

Nonmelanoma skin cancer

JOSEPH SCOTTO

THOMAS R. FEARS

KENNETH H. KRAEMER

JOSEPH F. FRAUMENI, JR.

Nonmelanoma skin cancer (NMSC) is the most common malignant neoplasm in Caucasian populations around the world, and usually refers to either basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) (Weinstock, 1994a). Although it is established that ultraviolet (UV) radiation from the sun is the dominant risk factor, epidemiologic study of these tumors has been limited by the fact that most patients are customarily seen and treated in the offices of physicians and not hospitalized (Scotto et al, 1983). Since the primary source of data for cancer registries is the inpatient hospital file, routinely collected statistics on NMSC are usually very incomplete and not comparable with other forms of cancer. Thus, population-based estimates of NMSC incidence require special surveys involving the collection of data from office records and outpatient files. These are formidable undertakings, especially in view of the large number of cases that are diagnosed in the general population.

Another obstacle to investigation is the perception that NMSC is a relatively trivial condition. The cure rates are close to 99%, with only a small percentage of cancers being metastatic or resulting in death (Preston and Stern, 1992), yet the tumors can result in substantial morbidity. The incidence rates for BCC and SCC have steadily increased with time, and these tumors represent a major health and economic problem in the United States and other parts of the world (National Institutes of Health [NIH], 1991; Miller and Weinstock, 1994; Marks, 1995). In addition, there is mounting concern about the future risks of all forms of skin cancer, including melanoma, in view of evidence that release of chlorofluorocarbons and other pollutants may deplete the stratospheric ozone layer that limits the amount of UV radiation reaching the earth's surface (Armstrong, 1994).

Both SCC and BCC of the skin are derived from ke-

ratinocytes (Preston and Stern, 1992; Sober and Borstein, 1995). While SCC develops from epidermal squamous cells that differentiate toward keratin formation, BCC is believed to arise from basal cells that differentiate toward glandular structures. BCC is generally more common, whereas SCC tends to be more invasive and accounts for most of the deaths attributed to these tumors (Weinstock, 1994b). It is estimated that less than one in 500 patients with SCC die of this cancer, thus causing about 1,500 deaths in the United States each year (Preston and Stern, 1992). This number is roughly one-fourth of the mortality attributed to melanoma, a less common but far more lethal tumor. Although the available statistics on NMSC often combine the cell types, epidemiologic distinctions are evident from the specially collected incidence data available in certain countries, including the United States. However, the potential for misclassification should be kept in mind, particularly when using routinely collected statistics that have recorded dramatic increases in incidence and mortality from NMSC resulting from the inclusion of AIDS-related Kaposi sarcoma (Weinstock, 1993; Devesa et al, 1995). When appropriate data collection and adjustments are made to ensure that the NMSC category includes only BCC and SCC, there is a consistent upward incidence trend (Miller and Weinstock, 1994) in the face of declining mortality (Weinstock, 1993).

DEMOGRAPHIC PATTERNS

Despite the inherent difficulties in assembling and comparing incidence data, the risks of BCC and SCC have consistently shown positive relationships with exposure to solar UV radiation and inverse relationships with the degree of skin pigmentation characteristic of the population (International Agency for Research on Cancer

[IARC], 1992). Thus in the United States, these tumors are much more common among whites than blacks, Asians, Hispanics, and Native Americans. Around the world, the highest rates have been reported in the white populations of Australia and South Africa, followed by Ireland, where there is comparatively low insolation but a susceptible skin phenotype related to Celtic ancestry (Giles et al, 1988; Green and Battistutta, 1990; Marks et al, 1993).

In the United States, the National Cancer Institute (NCI) has conducted two special surveys of NMSC utilizing the same protocol for identifying and recording cases (see further details in Chapter 17). The first survey covered four areas of the country over a 6-month period in 1971–72, while the second survey involved eight locations over a 1-year period in 1977–78, plus two more locations during 1979–80. An enormous racial differential was noted, with the annual average incidence rate for NMSC being 250 per 100,000 among whites compared with 3 to 4 per 100,000 among blacks. Using data from these surveys, incidence appeared to increase about 15–20% between 1971–72 and 1977–80. When rates from these surveys and others in the United States are projected to 1994 and 1995, the annual incidence of NMSC is estimated to be about 800,000 to 1.2 million cases, which nearly rivals the magnitude of all non-cutaneous malignancies (Miller and Weinstock, 1994; American Cancer Society, 1995).

When the cell-type patterns for the white population are analyzed from the second skin cancer survey, 1977–80, the age-adjusted rates for BCC were about four times higher than the rates for SCC in males, and six times higher in females (Table 60–1). The male-to-female ratio was 1.6 for BCC and 2.8 for SCC. Similar ratios were noted in a skin cancer survey in Texas (Yianias et al, 1988). As shown in Figure 60–1 (white males) and Figure 60–2 (white females), the rates in all parts of the country rose continuously with advancing age, with a tendency to level off in the oldest groups. The increase with age was more pronounced for SCC than BCC. Both cell types showed a latitudinal gradient, with higher rates and earlier onset in areas located in the South.

Figures 60–3 and 60–4 show the age-specific inci-

TABLE 60–1. Annual Age-Adjusted Incidence Rates (per 100,000) for Nonmelanoma Skin Cancer by Cell Type and Sex, U.S. White Population, 1977–80

	Basal Cell Carcinoma	Squamous Cell Carcinoma
Male	257.7	68.3
Female	154.8	23.9
Both sexes	198.5	42.7
Male/female ratio	1.6	2.8

dence rates for each cell type according to sex. The male and female rates for BCC were similar at younger ages, with a male predominance at older ages. The disparity between males and females tended to arise at an earlier age among those in southern areas. In contrast, the male excess of SCC was evident throughout life.

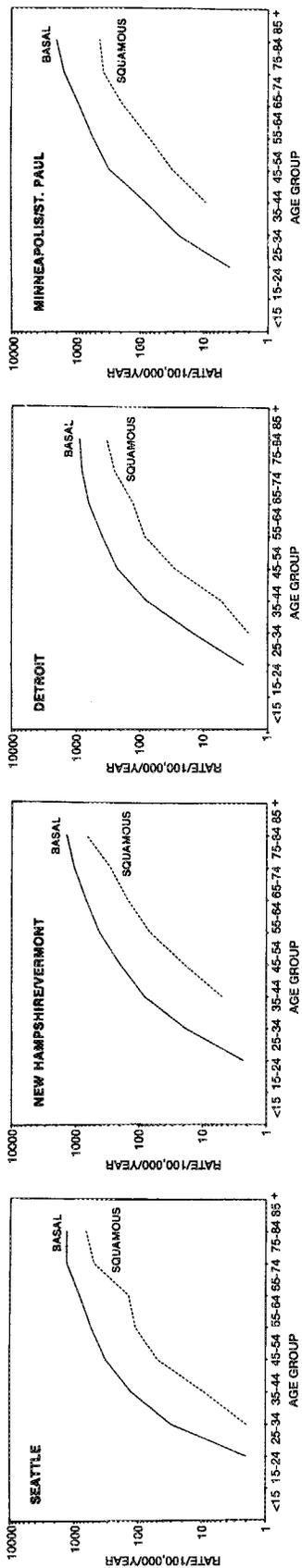
Tumors arose on the face, head, and neck in about 80% of patients with NMSC (Table 60–2). This pattern contrasts with the more even anatomic distribution of melanoma, its frequency being highest on the trunk in males and the lower extremities in females (Scotto and Nam, 1980; Scotto et al, 1991). The anatomic distribution by sex is shown for BCC in Figure 60–5 and for SCC in Figure 60–6. The tendency to affect the face, head, and neck was greater for BCC than SCC. Both types showed a predilection for the ears in males and the nose in females. A male predominance for SCC of the lip was also seen, consistent with the risk factors of tobacco smoking and outdoor work (Lindqvist, 1979). Also noteworthy was the tendency for SCC to affect the upper extremities, especially in females, with the hands being most susceptible. However, the proportion of tumors arising on the trunk was somewhat greater for BCC than SCC.

Figures 60–7a and 60–7b show the age-adjusted incidence rates by sex and anatomic site for BCC and SCC, respectively. The male excess of both tumors affected all sites except the lower extremities. At this location, women have higher rates for all forms of skin cancer, including melanoma, which is consistent with the greater sunlight exposure of the lower legs among females (Lee and Yongchaiyudha, 1971; IARC, 1992). While the rates were generally lower for SCC than BCC, the rates for SCC of the upper extremities were higher. In the upper extremities, the risk of SCC on the hands was about twice that on the arms, whereas the risk of BCC on the hands was about six times lower than on the arms.

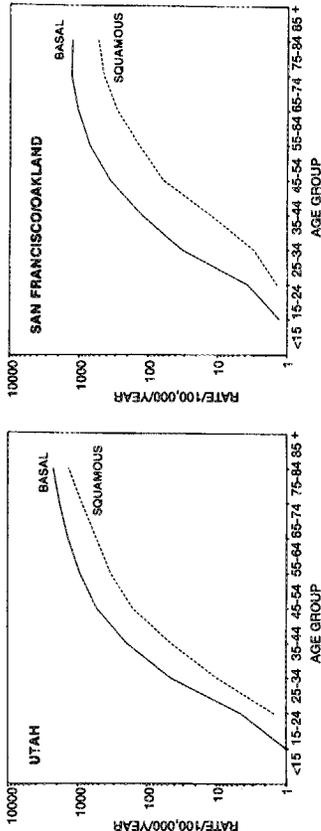
The age-adjusted incidence rates for BCC and SCC (Scotto, 1986), along with skin melanoma (Ries et al, 1990), are displayed by geographic area and estimated UVB exposure (Scotto et al, 1976a, 1988) in Figure 60–8 (white males) and Figure 60–9 (white females). The slopes are steeper for SCC than for BCC, which is consistent with international patterns showing that the ratio of BCC to SCC declines with decreasing latitude and increasing sunlight exposure (Urbach, 1971). The latitudinal gradient appears least pronounced for melanoma (Scotto and Fears, 1987), which is consistent with evidence that intermittent sunlight exposures and susceptibility factors such as dysplastic nevi are especially important in the development of this tumor (Greene and Fraumeni, 1979; IARC, 1992).

