Keratinocyte Carcinoma

ABSTRACT  Keratinocyte carcinoma is by far the most common cancer in the United States. Basal cell carcinomas and squamous cell carcinomas account for approximately 80% and 20% of cases of KC, respectively. The term nonmelanoma skin cancer is commonly used to refer to squamous cell carcinomas and basal cell carcinomas; however, other types of nonmelanoma skin cancer, such as adnexal tumors and sarcomas, are less common and differ in their cell type, behavior, and epidemiologic features from KC. Primary care clinicians are well positioned to diagnose KC and to educate patients about preventive measures such as sun protection and self-examination. Here we review epidemiologic data and strategies for prevention, diagnosis, and clinical management of KC. (CA Cancer J Clin 2003;53:292–302.) © American Cancer Society, 2003.

INTRODUCTION

Descriptive Epidemiology

Approximately 1 million cases of keratinocyte carcinoma (KC) occur annually in the United States, a figure that approaches the total incidence of all noncutaneous cancers combined. In addition, an estimated 1,000 to 2,000 deaths result each year from KC in the United States, with population-based case-fatality rates of approximately 0.05% and 0.7% for basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), respectively. In contrast, melanoma occurs less frequently, but more commonly causes death, with 54,200 new cases and 7,600 deaths estimated for 2003. Nevertheless, melanoma accounts for a minority of skin cancer deaths among white persons older than 85 years and among black persons. A study of the records of the US National Center for Health Statistics indicated that the nonmelanoma skin cancer mortality rate decreased by 20% to 30% from 1969 to 1988. Morbidity from KC is poorly quantified but represents a major public health burden. The incidence of KC appears to be increasing, as for melanoma, although the magnitude of the increase is difficult to determine because conventional cancer registries, such as the Surveillance, Epidemiology, and End Results (SEER) Program exclude KC. One analysis of a large prepaid health insurance program in the northwestern United States indicated that from the 1960s to the 1980s, the age-adjusted incidence of SCC increased 2.6 times in men and 3.1 times in women. A study of KC incidence in New Hampshire found that between 1979–1980 and 1993–1994, the age-adjusted incidence rates of SCC increased by 235% in men and 350% in women, whereas incidence rates of BCC increased by more than 80% in both men and women. However, a review of data in the Southeastern Arizona Skin Cancer Registry between 1985 and 1996 indicated that age-adjusted incidence rates of SCC and BCC were not increasing as rapidly as predicted elsewhere. Increases in the incidence of KC have also been reported in Australia and Europe. Based on data from national surveys in Australia, the age-adjusted rate of treated KC in that country increased by nearly 35% from 1985 to 1995; 20% for BCC and 93% for SCC. The cause of the increasing incidence in KC (and melanoma) is largely speculative, but changes in sun exposure habits are believed to be a factor. Some authors have also hypothesized that stratospheric ozone depletion may play a role.

RISK FACTORS

Many host and environmental factors contribute to the risk for developing KC. Skin color is a major risk factor for KC; the incidence rates in nonwhite populations are less than 2% of the rates among white populations. Persons
with a light complexion, who burn easily, and
tan poorly are at greatest risk. Increasing age,
male gender, and precancerous skin lesions are
other host risk factors. In addition, SCC may
arise from chronic ulcers or scars, particularly
scars resulting from thermal burns.

Ultraviolet light exposure is the most impor-
tant environmental factor related to the devel-
opment of KC. The association between
sunlight exposure and skin cancer has long
been known: Paul Gerson Unna first described
in 1894 precancerous histopathologic changes
of the skin occurring in sailors. Cumulative
lifetime ultraviolet light exposure and recent
ultraviolet exposure are risk factors for SCC,
whereas intermittent, intense exposure may be
more important in melanoma, although this is
not definitively proven. The data for the
importance of different exposure patterns for
BCC are less certain, although ultraviolet light
is a proven cause of all three of these common
skin cancers. The most highly carcinogenic ul-
traviolet wavelengths for inducing SCC in an-
imals have long been recognized to be 290 to
320 nm (UVB). More recent animal studies
have shown that the longer wavelengths, 320
to 400 nm (UVA), can induce SCC in mice,
although less effectively. The shortest ultra-
violet wavelengths, 200 to 290 nm (UVC), are
absorbed by the ozone layer and do not reach
the earth’s surface. A latitudinal gradient is ob-
served in the incidence of KC, which is more
marked for SCC than BCC.

Immunosuppressed persons are at increased
risk for the development of KC, and the SCC:
BCC ratio is higher in these patients. One
study of 764 renal transplant patients in the
Netherlands found that the overall incidence of
SCC was 250 times greater than that of the
general Dutch population, and the BCC rate
was 10 times greater. Other environmental
risk factors for KC include exposure to ionizing
radiation, phototherapy with psoralens, ex-
posure to polycyclic hydrocarbons, and arsenic
ingestion. An association between smoking and
SCC of the skin has been reported in case-
control and prospective studies. There
does not seem to be a relation between BCC
and cigarette smoking. Smoking and ultraviolet
radiation are risk factors for SCC of the lip.

