (suppl 7)
23. Stern RS, Thibodeau LA, Kleinerman RA, et al: Risk of cutaneous carcinoma in patients treated with oral methoxsalen

photochemotherapy for psoriasis. *N Engl J Med* 300:809-813, 1979

24. Rhodes AR, Weinstock MA, Fitzpatrick TB, et al: Risk factors for cutaneous melanoma. A practical method for recognizing predisposed individuals. *JAMA* 258:3146-3154, 1987

25. Lawler PE, Schrieber S: Cutaneous malignant melanoma: Nursing's role in prevention and early detection. *Oncol Nurs Forum* 16:345-352, 1989

26. Pathak MA, Fitzpatrick TB, Greiter F, et al: Preventive treatment of sunburn, dermatoheliosis, and skin cancer with sun-protective agents, in Fitzpatrick T, Eisen A, Wolff K, Freedberg I, Austen KF (eds): *Dermatology in General Medicine* (ed 3). New York, NY, McGraw-Hill, 1987, pp 1507-1522

27. Schwartz RA, Stoll HL: Epithelial precancerous lesions, in Fitzpatrick T, Eisen A, Wolff K, Freedberg I, Austen KF (eds): *Dermatology in General Medicine* (ed 3). New York, NY, McGraw-Hill, 1987, pp 733-746

28. Lee MM, Wick, MW: Bowen's disease. *CA* 40:237-242, 1990

29. Ghadially FN: Keratoacanthoma, in Fitzpatrick T, Eisen A, Wolff K, Freedberg I, Austen KF (eds): *Dermatology in General Medicine* (ed 3). New York, McGraw-Hill Book Company, 1987, pp 766-772

30. Lowy DR: Carcinogenesis: Viral, in Fitzpatrick T, Eisen A, Wolff K, Freedberg I, Austen KF (eds): *Dermatology in General Medicine* (ed 3). New York, NY, McGraw-Hill, 1987, pp 730-733

31. Tucker MA: Individuals at high risk of melanoma, in MacKie RM (ed): *Pigment Cell*, vol 9. Basel, Switzerland, Karger, 1988, pp 95-109

32. Scotto J, Fears TR: The association of solar ultraviolet and skin melanoma incidence among Caucasians in the United States. *Cancer Invest* 5:275-283, 1987

33. National Institutes of Health Consensus Conference: Precursors to malignant melanoma. *JAMA* 251:1864-1866, 1984

34. Elwood JM, Gallagher RP, Hill GB, et al: Cutaneous melanoma in relation to intermittent and constant sun exposure. The Western Canada Melanoma Study. *Int J Cancer* 35:427-433, 1985

35. Elwood JM, Williamson C, Stapleton PJ: Malignant melanoma in relation to moles, pigmentation, and exposure to fluorescent and other lighting sources. *Br J Cancer* 53:65-74, 1986

36. Green A, MacLennan R, Siskind V: Common acquired naevi and the risk of malignant melanoma. *Int J Cancer* 35:297-300, 1985

37. Green A, Siskind V, Bain C, et al: Sunburn and malignant melanoma. *Br J Cancer* 51:393-397, 1985

38. Østerlind A, Tucker MA, Hou-Jensen K, et al: The Danish case-control study of cutaneous malignant melanoma. I. Importance of host factors. *Int J Cancer* 42:200-206, 1988

39. Østerlind A, Tucker MA, Stone BJ, et al: The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. *Int J Cancer* 42:319-324, 1988

40. Beral V, Evans S, Shaw H, et al: Cutaneous factors related to the risk of malignant melanoma. *Br J Dermatol* 109:165-172, 1983

41. Elwood JM, Gallagher RP, Hill GB, et al: Pigmentation

and skin reaction to sun as risk factors for cutaneous melanoma: Western Canada Melanoma Study. *Br Med J* 288:99-102, 1984

42. Gellin GA, Kopf AW, Garfinkel L: Malignant melanoma. A controlled study of possibly associated factors. *Arch Dermatol* 99:43-48, 1969

43. Holman CDJ, Armstrong BK: Pigmentary traits, ethnic origin, benign nevi, and family history as risk factors for cutaneous malignant melanoma. *J Natl Cancer Inst* 72:257-266, 1984

44. Klepp O, Magnus K: Some environmental and bodily characteristics of melanoma patients. A case-control study. *Int J Cancer* 23:482-486, 1979

45. Swerdlow AJ, English J, MacKie RM et al: Benign melanocytic naevi as a risk factor for malignant melanoma. *Br Med J* 292:1555-1559, 1986

46. Kopf AW, Lindsay AC, Rogers GS, et al: Relationship of nevocytic nevi to sun exposure in dysplastic nevus syndrome. *J Am Acad Dermatol* 12:656-662, 1985

47. Rigel DS, Rivers JK, Kopf AW, et al: Dysplastic nevi—Markers for increased risk for melanoma. *Cancer* 63:386-389, 1989