The UVB gradients in the incidence of NMSC are depicted according to anatomic site in Figures 60–10 and

NORTHERN REGION (LATITUDES 40-50 DEGREES NORTH)



MID REGION (LATITUDES 36-40 DEGREES NORTH)



SOUTHERN REGION (LATITUDES 30-35 DEGREES NORTH)

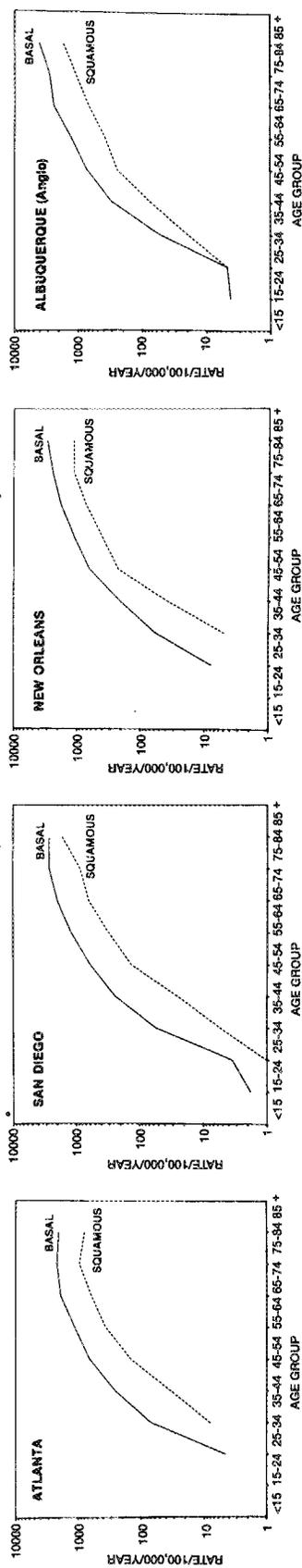
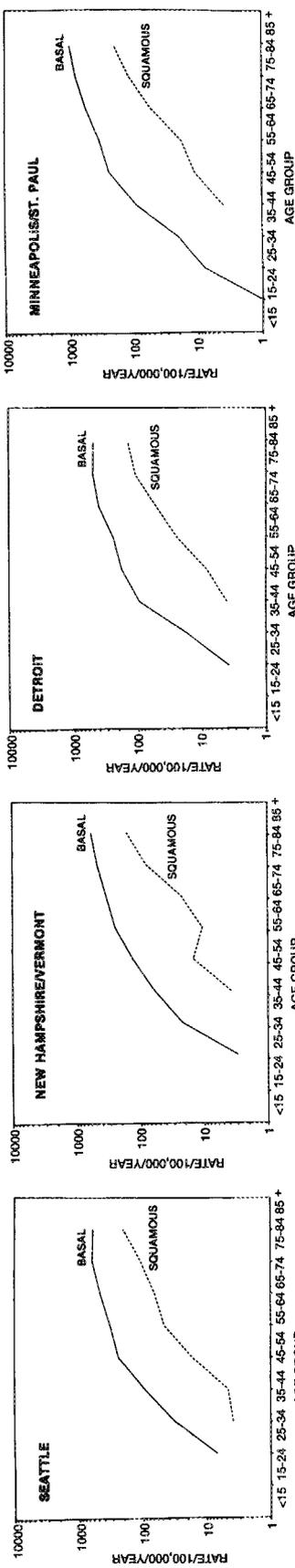
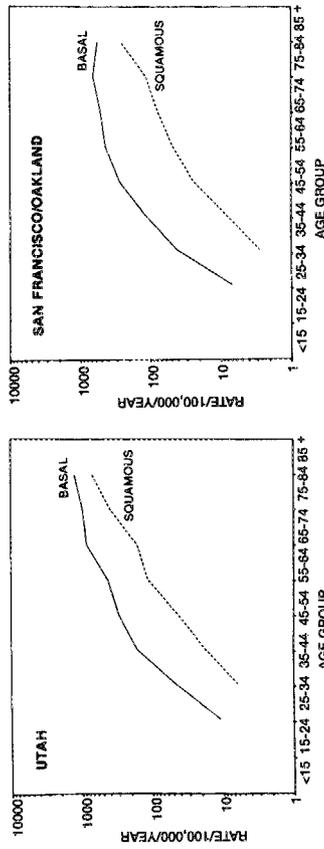


FIG. 60-1. Annual age-specific incidence rates for nonmelanoma skin cancer among white males according to cell type, in selected regions of the United States (1977-80).

NORTHERN REGION (LATITUDES 40-50 DEGREES NORTH)



MID REGION (LATITUDES 36-40 DEGREES NORTH)



SOUTHERN REGION (LATITUDES 30-35 DEGREES NORTH)

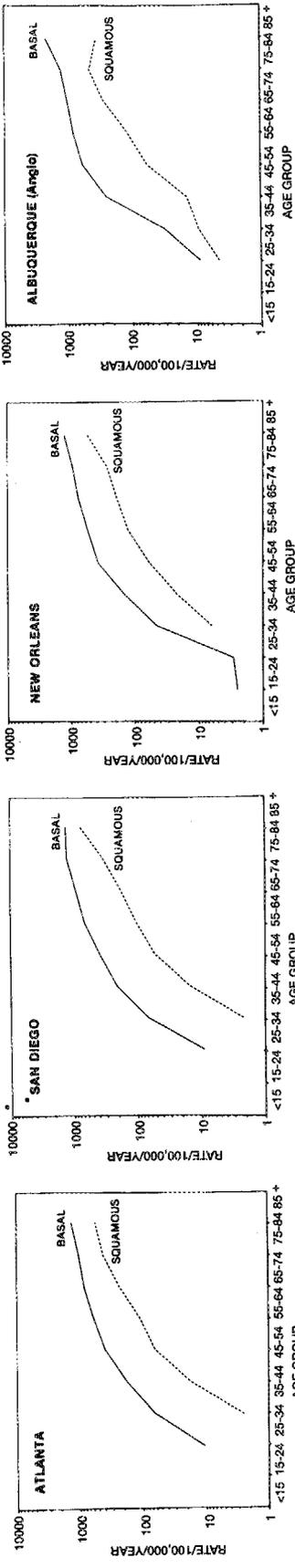


FIG. 60-2. Annual age-specific incidence rates for nonmelanoma skin cancer among white females according to cell type, in selected regions of the United States (1977-80).

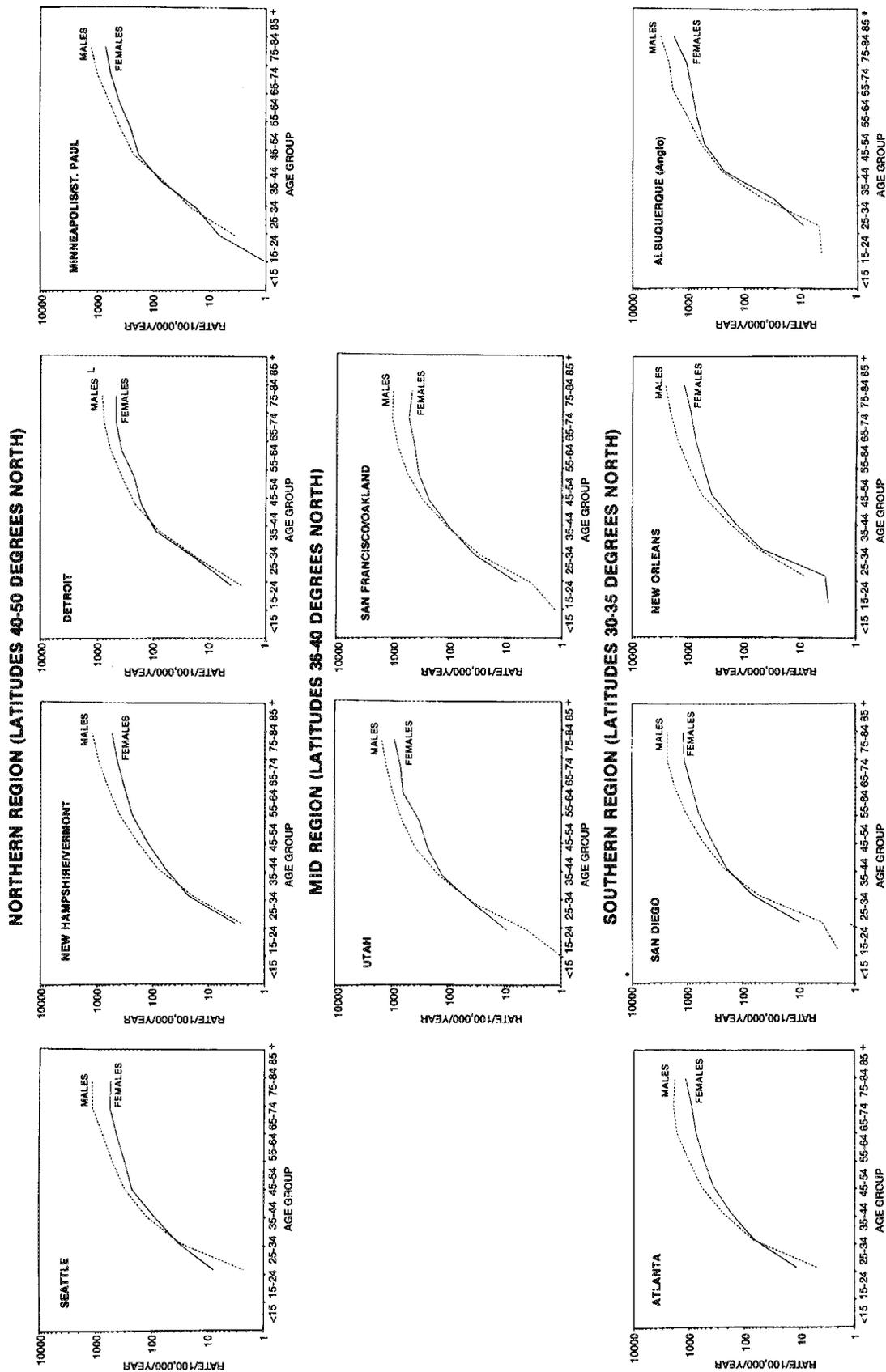


FIG. 60-3. Annual age-specific incidence rates for basal cell carcinoma of the skin according to sex, in selected regions of the United States (1977-80).

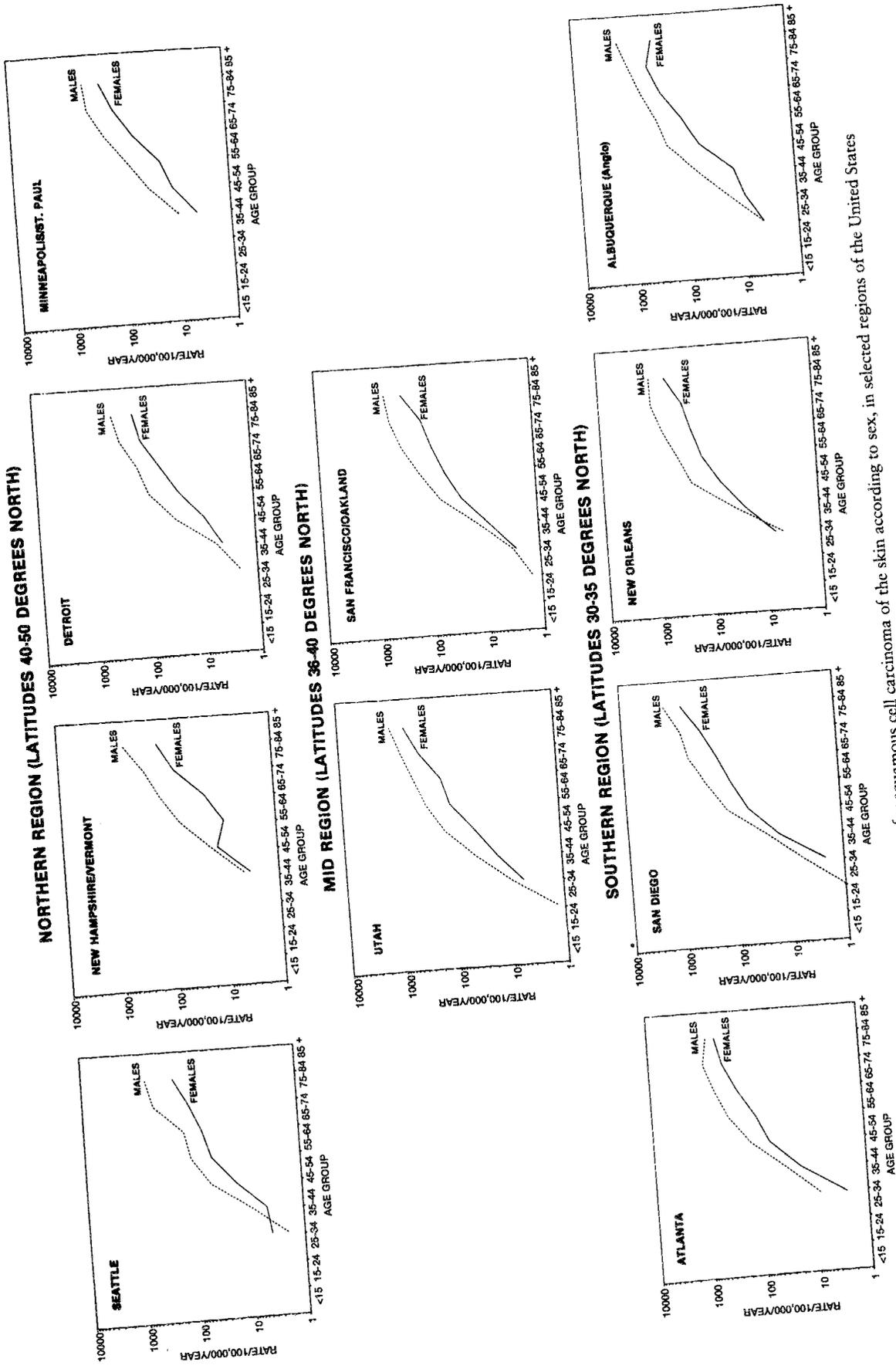


FIG. 60-4. Annual age-specific incidence rates for squamous cell carcinoma of the skin according to sex, in selected regions of the United States (1977-80).

TABLE 60-2. Percentage of Tumors by Anatomic Site for Nonmelanoma Skin Cancer and Melanoma among White Males and Females in the United States

	Nonmelanoma Skin Cancer (Percent)		Melanoma ^a (Percent)	
	Male	Female	Male	Female
Face, head, and neck	80	81	27	17
Upper extremities	11	9	22	26
Trunk	7	6	38	22
Lower extremities	2	4	13	35

^aFrom Scotto and Nam (1980)

60-11 for white males and females, respectively. For each site, incidence rates rose as UVB increased, with dose-response slopes being steepest for tumors of the upper extremities among men and women. For tumors of the upper extremities, the biological amplification factor (BAF, i.e., the relative change in rate due to a relative change in dose) using a power model (Fears and Scotto, 1983) was estimated to be about 2.8 and 2.5 for males and females, respectively. In contrast, the slopes were most shallow for tumors of the trunk, with BAFs

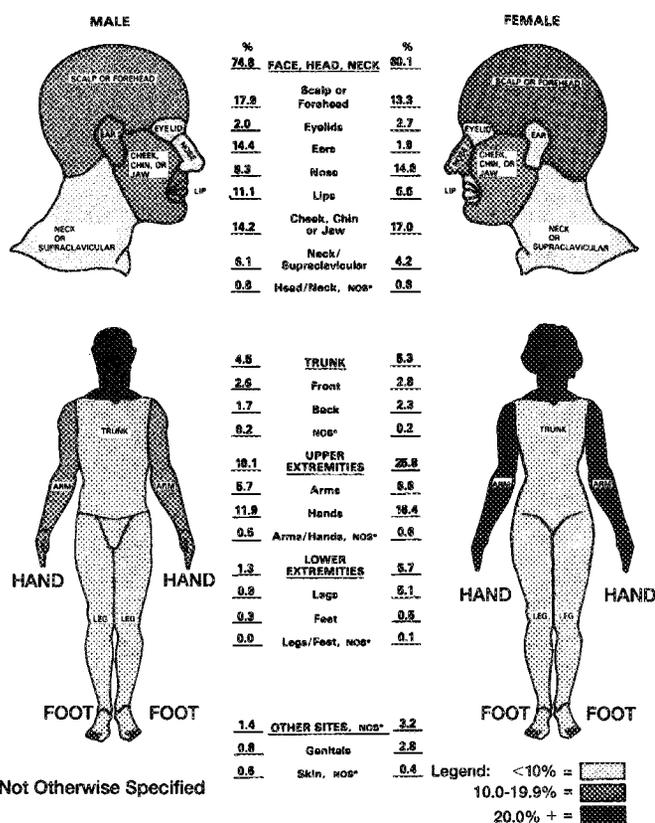


FIG. 60-6. Percentage of cases with squamous cell carcinoma of the skin by anatomic site among white males and females in the United States (1977-78).

estimated around 1.2 for males and 1.0 for females. These findings suggest that NMSC of the trunk, like skin melanoma (Fears et al, 1977; Scotto et al, 1991), may be less influenced by changes in surface measurements of UVB radiation than by lifestyle variations in sun exposure habits.

As shown in Table 60-3, the rising incidence of NMSC in the United States during the 1970s was seen in both sexes and affected mainly BCC. An upward trend was apparent also when confining analysis to the two areas common to both NCI surveys (San Francisco-Oakland and Minneapolis-St. Paul), although it is difficult to exclude the possibility of more complete case findings. After adjusting for the month of diagnosis, the rise in incidence of BCC was about 15-20% over the 6-year period, with a slight increase in SCC among women only. When analyzed by anatomic site, the increase in BCC was greatest on the trunk of males, while an increase in SCC was apparent on the upper extremities of females. Incidence rates have also risen disproportionately for melanomas of the male trunk (Scotto et al, 1991). More recent surveys in the United States, Australia, and other countries have continued to show an upward trend for all types of skin cancer including

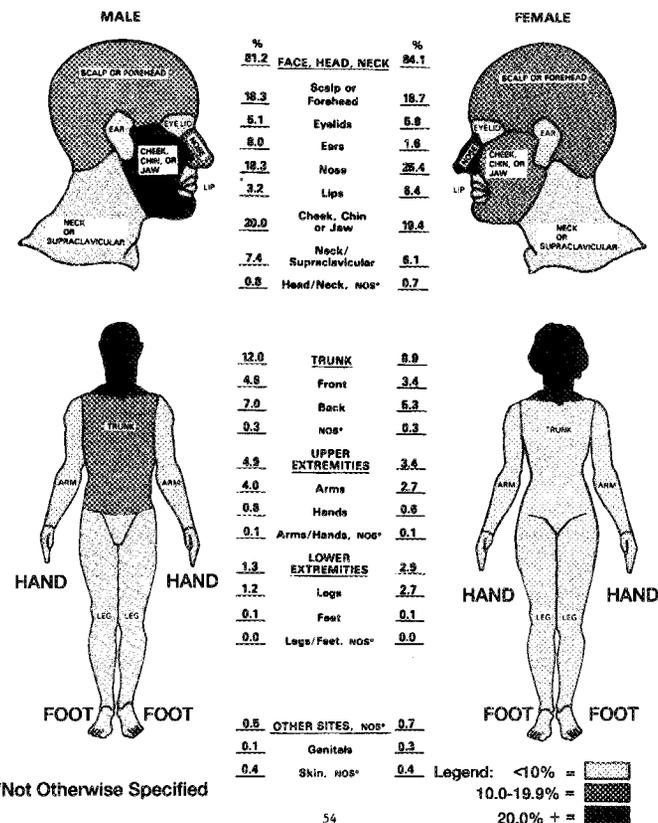


FIG. 60-5. Percentage of cases with basal cell carcinoma of the skin by anatomic site among white males and females in the United States (1977-78).

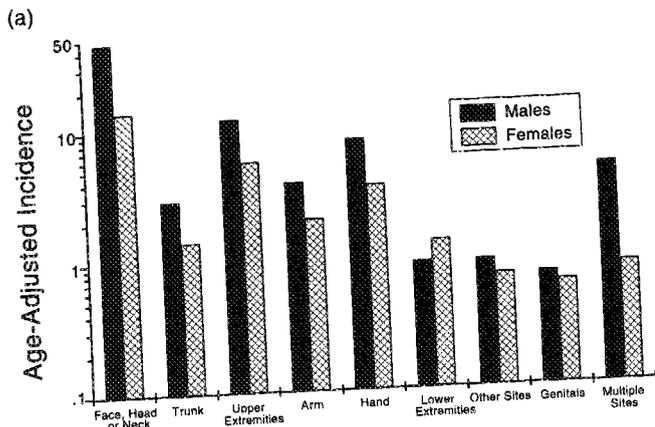
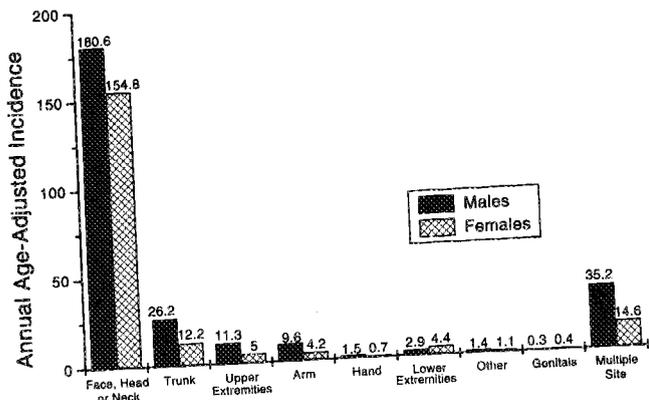


FIG. 60-7. A: Annual age-adjusted incidence rates for basal cell carcinoma of the skin by anatomic site among white males and females in the United States (1977-80). B: Annual age-adjusted incidence rates for squamous cell carcinoma of the skin by anatomic site among white males and females in the United States (1977-80).

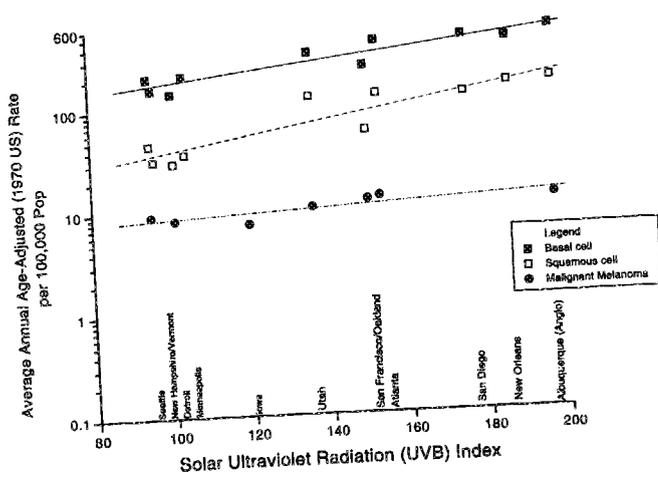


FIG. 60-8. Annual age-adjusted incidence rates for basal and squamous cell carcinomas (1977-80) and melanoma of the skin (SEER data, 1973-87) among white males according to UVB index at selected areas of the United States, with regression lines based on exponential models.