48. MacKie RM, Freudenberger T, Aitchison TC: Personal risk-factor chart for cutaneous melanoma. *Lancet* 2:487-490, 1989

49. Evans RD, Kopf AW, Lew RL, et al: Risk factors for the development of malignant melanoma—I: Review of case-control studies. *J Dermatol Surg Oncol* 14:393-408, 1988

50. Gallagher RP, Elwood JM, Threlfall WJ, et al: Socio-economic status, sunlight exposure, and risk of malignant melanoma: The Western Canada Melanoma Study. *J Natl Cancer Inst* 79:647-652, 1987

51. Holman CDJ, Armstrong BA, Heenan PJ: A theory of the etiology and pathogenesis of human cutaneous malignant melanoma. *J Natl Cancer Inst* 71:651-656, 1983

52. MacKie RM, Aitchison T: Severe sunburn and subsequent risk of primary cutaneous malignant melanoma in Scotland. *Br J Cancer* 46:955-960, 1982

53. English DR, Armstrong BK: Identifying people at high risk cutaneous malignant melanoma: Results of a case control study in Western Australia. *Br Med J* 296:1285-1288, 1988

54. Holman CDJ, Armstrong BK: Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: An analysis separating histogenic types. *J Natl Cancer Inst* 73:75-82, 1984

55. Holman CDJ, Armstrong BK, Heenan PJ: Relationship of cutaneous malignant melanoma to individual sunlight-exposure habits. *J Natl Cancer Inst* 76:403-414, 1986

56. Armstrong BK, De Klerk NH, Holman CDJ: Etiology of common acquired melanocytic nevi: Constitutional variables, sun exposure, and diet. *J National Cancer Inst* 77:329-335, 1986

57. Greene MH, Clark WH Jr, Tucker MA, et al: Acquired precursors of cutaneous malignant melanoma in familial dysplastic nevus syndrome. *N Engl J Med* 312:91-97, 1985

58. Lynch HT, Frichot BC, Lynch JF: Familial atypical multiple mole melanoma syndrome. *J Med Genet* 15:352-356, 1978

59. Greene MH, Clark WH Jr, Tucker MA, et al: High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. *Ann Intern Med* 102:458-465, 1985

60. Kopf AW, Hollman LJ, Rogers GS, et al: Familial malignant melanoma. *J Am Med Assoc* 256:1915-1919, 1986
61. Crutcher WA, Sagebiel RW: Prevalence of dysplastic naevi in a community practice. *Lancet* 1:729, 1984
62. Cooke KR, Spears GFS, Elder DE, et al: Dysplastic naevi identified in a cross-sectional survey. *Cancer* 63:1240-1244, 1989
63. Norland JJ, Kirkwood J, Forget BM, et al: Demographic study of clinically atypical (dysplastic) nevi in patients with melanoma and comparison subjects. *Cancer Res* 45:1855-1861, 1985
64. Kraemer KH, Tucker MA, Tarone R, et al: Risk of cutaneous melanoma in dysplastic nevus syndrome types A and B. *N Engl J Med* 315:1615-1616, 1986
65. Tucker MA, Boice JD Jr, Hoffman DA: Second cancer following cutaneous melanoma and cancers of the brain, thyroid, connective tissue, bone and eye in Connecticut, 1935-82. *Multiple Primary Cancers in Connecticut and Denmark*. Bethesda, MD, NIH, 1985. pp 161-189 (NCI Monograph 68, NIH Publication No. 85-2714)
66. Adam SA, Sheaves JK, Wright NH, et al: A case-control study of the possible association between oral contraceptives and malignant melanoma. *Br J Cancer* 44:45-50, 1981
67. Østerlind A, Tucker MA, Stone BJ, et al: The Danish case-control study of cutaneous malignant melanoma. III. Hormonal and reproductive factors in women. *Int J Cancer* 42:821-824, 1988
68. Østerlind A, Tucker MA, Stone BJ, et al: The Danish case-control study of cutaneous malignant melanoma. IV. No association with nutritional factors, alcohol, smoking or hair dyes. *Int J Cancer* 42:825-828, 1988
69. Sorahan T, Grimley RP: The aetiological significance of sunlight and fluorescent lighting in malignant melanoma: A case-control study. *Br J Cancer* 52:765-769, 1985
70. Stryker WS, Stampfer MJ, Stein EA, et al: Diet, plasma levels of beta-carotene and alpha-tocopherol, and risk of malignant melanoma. *Am J Epidemiol* 131:597-611, 1990
71. Reynolds P, Austin D, Thomas J: Familial and occupational risks associated with malignant melanoma of the skin. *Am J Epidemiol* 116:570, 1982
72. Weinstock MA: The epidemic of squamous cell carcinoma. *JAMA* 262:2138-2140, 1989 (editorial)