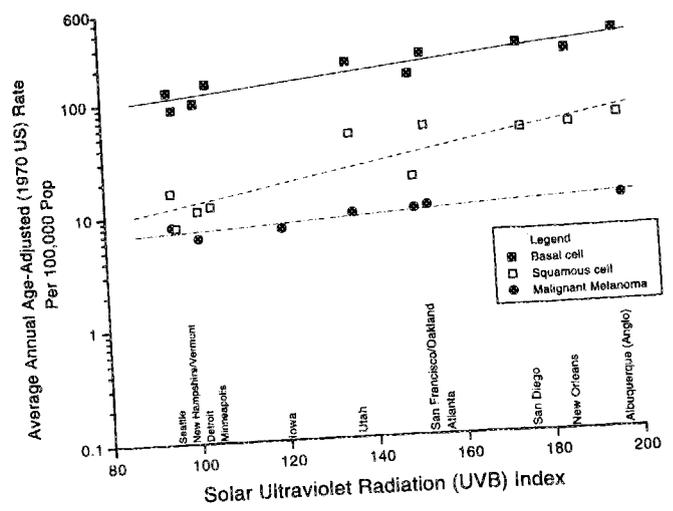


FIG. 60-9. Annual age-adjusted incidence rates for basal and squamous cell carcinomas (1977-80) and melanoma of the skin (SEER data, 1973-87) among white females according to UVB index at selected areas of the United States, with regression lines based on exponential models.

melanoma (Glass and Hoover, 1989; Gallagher et al, 1990; Chuang et al, 1990; Coebergh et al, 1991; Wallberg and Skog, 1991; Kaldor et al, 1993; Marks et al, 1993).

In the second NCI survey, only 68 black patients with NMSC were reported, with 67 being recorded as BCC or SCC (Table 60-4). The annual age-adjusted incidence rates for blacks varied from 6.1 per 100,000 population in Atlanta to 2.2 in Detroit. Although the number of cases is small, a latitudinal gradient was suggested for both cell types. A predominance of SCC was seen among blacks, with about 80% of the cases arising on the lower extremities. In addition, SCC rates were slightly higher among black females than males, resulting from a relative excess of tumors on the trunk, extremities, and genital area, while a deficit of SCC appeared on sun-exposed sites. A relative excess of SCC compared to BCC has previously been reported among blacks, particularly on covered areas of the skin and lower extremities (Halder and Bang, 1989). The tumors in blacks tend to be invasive and are often associated with predisposing conditions such as burn scars and chronic ulcers. The reason for the sex difference in the site distribution of SCC is unclear, although a high incidence of SCC involving the anal region has been reported among black women (Halder and Bang, 1988).

Also shown in Table 60-4 are the intermediate rates for BCC and SCC among Hispanics, as compared with non-Hispanic whites and blacks. The ethnic gradient was similar among men and women, but less pronounced for SCC than BCC. The anatomic distribution among Hispanics more closely resembled the pattern for whites than for blacks, with a particularly high proportion of tumors arising on the head, face, and neck.

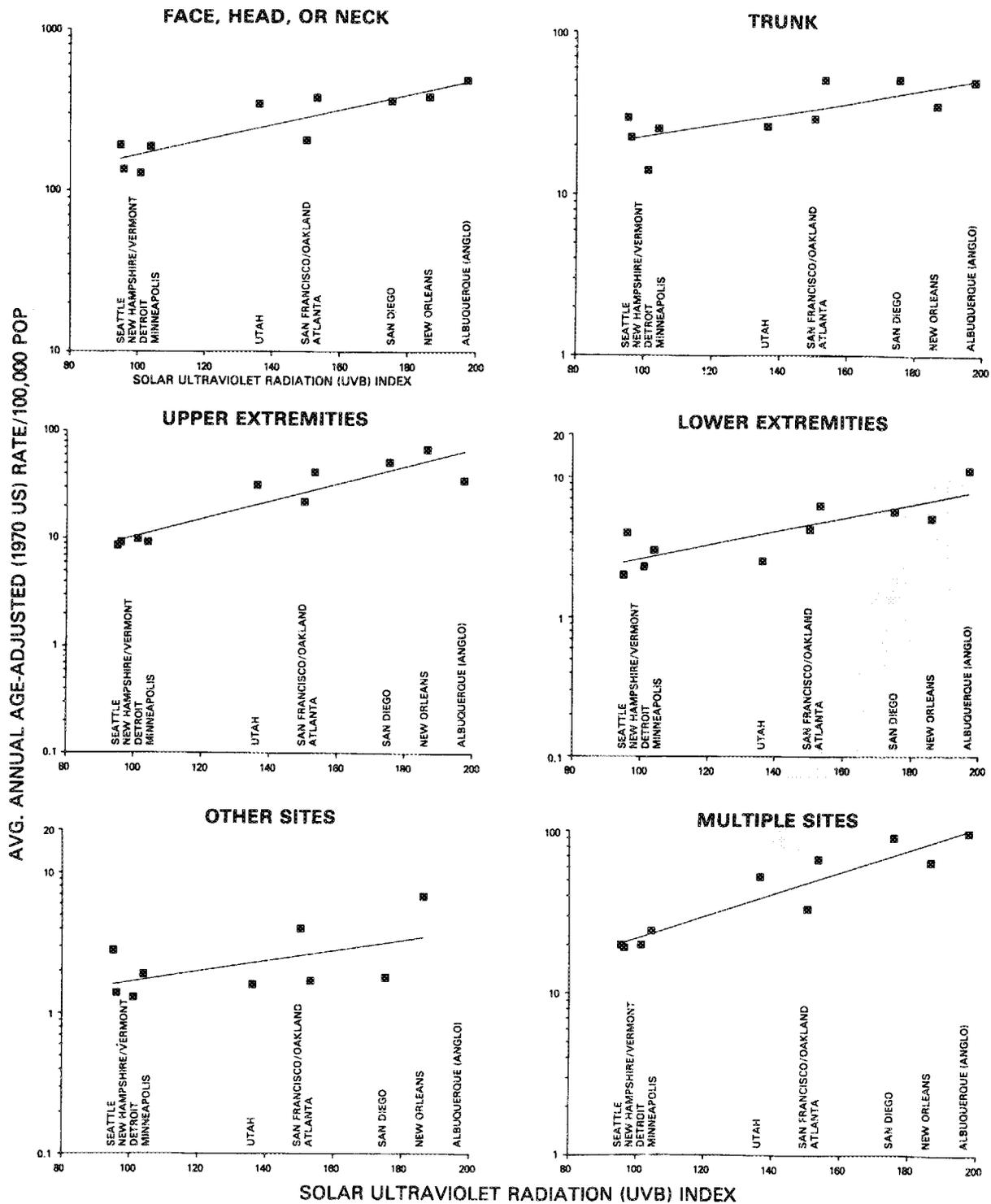


FIG. 60-10. Annual age-adjusted incidence rates for nonmelanoma skin cancer according to UVB index and anatomic site among white males in the United States (1977-80).

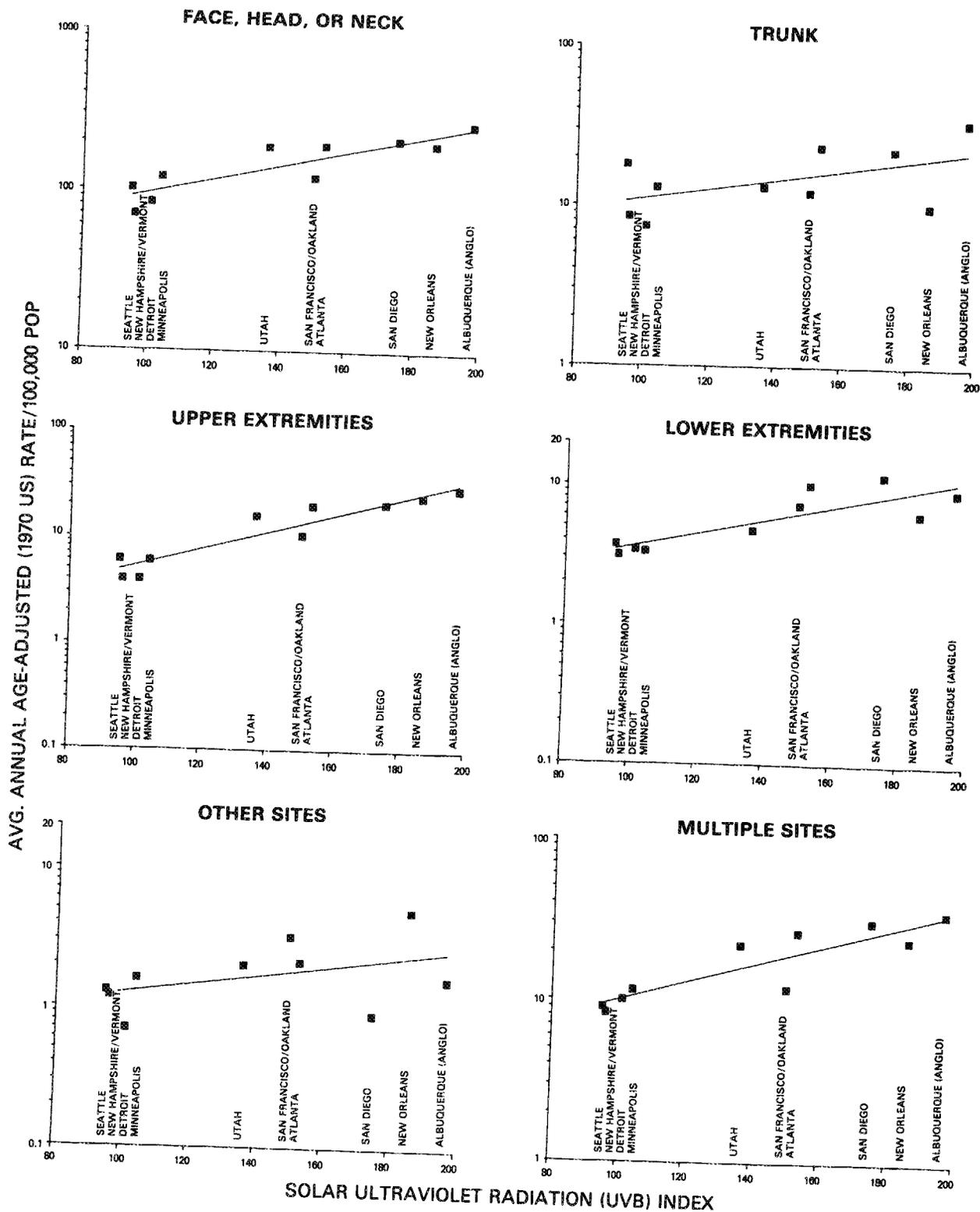


FIG. 60-11. Annual age-adjusted incidence rates for nonmelanoma skin cancer according to UVB index and anatomic site among white females in the United States (1977-80).

TABLE 60-3. Annual Age-Adjusted Incidence Rates (per 100,000) for Nonmelanoma Skin Cancer among White Males and Females in the United States, 1971-1972 and 1977-1978

	1971-1972 Survey ^a	1977-1978 Survey ^b
ALL SURVEY AREAS		
Basal Cell Carcinoma		
Male	202.1	246.6
Female	115.8	150.1
Squamous Cell Carcinoma		
Male	65.5	65.4
Female	21.8	23.6
SAN FRANCISCO-OAKLAND		
Basal Cell Carcinoma		
Male	197.9	239.0
Female	117.2	145.1
Squamous Cell Carcinoma		
Male	51.7	56.3
Female	15.8	18.4
MINNEAPOLIS-ST. PAUL		
Basal Cell Carcinoma		
Male	165.0	213.1
Female	102.8	144.0
Squamous Cell Carcinoma		
Male	36.5	36.6
Female	12.3	11.8

^aIncludes 4 areas

^bIncludes 8 areas

ENVIRONMENTAL FACTORS

Ultraviolet Radiation

The dominant risk factor for NMSC is UV radiation from the sun (IARC, 1992; Kricker et al, 1994). The evidence is based on (1) the tendency for tumors to arise on sun-exposed surfaces; (2) the high rates among occupational groups with outdoor exposures; (3) the generally inverse correlation between incidence rates and distance from the equator; (4) the predisposition of light-skinned populations, notably fair-complexioned people who sunburn easily, and the resistance of dark-skinned populations with protective melanin pigment; (5) the high rates among individuals with evidence of UV skin damage, actinic keratoses, and prior skin cancer; (6) the capacity of UV radiation in repeated doses to induce skin cancer in experimental animals, particularly in the UVB spectral range (290-320 nm) that causes delayed erythema in human skin; (7) the exceptionally high risk of skin cancer among persons with genetic diseases characterized by intolerance to sunlight (i.e., xeroderma pigmentosum and albinism); and (8) the highly specific mutations of the *p53* tumor-suppressor gene in SCC that are characteristic of UV-induced

changes in model systems (Brash et al, 1991; Ziegler et al, 1994).

The available epidemiologic evidence suggests that the risk of NMSC is related to cumulative lifetime UV exposure (Fears et al, 1977; Hoffman, 1987; IARC, 1992), while studies in laboratory animals suggest that the risk is proportional to the square root of the annual dose (Blum, 1976; Kelfkens et al, 1990; United Nations Environmental Programme [UNEP], 1990). The effects of chronic, repeated exposures to UV radiation are most apparent for SCC, whereas intermittent sun-intensive exposures with sunburning tend to be associated with melanoma. However, a role for intermittent exposures in BCC is suggested by the temporal, geographic, and anatomic patterns of this tumor (Gallagher et al, 1990) and the reported absence of dose dependence at high exposure levels (Strickland et al, 1989). Recent studies also suggest that, like melanoma, the risk of BCC is related especially to sun exposures and sunburning during childhood, while the risk of SCC is not (Gallagher et al, 1995a, 1995b).

Whether the UVB exposure is cumulative or intermittent, its intensity is limited by the ozone layer in the stratosphere; however, this protective barrier may be impaired by various human activities, including the release of chlorofluorocarbons used in aerosol propellants, refrigerators, and air conditioners. Depletion of this layer is likely to enhance the penetration of UVB radiation that reaches the earth's surface and thus further increase the incidence of NMSC and melanoma (Armstrong, 1994). For each 1% relative decrease in stratospheric ozone, about a 4% or greater increase in NMSC may be expected, depending on cell type and anatomic site (see further details in Chapter 17).

Ionizing Radiation

Skin cancers were the first neoplasms related to ionizing radiation, with case reports in 1902 among early radiation workers, particularly in areas with chronic radio-dermatitis. It has been difficult to evaluate skin cancer in studies of populations heavily exposed to ionizing radiation, because of the low case-fatality rate, the substantial underreporting of skin cancer to tumor registries, and the high background rate in the general population. Nevertheless, excess risks of NMSC have been described among radiologists, uranium miners, and atomic bomb survivors, and following X-ray therapy for tinea capitis of the scalp, enlargement of the thymus gland in infancy, lymphoid hyperplasia, and various benign skin diseases (Shore, 1990; United Nations, 1994). Taken together, the studies provide no indication of a dose threshold and suggest a dose-response relation that is linear in nature. The risks appear to be potenti-

TABLE 60-4. Number of Cases and Annual Age-Adjusted Incidence Rates (per 100,000) for Nonmelanoma Skin Cancer by Cell Type and Sex among Non-Hispanic White, Hispanic, and Black Males and Females in the United States, 1977-1980, with Percentage Distribution of Cases by Anatomic Site

	Basal Cell Carcinoma			Squamous Cell Carcinoma		
	Whites ^a	Hispanics ^a	Blacks ^b	Whites ^a	Hispanics ^a	Blacks ^b
MALES						
Face, head, or neck	68.1%	75.2%	69.2%	66.9%	77.4%	42.9%
Trunk	9.8	6.0	7.7	4.3	0.0	0.0
Upper extremities	5.7	4.0	0.0	18.9	9.7	7.1
Lower extremities	1.1	0.7	23.1	1.2	3.2	28.6
Other sites/NOS	0.6	2.0	0.0	1.1	9.7	7.1
Multiple sites	14.7	12.1	0.0	7.6	0.0	14.3
No. cases	8788	149	13	2425	31	14
Age-adjusted rate (SE × 1.96) ^c	360.1 (7.6)	51.6 (8.5)	1.9 (1.1)	101.1 (4.0)	10.0 (3.9)	2.2 (1.2)
FEMALES						
Face, head, or neck	75.4%	83.8%	64.6%	57.1%	75.9%	17.4%
Trunk	6.9	2.8	5.9	5.8	3.4	21.7
Upper extremities	4.0	2.8	5.9	24.6	13.8	8.7
Lower extremities	3.3	1.4	11.8	5.5	0.0	30.5
Other sites/NOS	0.9	1.4	5.9	2.3	6.9	17.4
Multiple sites	9.5	7.8	5.9	4.7	0.0	4.3
No. cases	6446	142	17	1167	29	23
Age-adjusted rate (SE × 1.96) ^c	210.7 (5.2)	37.2 (6.2)	2.0 (1.0)	35.4 (2.1)	7.9 (2.9)	2.5 (1.1)

^aIncludes San Francisco-Oakland, New Mexico, New Orleans, and San Diego

^bIncludes San Francisco-Oakland, Detroit, New Orleans, and Atlanta

^cStandard error provides factor for 95% confidence limits on the mean of the age-adjusted rate

ated by exposure to UV radiation and by susceptible skin phenotype. The epidemiologic findings are consistent with the capacity of ionizing radiation to induce skin cancers in laboratory animals (National Research Council, 1990).

Chemicals

Studies of chemical skin carcinogenesis in rodents have provided important evidence for a multistage process of cancer development, and are yielding new insights into the genetic, biological, and biochemical alterations involved at various stages of carcinogenesis (Yuspa, 1994). The first stage, initiation, may result from limited exposure to a low dose of an agent given once or for a short time, and it rapidly produces an irreversible cellular change involving a mutation in the DNA. The next stage, promotion, follows repeated exposure to a tumor promoter that causes an expanded clone of initiated cells. Further genetic and epigenetic changes are needed for the subsequent stages of premalignant proliferation and malignant conversion. If a large dose or repeated exposure to an initiator results in tumor formation, the agent may be considered a complete carcinogen with

both initiating and promoting activity. Table 60-5 lists some chemical and physical agents to which humans may be exposed and that have been identified as initiators or promoters of skin cancer in laboratory animals.

Several chemical carcinogens have been linked to an increased risk of skin cancer. Polycyclic aromatic hydrocarbons (PAHs), which are skin carcinogens in laboratory animals, occur as chemical mixtures in coal tars, pitch, asphalt, soot, creosotes, anthracenes, paraffin waxes, and lubricating and cutting oils. In 1775, Percivall Pott reported an excess of scrotal cancer among British chimney sweeps exposed to soot, the first recognition of an environmental cancer. In a series of studies from Great Britain over the past century, exposures to mineral oils have been linked to SSC of the skin and scrotum among shale oil workers, jute processors, tool setters operating automatic lathes, and mule spinners (Bingham et al, 1979). In the United States, an excess risk of skin and scrotal cancers has been reported among wax pressmen (Hendricks et al, 1959), while increases in risk have been documented among metal workers exposed to poorly refined cutting oils in France and among machine operators exposed to lubricating oils in Great Britain (Kipling and Waldron, 1976). Skin and lung

TABLE 60-5. *Chemical and Physical Agents that Initiate or Promote Nonmelanoma Skin Cancer in Laboratory Animals**

Initiators	Promoters
POLYCYCLIC AROMATIC HYDROCARBONS	PHORBOL ESTERS
Benz[a]pyrene	Croton oil
Tobacco tar	AROMATICS
Dibenz[a,h]anthracene	Phenol
NITROSAMINES	Anthralin
N,N'-Dimethylnitrosourea	PHYSICAL AGENTS
Methyl-nitro-nitrosoguanidine	Ultraviolet radiation
ALKYLATING AGENTS	Abrasion
β -Propriolactone	Wounding
Bis(chloromethyl) ether	OTHERS
Nitrogen mustard	Benzoyl peroxide
Cisplatin	Cigarette smoke condensate
PHYSICAL AGENTS	Retinoic acid
Ultraviolet radiation	Tetrachlorodibenzodioxin
Ionizing radiation	Dihydrotelocidin (fungal product)
OTHERS	
Urethane	
Dinitropyrene	

*Modified from Yuspa and Dlugosz (1991)

cancers also occur excessively among workers exposed to coal gas and tar (Doil et al, 1972), among roofers (Partanen and Boffetta, 1994), and among foundry workers (Partanen et al, 1994). The carcinogenicity of medicinal crude tar ointments has been argued for some time, and the epidemiologic evidence to date appears inconclusive based on studies of psoriasis patients treated with topical tar (Stern and Laird, 1994).

Inorganic arsenic, when taken internally for a prolonged time, is well-documented as a skin carcinogen (Brown et al, 1989; IARC, 1980). Exposure may result from medicinal agents used in the past (e.g., Fowler's solution), contaminated drinking water, or occupational exposures including agricultural pesticides. Arsenical skin cancers may be squamous or basal cell tumors and tend to arise at multiple sites, unexposed surfaces, and unusual locations, such as the palms and soles. It is also characteristic for the tumors to occur in association with hyperpigmentation and multiple keratoses of the skin. A dose-response relationship between chronic arsenic exposure and skin cancer prevalence has been reported in Taiwanese villages where artesian wells contain high levels of arsenic (Hsueh et al, 1995). It is noteworthy that arsenic has shown only limited evidence for carcinogenicity in laboratory studies, so that the carcinogenic mechanisms are probably different from those of other chemical carcinogens.

Psoralens, used in combination with UVA (long wavelength UV, 320-400 nm) for the treatment of psoriasis, have been linked to skin cancers, especially at sites not ordinarily exposed to the sun. In a recent follow-up averaging 13 years, Stern and Laird (1994) re-

ported that one-fourth of the patients exposed to high doses of psoralens and UVA radiation (PUVA) developed SCC, with a relative risk six times higher than those exposed to lower doses of PUVA. This association has heightened concern about the potential hazards of photosensitizers in various preparations, including tanning aids, cosmetics, and medicines (Wei et al, 1994a). The use of methotrexate in treating psoriasis may also increase the risk of SCC (Stern and Laird, 1994).

An increased risk of NMSC has been reported in several occupational groups including pesticide applicators (Wang and MacMahon, 1979), chemical and printing workers (Whitaker et al, 1979), and hairdressers (Pukala et al, 1992), but the specific exposures responsible for these associations are not clear.

Dietary Factors

Recent studies have suggested that the risk of NMSC may be decreased by low-fat diets or by micronutrients (Kune et al, 1992; Black et al, 1994; Wei et al, 1994b), but the findings have not been consistent (Hunter et al, 1992). The positive results, however, are in line with studies in laboratory animals and warrant further investigation.

Cigarette Smoking

An excess risk of squamous cancers of the lip has been documented among smokers, and there is some evidence that smoking may increase the risk of SCC at other cutaneous sites (Aubry and MacGibbon, 1985; Karagas et al, 1992). Further studies are needed to clarify this association and the mechanisms that may be involved.

Trauma, Burns and Scars

SCC may arise as a complication of tropical ulcers, burns and scars, sinuses and fistulas, or sites of chronic infection and inflammation (Kaplan, 1987). The formation of skin cancers in nonhealing scar tissue has been referred to as Marjolin's ulcer (Fleming et al, 1990). Although these predisposing conditions are seen especially in Africa and Asia, they play a role in some cases of SCC observed in African-Americans (Halder and Bridgeman-Shah, 1995). The spectrum of lesions includes tropical phagedenic ulcers in Africa which arise on the lower legs and feet from repeated trauma, become chronically infected, and often progress to SCC (Camain et al, 1972). The kangri cancer of Kashmir, India, complicates burn scars on the lower abdomen and thighs of people who warm themselves by baskets (kangri) containing clay pots with burning charcoal (Svindland, 1980). A related condition occurs in Japan, where kairo cancer results from woodburning heating

devices (kairo) full of warm ashes (Everall and Dowd, 1978). Similarly, kang cancer has been reported among people who sleep on heated brick beds (kang) in northern China (Laycock, 1948). In these instances, the cancers associated with burn scars may be promoted by polycyclic hydrocarbons released from the heat-generating devices. In India, dhoti cancer develops on the groin, flank and buttocks of people who traditionally wrap loincloths (dhotis) tightly around their bodies (Mulay, 1963). In addition, case reports suggest that SCC may occur excessively in the scars of various inflammatory skin diseases such as tuberculosis, leprosy, syphilis, pemphigus vulgaris, and discoid lupus erythematosus (Halder and Bridgeman-Shah, 1995), although treatment with X rays, UV light, or certain drugs may contribute to the development of tumors.

HOST FACTORS

Pigmentation

Skin color is determined by the genetically regulated amount of melanin pigment produced by melanocytes. Depending on the quantity of pigment in these cells, the skin is protected from the cumulative damage produced by UV radiation (Marks, 1995). Thus dark-skinned individuals tend to be resistant to all forms of UV-induced skin cancer and precursor lesions, while light-skinned individuals are prone. Most susceptible are those with fair complexions that tend to freckle and burn rather than tan easily (Krickler et al, 1991). This phenotype is seen especially among persons of Celtic heritage, with some but not all studies suggesting an exceptional risk of skin cancer in relation to Celtic ancestry (Krickler et al, 1994).

Precursor Lesions

Actinic (solar) keratosis and Bowen's disease (SCC *in situ*) are precursor lesions for invasive SCC (Sober and Burstein, 1995). The progression rate of actinic keratosis is low, with about one keratosis per 1,000 per year converting to SCC. Actinic keratosis is associated with cumulative sunlight exposure and a susceptible skin phenotype, and occurs only on sun-exposed surfaces. Similar forms of keratosis can be produced by ionizing radiation, inorganic arsenic, and polycyclic hydrocarbons. Bowen's disease is an indolent lesion that mainly affects older people, with about three-fourths of the lesions occurring on sun-exposed surfaces. Progression to invasive SCC eventually occurs in about 5% of lesions. When Bowen's disease affects non-sun-exposed surfaces, inorganic arsenic may be the culprit. Some surveys have indicated that patients with Bowen's disease

are prone to internal cancers, but recent population-based studies have revealed no excess risk of subsequent malignancies (Chute et al, 1991). In contrast to SCC, there is no known precursor lesion for BCC.

Genetic Predisposition

Several rare hereditary diseases predispose to NMSC, primarily by increasing susceptibility to the effects of UV radiation, and they provide important clues to mechanisms of skin carcinogenesis in the general population. The nevoid basal cell carcinoma syndrome is a dominantly inherited disorder consisting of multiple BCC and various developmental defects, including jaw cysts, skeletal anomalies, skin pits on the palms and soles, soft-tissue calcifications, and hypertelorism (Gorlin, 1987). A gene for this disorder has been located on chromosome 9q (Farndon et al, 1992). The basal cell tumors usually arise around puberty, but may appear as late as 40 years of age. It has been estimated that about one in 200 patients with BCC may have the syndrome, with the proportion rising to one in five when tumors develop before age 19 (Springate, 1986). There is a high risk of ovarian fibromas and medulloblastoma, which may be the presenting manifestation of the syndrome in children. The production of basal cell tumors in the syndrome is enhanced by exposure to sunlight and, most remarkably, to ionizing radiation that may be used to treat medulloblastoma (Strong, 1977). Another dominantly inherited condition is multiple self-healing squamous epitheliomata, which progress intermittently to invasive SCC but then spontaneously remit (Goudie et al, 1993). The mechanisms of tumor resolution are unclear, but the gene has been localized to a region of chromosome 9q that also contains the gene for nevoid basal cell carcinoma syndrome.

Xeroderma pigmentosum (XP) is a progressive sun-sensitive, autosomal recessive disease that develops during early childhood (Cleaver and Kraemer, 1995). In XP patients under age 20, there is a 1000-fold increased frequency of BCC, SCC, and melanoma on sun-exposed portions of the body, including the anterior eye and tongue (Kraemer et al, 1994). About 20% of patients have neurological abnormalities such as mental retardation, microcephaly, ataxia, choreoathetosis, and deafness (Kraemer et al, 1987). Despite extensive clinical and genetic heterogeneity in XP, all cases exhibit defects in the ability of cells to repair DNA damage induced by UV light (Bootsma, 1993). Using XP as a model, a recent population-based study in Maryland observed that non-XP patients with BCC have a reduced DNA repair capacity (Wei et al, 1993, 1994c). However, a subsequent study from Australia did not find these defects in patients with BCC or SCC (Hall et al, 1994).

Other recessively inherited states are prone to skin cancer. Since melanin pigment is absent, albinism greatly predisposes to skin cancer, especially SCC on sun-exposed areas (Witkop et al, 1989). Epidermodysplasia verruciformis consists of multiple benign verrucous tumors (warts) that develop in early childhood as a result of susceptibility to various types of human papillomaviruses (HPV) (Tyring, 1993). A high frequency of SCC has been reported, particularly in sun-exposed areas, with malignant conversion related mainly to HPV types 5 and 8. In the general population, HPVs are closely linked to squamous cancers involving anogenital skin, particularly HPV-16, but there has been no consistent association with other skin cancers except possibly in the setting of immunosuppression (Euvrard et al, 1993).

In addition, squamous cancers of the skin, mouth, and esophagus occur excessively in the scars of patients with the recessive and dominant types of dystrophic epidermolysis bullosa (Goldberg et al, 1988). Dyskeratosis congenita is a sex-linked recessive trait featuring skin pigmentation and atrophy, nail dysplasia, and leukoplakia of the mucous membranes (Sirinavin and Trowbridge, 1975). The condition often shows stigmata of Fanconi's aplastic anemia and carries a high risk of SCC involving the skin and mucous membranes.

In the general population, genetic determinants of skin color and complexion are responsible for the ethnic variations in NMSC, while other heritable factors may contribute to the familial tendency (Czarnecki et al, 1992; Wei et al, 1994a), the association reported with certain HLA antigens (Czarnecki et al, 1991), and possibly the increased risk with age (Wei et al, 1993).

Immunologic Factors

There is clear evidence that immunosuppressive states may predispose to various kinds of skin cancer, including melanoma. Most striking are the elevated risks of SCC among kidney transplant recipients receiving immunosuppressive drugs, including azathioprine and cyclosporine (Hoover and Fraumeni, 1973; Hartvelt et al, 1990). The excess risk is primarily on exposed areas of the skin and is further increased in sunny climates. To a lesser extent, an excess risk of SCC extends to other conditions that are treated with immunosuppressive drugs or are complicated by immunodeficiency (Kinlen, 1982). However, it is not clear whether the risk of NMSC is increased among patients infected with human immunodeficiency virus (HIV) (Lobo et al, 1992). The epidemiologic findings are intriguing in view of experimental evidence that UV radiation has an immunosuppressive effect that may promote its carcinogenic properties (Kripke, 1994).

PREVENTIVE MEASURES

The leading cause of nonmelanoma skin cancer is UV radiation from the sun, which accounts for the vast majority of SCC and BCC. Therefore, the risk of skin cancer can be substantially lowered by minimizing exposure to UV radiation. In particular, sunlight should be avoided during the middle of the day, especially between 11 a.m. to 1 p.m., when UVB exposures can be reduced by nearly 50% (Scotto et al, 1976b). The "shadow rule" may be used as a simple guide: Protect yourself from sunlight when your shadow is shorter than your height (Holloway et al, 1992). This rule avoids the need for watches, can be taught to children, holds true in all time zones, and is independent of daylight savings time. Also recommended are protective clothing and sunscreens with a sun protection factor (SPF) of at least 15, especially for fair-complexioned persons who sunburn easily. These measures should aid in halting the upward trend in the incidence of skin cancer, including melanoma, which may be attributed to increasing sunlight exposures from changing clothing styles and leisure time activities of the population (Marks, 1995). Special efforts are needed to protect infants and children, since NMSC risks are related to cumulative lifetime exposures and vulnerability appears greatest in early life (Marks et al, 1990).

There is widespread concern that exposures to UV radiation will increase if the stratospheric ozone layer is modified by chlorofluorocarbon emissions and certain other pollutants, and international cooperation will be needed if regulatory measures are to be effective. In addition, it is important to protect against the hazards of UV exposures from artificial sources, including sun lamps, tanning salons, and certain industrial operations such as welding, and to be wary of the potential enhancement of UV damage by photosensitizing and immunosuppressive agents. Steps should also be taken to limit unnecessary exposures to ionizing radiation, polycyclic hydrocarbons, and inorganic arsenic, although their contributions to the skin cancer burden of the population may be limited.

Since skin tumors are easily visible and accessible, screening and educational programs for high-risk individuals will help ensure the early detection and treatment of precancerous lesions and skin cancer (Kopf et al, 1995; Rhodes, 1995). Regular examinations are especially recommended for individuals with a history of skin cancer or multiple keratoses, severely sun-damaged skin, genetic predisposition or immunologic impairment, and significant exposure to chemical carcinogens or ionizing radiation (Preston and Stern, 1992). In addition, high-dose oral retinoids have been found to be effective in the prevention of new skin cancers among patients with xeroderma pigmentosum (Kraemer et al,

1988). However, chemoprevention with high-dose retinoids is toxic and low-dose isotretinoin was not effective in preventing new tumors arising among patients previously treated for basal cell cancers (Tangrea et al, 1992). By focusing on groups at high risk of skin cancer, it should be possible to further investigate the potential benefits of dietary modification, chemopreventive measures, and other interventions (Greenberg et al, 1990; Black et al, 1994).

REFERENCES

- AMERICAN CANCER SOCIETY. 1995. Cancer Facts and Figures 1995. Atlanta, GA, American Cancer Society.
- ARMSTRONG BK. 1994. Stratospheric ozone and health. *Int J Epidemiol* 23:873-885.
- AUBRY F, MACGIBBON B. 1985. Risk factors of squamous cell carcinoma of the skin: A case-control study in the Montreal region. *Cancer* 55:907-911.
- BINGHAM E, TROSSET RP, WARSHAWSKY D. 1979. Carcinogenic potential of petroleum hydrocarbons: A critical review of the literature. *J Environ Pathol Toxicol* 3:483-563.
- BLACK HS, HERD JA, GOLDBERG LH, et al. 1994. Effect of a low-fat diet on the incidence of actinic keratosis. *N Engl J Med* 330:1272-1275.
- BLUM HF. 1976. Ultraviolet radiation and skin cancer: In mice and men. *Photochem Photobiol* 24:249-254.
- BOOTSMA D. 1993. The genetic defect in DNA repair deficiency syndromes. *Eur J Cancer* 29A:1482-1488.
- BRASH DE, RUDOLPH JA, SIMON JA, et al. 1991. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc Natl Acad Sci USA* 88:10124-10128.
- BROWN KG, BOYLE KE, CHEN CW, GIBB HJ. 1989. A dose-response analysis of skin cancer from inorganic arsenic in drinking water. *Risk Anal* 9:519-528.
- CAMAIN R, TUYNS AJ, SARRAT H, et al. 1972. Cutaneous cancer in Dakar. *J Natl Cancer Inst* 48:33-49.
- CHUANG TY, POPESCU NA, SU WP, CHUTE CG. 1990. Squamous cell carcinoma: A population-based incidence study in Rochester, Minn. *Arch Dermatol* 126:185-188.
- CHUTE CG, CHUANG TY, BERGSTRALH EJ, SU WPD. 1991. The subsequent risk of internal cancer with Bowen's disease. *JAMA* 266:816-819.
- CLEAVER JE, KRAEMER KH. 1995. Xeroderma pigmentosum and Cockayne syndrome. In Scriver CR, Beaudet AL, Sly WS, Valle D (eds): *The Metabolic and Molecular Bases of Inherited Disease*. New York, McGraw-Hill, Inc., pp. 4393-4419.
- COEBERGH JW, NEUMANN HA, VRINTS LW, et al. 1991. Trends in the incidence of nonmelanoma skin cancer in the SE Netherlands 1975-1988: A registry-based study. *Br J Dermatol* 125:353-359.
- CZARNECKI D, ZALCBERG J, MEEHAN C, et al. 1992. Familial occurrence of multiple nonmelanoma skin cancer. *Cancer Genet Cytogenet* 61:1-5.
- CZARNECKI DB, LEWIS A, NICHOLSON I, TAIT B. 1991. Multiple nonmelanoma skin cancer associated with HLA DR7 in southern Australia. *Cancer* 68:439-440.
- DEVESA SS, BLOT WJ, STONE BJ, et al. 1995. Recent cancer trends in the United States. *J Natl Cancer Inst* 87:175-182.
- DOLL R, VESSEY MP, BEASLEY RW, et al. 1972. Mortality of gas-workers: Final report of a prospective study. *Br J Indust Med* 29:394-406.
- EUVRARD S, CHARDONNET Y, POUTEIL-NOBLE C, et al. 1993. Association of skin malignancies with various and multiple carcinogenic and noncarcinogenic human papillomaviruses in renal transplant recipients. *Cancer* 72:2198-2206.
- EVERALL JD, DOWD PM. 1978. Influence of environmental factors excluding ultraviolet radiation on the incidence of skin cancer. *Bull Cancer (Paris)* 65:241-248.
- FARNDON PA, DEL MASTRO RG, EVANS DGR, KILPATRICK MW. 1992. Location of gene for Gorlin syndrome. *Lancet* 339:581-582.
- FEARS TR, SCOTTO J. 1983. Estimating increases in skin cancer morbidity due to increases in ultraviolet radiation exposure. *Cancer Invest* 1:119-126.
- FEARS TR, SCOTTO J, SCHNEIDERMAN MA. 1977. Mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States. *Am J Epidemiol* 105:420-427.
- FLEMING MD, HUNT JL, PURDUE GF, SANDSTAD J. 1990. Marjolin's ulcer: A review and reevaluation of a difficult problem. *J Burn Care Rehabil* 11:460-469.
- GALLAGHER RP, HILL GB, BAJDIK CD, et al. 1995a. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer: I. Basal cell carcinoma. *Arch Dermatol* 131:157-163.
- GALLAGHER RP, HILL GB, BAJDIK CD, et al. 1995b. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer: II. Squamous cell carcinoma. *Arch Dermatol* 131:164-169.
- GALLAGHER RP, MA B, MCLEAN DI, et al. 1990. Trends in basal cell carcinoma, squamous cell carcinoma, and melanoma of the skin from 1973 through 1987. *J Am Acad Dermatol* 23:413-421.
- GILES GG, MARKS R, FOLEY P. 1988. Incidence of non-melanocytic skin cancer treated in Australia. *BMJ* 296:13-17.
- GLASS AG, HOOVER RN. 1989. The emerging epidemic of melanoma and squamous cell skin cancer. *JAMA* 262:2097-2100.
- GOLDBERG GI, EISEN AZ, BAUER EA. 1988. Tissue stress and tumor promotion: Possible relevance to epidermolysis bullosa. *Arch Dermatol* 124:737-741.
- GORLIN RJ. 1987. Nevoid basal-cell carcinoma syndrome. *Medicine* 66:98-113.
- GOUDIE DR, YUILLE MAR, LEVERSHA MA, et al. 1993. Multiple self-healing squamous epitheliomata (ESS1) mapped to chromosome 9q22-q31 in families with common ancestry. *Nature Genetics* 3:165-169.
- GREEN AC, BATTISTUTTA D. 1990. Incidence and determinants of skin cancer in a high-risk Australian population. *Int J Cancer* 46:356-361.
- GREENBERG ER, BARON JA, STUKEL TA, et al. 1990. A clinical trial of beta-carotene to prevent basal-cell and squamous-cell cancers of the skin. *New Engl J Med* 323:789-795.
- GREENE MH, FRAUMENI JF JR. 1979. The hereditary variant of malignant melanoma. In Clark WH, Goldman LI, Mastrangelo MJ (eds): *Human Malignant Melanoma*. New York, Grune and Stratton, pp. 139-166.
- HALDER RM, BANG KM. 1988. Skin cancer in blacks in the United States. *Dermatol Clin* 16:397-405.
- HALDER RM, BRIDGEMAN-SHAH S. 1995. Skin cancer in African Americans. *Cancer* 75:667-673.
- HALL J, ENGLISH DR, ARTUSO M, et al. 1994. DNA repair capacity as a risk factor for non-melanocytic skin cancer: A molecular epidemiological study. *Int J Cancer* 58:179-184.
- HARTEVELT MM, BAVINCK JN, KOOTTE AM, et al. 1990. Incidence of skin cancer after renal transplantation in the Netherlands. *Transplantation* 49:506-509.
- HENDRICKS NV, BERRY CM, LIONE JG, et al. 1959. Cancer of the scrotum in wax pressmen. *AMA Arch Ind Hyg* 19:524-529.
- HOFFMAN JS. 1987. Assessing the Risks of Trace Gases that Can Modify the Stratosphere. Vol 1: Executive Summary, Office of Air and Radiation. Washington, D.C., U.S. Environmental Protection Agency, pp. ES 1-64.
- HOLLOWAY L. 1992. Atmospheric sun protection factor on clear days: Its observed dependence on solar zenith angle and its relevance

- to the shadow rule for sun protection. *Photochem Photobiol* 56:229-234.
- HOOPER R, FRAUMENI JF JR. 1973. Risk of cancer in renal transplant recipients. *Lancet* 2:55-57.
- HSUEH YM, CHENG GS, WU MM, et al. 1995. Multiple risk factors associated with arsenic-induced skin cancer: Effects of chronic liver disease and malnutritional status. *Br J Cancer* 71:109-114.
- HUNTER DJ, COLDITZ GA, STAMPFER MJ, et al. 1992. Diet and risk of basal cell carcinoma of the skin in a prospective cohort of women. *Ann Epidemiol* 2:231-239.
- INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. 1980. IARC: Monographs on the Evaluation of Carcinogenic Risk of Chemical to Man, Vol. 23, Some Metals and Metallic Compounds. Lyon, pp 39-141.
- INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. 1992. Solar and Ultraviolet Radiation. IARC Monogr Eval Carcinog Risks Hum 55. Lyon, International Agency for Research on Cancer.
- KALDOR J, SHUGG D, YOUNG B, et al. 1993. Non-melanoma skin cancer: Ten years of cancer-registry-based surveillance. *Int J Cancer* 53:886-891.
- KAPLAN RP. 1987. Cancer complicating chronic ulcerative and scarifying mucocutaneous disorders. *Adv Dermatol* 2:19-46.
- KARAGAS MR, STUKEI TA, GREENBERG ER, et al. 1992. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. *JAMA* 267:3305-3310.
- KELFKENS G, DE GRUIJL FR, VAN DER LEUN JC. 1990. Ozone depletion and increase in annual ultraviolet radiation dose. *Photochem Photobiol* 52:819-823.
- KIPLING MD, WALDRON HA. 1976. Polycyclic aromatic hydrocarbons in mineral oil, tar, and pitch, excluding petroleum pitch. *Prev Med* 5:262-278.
- KINLEN L. 1982. Immunosuppressive therapy and cancer. *Cancer Surv* 1:565-583.
- KOPF AW, SALOPEK TG, SLADE J, et al. 1995. Techniques of cutaneous examination for the detection of skin cancer. *Cancer* 75:684-690.
- KRAEMER KH, DIGIOVANNA JJ, MOSHELI AN, et al. 1988. Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. *N Engl J Med* 318:1633-1637.
- KRAEMER KH, LEE MM, ANDREWS AD, LAMBERT WC. 1994. The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer: The xeroderma pigmentosum paradigm. *Arch Dermatol* 130:1018-1021.
- KRAEMER KH, LEE MM, SCOTTO J. 1987. Xeroderma pigmentosum: Cutaneous, ocular, and neurological abnormalities in 830 published cases. *Arch Dermatol* 123:241-250.
- KRICKER A, ARMSTRONG BK, ENGLISH DR. 1994. Sun exposure and non-melanocytic skin cancer. *Cancer Causes Control* 5:367-392.
- KRICKER A, ARMSTRONG BK, ENGLISH DR, HEENAN PJ. 1991. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer: A case-control study. *Int J Cancer* 48:650-662.
- KRIPKE ML. 1994. Ultraviolet radiation and immunology: Something new under the sun. *Cancer Res* 54:6102-6105.
- KUNE GA, BANNERMAN S, FIELD B, et al. 1992. Diet, alcohol, smoking, serum β -carotene, and vitamin A in male nonmelanocytic skin cancer patients and controls. *Nutr Cancer* 18:237-244.
- LAYCOCK HT. 1948. The "kang cancer" of North-West China. *BMJ* 1:982.
- LEE JA, YONGCHAIYUDHA S. 1971. Incidence of and mortality from malignant melanoma by anatomical site. *J Natl Cancer Inst* 47:253-263.
- LINDQVIST C. 1979. Risk factors in lip cancer: A questionnaire survey. *Am J Epidemiol* 109:521-530.
- LOBO DV, CHU P, GREKIN RC, BERGER TG. 1992. Nonmelanoma skin cancers and infection with the human immunodeficiency virus. *Arch Dermatol* 128:623-627.
- MARKS R. 1995. An overview of skin cancers: Incidence and causation. *Cancer* 75:607-612.
- MARKS R, JOLLEY D, LECTSAS S, FOLEY P. 1990. The role of childhood exposure to sunlight in the development of solar keratoses and non-melanocytic skin cancer. *Med J Aust* 152:62-66.
- MARKS R, STAPLES M, GILES GG. 1993. Trends in non-melanocytic skin cancer treated in Australia: The second national survey. *Int J Cancer* 53:585-590.
- MILLER DL, WEINSTOCK MA. 1994. Nonmelanoma skin cancer in the United States: Incidence. *J Am Acad Dermatol* 30:774-778.
- MULAY DM. 1963. Skin cancer in India. *Natl Cancer Inst Monogr* 10:215-223.
- NATIONAL INSTITUTES OF HEALTH. 1991. Summary of the Consensus Development Conference on Sunlight, Ultraviolet Radiation, and the Skin. *J Am Acad Dermatol* 24:608-612.
- NATIONAL RESEARCH COUNCIL. 1990. Committee on the Biological Effects of Ionizing Radiations (BEIR V): Health Effects of Exposure to Low Levels of Ionizing Radiation. Washington, D.C., National Academy Press, pp. 325-327.
- PARTENEN T, BOFFETTA P. 1994. Cancer risk in asphalt workers and roofers: Review and meta-analysis of epidemiologic studies. *Am J Ind Med* 26:721-740.
- PARTANEN T, PUKKALA E, VAINIO H, et al. 1994. Increased incidence of lung and skin cancer in Finnish silicotic patients. *J Occup Med* 36:616-622.
- PRESTON DS, STERN RS. 1992. Nonmelanoma cancers of the skin. *N Engl J Med* 327:1649-1662.
- PUKKALA E, NOKSO-KOIVISTO P, ROPONEN P. 1992. Changing cancer risk pattern among Finnish hairdressers. *Int Arch Occup Environ Health* 64:39-42.
- RHODES AR. 1995. Public education and cancer of the skin: What do people need to know about melanoma and nonmelanoma skin cancer? *Cancer* 75:613-636.
- RIES LAG, HANKEY BF, EDWARDS BK. 1990. Cancer statistics review 1973-87. NIH Publication 90-2789. Washington, D.C., U.S. Department of Health and Human Services.
- SCOTTO J. 1986. Nonmelanoma skin cancer—UVB effects. In Titus JG (ed): Effects of Changes in Stratospheric Ozone and Global Climate, Vol. 2: Stratospheric Ozone. Washington, D.C., U.S. Environmental Protection Agency, pp. 33-61.
- SCOTTO J, COTTON G, URBACH F, et al. 1988. Biologically effective ultraviolet radiation: Surface measurements in the United States, 1974 to 1985. *Science* 239:762-764.
- SCOTTO J, FEARS TR. 1987. The association of solar ultraviolet and skin melanoma incidence among Caucasians in the United States. *Cancer Invest* 5:275-283.
- SCOTTO J, FEARS TR, FRAUMENI JF JR. 1983. Incidence of Non-melanoma Skin Cancer in the United States. DHEW Publ. No. (NIH) 83-2433. Washington, D.C., U.S. Government Printing Office.
- SCOTTO J, FEARS TR, GORI GB. 1976a. Measurements of Ultraviolet Radiation in the United States and Comparisons with Skin Cancer Data. DHEW (NIH) 76-1029. Bethesda, National Cancer Institute.
- SCOTTO J, FEARS TR, GORI GB. 1976b. Ultraviolet exposure patterns. *Environ Res* 12:228-237.
- SCOTTO J, NAM JM. 1980. Skin melanoma and seasonal patterns. *Am J Epidemiol* 111:309-314.
- SCOTTO J, PITCHER H, LEE JAH. 1991. Indications of future decreasing trends in skin-melanoma mortality among whites in the United States. *Int J Cancer* 49:490-497.
- SHORE RE. 1990. Overview of radiation-induced skin cancer in humans. *Int J Radiat Biol* 57:809-827.
- SIRINAVIN C, TROWBRIDGE AA. 1975. Dyskeratosis congenita: Clinical features and genetic aspects. Report of a family and review of the literature. *J Med Genet* 12:339-354.
- SOBER AJ, BURSTEIN JM. 1995. Precursors to skin cancer. *Cancer* 75:645-650.

- SPRINGATE JE. 1986. The nevoid basal cell carcinoma syndrome. *J Pediatr Surg* 21:908-910.
- STERN RS, LAIRD N. 1994. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 73:2759-64.
- STRICKLAND PT, VITASA BC, WEST SK, et al. 1989. Quantitative carcinogenesis in man: Solar ultraviolet B dose dependence of skin cancer in Maryland watermen. *J Natl Cancer Inst* 81:1910-1913.
- STRONG LC. 1977. Theories of pathogenesis: Mutation and cancer. *In* Mulvihill JJ, Miller RW, Fraumeni JF Jr (eds): *Genetics of Human Cancer*. New York, Raven Press, pp. 401-415.
- SVINDLAND HB. 1980. Kangri cancer in the brick industry. *Contact Dermatitis* 6:24-26.
- TANGREA JA, EDWARDS BK, TAYLOR PR, et al. 1992. Long-term therapy with low-dose isotretinoin for prevention of basal cell carcinoma: A multicenter clinical trial. *J Natl Cancer Inst* 84:328-332.
- TYRING SK. 1993. Human papillomaviruses in skin cancer. *Cancer Bull* 45:212-219.
- UNITED NATIONS ENVIRONMENT PROGRAMME ENVIRONMENTAL EFFECTS PANEL. 1990. Environmental effects of ozone depletion. Nairobi, United Nations Environment Programme.
- UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS OF ATOMIC RADIATION. 1994. Sources and Effects of Ionizing Radiation. (UNSCEAR 1994 Report to the General Assembly. New York, United Nations, p. 30.
- URBACH F. 1971. Geographic distribution of skin cancer. *J Surg Oncol* 3:219-234.
- WALLBERG P, SKOG E. 1991. The incidence of basal cell carcinoma in an area of Stockholm County during the period 1971-1980. *Acta Derm Venereol (Stockh)* 71:134-137.
- WANG HH, MACMAHON B. 1979. Mortality of pesticide applicators. *J Occup Med* 21:741-744.
- WEI Q, MATANOSKI GM, FARMER ER, et al. 1993. DNA repair and aging in basal cell carcinoma: A molecular epidemiology study. *Proc Natl Acad Sci USA* 90:1614-1618.
- WEI Q, MATANOSKI GM, FARMER ER, et al. 1994a. DNA repair related to multiple skin cancers and drug use. *Cancer Res* 54:437-440.
- WEI Q, MATANOSKI GM, FARMER ER, et al. 1994b. Vitamin supplementation and reduced risk of basal cell carcinoma. *J Clin Epidemiol* 47:829-836.
- WEI Q, MATANOSKI GM, FARMER ER, et al. 1994c. DNA repair and susceptibility to basal cell carcinoma: A case-control study. *Am J Epidemiol* 140:598-607.
- WEINSTOCK MA. 1993. Nonmelanoma skin cancer mortality in the United States, 1969 through 1988. *Arch Dermatol* 129:1286-1290.
- WEINSTOCK MA. 1994a. Epidemiology of nonmelanoma skin cancer: Clinical issues, definitions, and classification. *J Invest Dermatol* 102:4S-5S.
- WEINSTOCK MA. 1994b. Epidemiologic investigation of nonmelanoma skin cancer mortality: The Rhode Island follow-back study. *J Invest Dermatol* 102:6S-9S.
- WHITAKER CJ, LEE WR, DOWNES JE. 1979. Squamous cell skin cancer in the North-west of England, 1967-69, and its relation to occupation. *Br J Ind Med* 36:43-51.
- WITKOP CJ, QUEVADO WC, FITZPATRICK TB, KING RA. 1989. Albinism. *In* Scriver CR, Beaudet AL, Sly WS, Valle D (eds): *The Metabolic Basis of Inherited Disease*, 6th ed. New York, McGraw-Hill pp. 2905-2947.
- YIANNIAS JA, GOLDBERG LH, CARTER-CAMPBELL S, et al. 1988. The ratio of basal cell carcinoma to squamous cell carcinoma in Houston, Texas. *J Dermatol Surg* 14:886-889.
- YUSPA SH. 1994. The pathogenesis of squamous cell cancer: Lessons learned from studies of skin carcinogenesis. *Cancer Res* 54:1178-1189.
- YUSPA SH, DLUGOSZ AA. 1991. Cutaneous carcinogenesis: natural and experimental. *In* Goldsmith L (ed): *Physiology, Biochemistry and Molecular Biology of the Skin*. New York, Oxford University Press, pp. 1365-1402.
- ZIEGLER A, JONASON AS, LEFFELL DJ, et al. 1994. Sunburn and p53 in the onset of skin cancer. *Nature* 372:773-776.