Several inherited syndromes are associated
with BCC and SCC, including xeroderma pig-
mentosum, nevoid BCC syndrome, epider-
modysplasia verruciformis, and albinism.
Xeroderma pigmentosum is an autosomal re-
cessive disease characterized by extreme sen-
sitivity to sunlight and the development of
widespread skin cancers because of defective
DNA repair after ultraviolet radiation. Basal
cell nevus syndrome is a rare autosomal dom-
inant disorder with many abnormalities,
including the development of multiple BCCs
early in life, jaw keratocysts, and skeletal de-
fects. Recently, patients with this syndrome
were found to have a mutation in the patched
gene of chromosome 9, which plays a role in
the regulation of cellular proliferation and dif-
fentiation. Mutations in this gene have
been reported to occur in approximately one-
third of sporadic BCCs studied, and sporadic
BCCs may also have mutations of related genes
(including smoothened) with products that inter-
act in the same signaling pathway. Patients
with epidermodysplasia verruciformis have a
defect in cell-mediated immunity, with suscep-
tibility to human papilloma virus and resultant
widespread verrucae of the skin. These persons
are at high risk for developing SCCs that are
associated with strains of the human papilloma
virus (particularly types 5 and 8) that are not
commonly found in immunocompetent per-
sons. Albinism is an uncommon group of
 disorders in which there is a decrease or ab-
sence of pigmentation that may affect the skin,
hair, and eyes. Patients with cutaneous forms
of albinism have an increased risk for skin
cancer.

**CLINICAL APPROACH TO SKIN CANCER**

Table 1 lists the common clinical features of
KC. BCC (Figures 1–7) is a slow-growing
tumor that most commonly affects the head
and neck. It is nearly always asymptomatic.
BCC may be categorized into four major clin-
ical subtypes: nodular, superficial, pigmented,
and morpheaform (or sclerotic). A nodular
BCC typically appears as a “pearly” translucent
dome-shaped papule or nodule that may have
visible telangiectases and may develop a central ulceration as it grows. The superficial subtype more frequently involves the trunk or extremities, and it presents as an erythematous papule or plaque that often has an irregular, raised, translucent border and may have surface scale and pinpoint erosions. The pigmented type usually has the characteristic pearly appearance of a BCC but also contains areas of pigment, so it may be misdiagnosed as a melanoma. Finally, the morpheaform type appears as a shiny, atrophic plaque that may be confused clinically with a scar. Histologically, this type often extends beyond the visible clinical margin; a study of 51 primary morpheaform BCCs reported an average subclinical extension of 7.2 mm, compared with 2.1 mm for 50 nodular BCCs.31 Metastases with all types of BCC are rare (reported range, 0.0028% to 0.55%) and generally occur only in advanced, deeply invasive lesions.32

SCC (Figures 8–12) most commonly appear on chronically sun-exposed skin, including the face, ears, and extensor hands, arms, or legs.28,29 SCC may grow more rapidly than BCC and may have associated pain or tenderness, although they are generally asymptomatic. The tumor may appear as a keratotic papule, erythematous plaque, or as an erythematous nodule. The lesion may become crusted or ulcerated with a purulent base. Physical examination of regional lymph nodes is commonly performed in patients with invasive SCC. A biopsy should be considered for patients with enlarged nodes.

The frequency of metastases for cutaneous SCC has been variously reported and depends on several prognostic factors. Marks33 estimates that the risk for metastasis is 10% to 15% in tumors of the lip and ear and 2% in tumors from other sun-exposed sites. A study of confirmed KC deaths occurring in Rhode Island from 1979 through 1987 found that 47% of fatal primary SCCs were located on the ear, although only 10% of incident SCCs were in this location.3 Other factors indicating a greater risk for metastasis (and local recurrence) include association with a scar, sinus tract, or chronic ulcer; size greater than 2 cm; depth greater than 4 mm; poor differentiation or perineural invasion histologically; and recurrent disease.34 SCC of the anogenital region also has a higher metastatic rate. Metastasis is initially to the regional lymph nodes in approximately 85% of cases and to distant viscera in 15% of cases.35

SCC in situ (Bowen disease) and actinic keratoses are considered precursor lesions to invasive SCC. SCC in situ appears as a well-demarcated erythematous, scaly plaque that is confined to the epidermis histologically. Actinic keratoses are rough, scaly erythematous papules or plaques of sun-exposed skin. It has been estimated that the risk for malignant transformation of an actinic keratosis to SCC within 1 year is 0.1%.36 Nonetheless, because multiple actinic keratoses frequently develop and these lesions are a marker of sun damage, persons with these lesions are at substantial risk for SCC.

Clinically, the differential diagnosis of KC includes benign neoplasms such as nevi or seborrheic keratoses. SCC and superficial BCC may be confused with scaly dermatologic conditions such as psoriasis or eczematous dermatitis. Hypertrophic actinic keratoses may be difficult to distinguish from early SCC without

| TABLE 1 |
|---|
| **Common Clinical Features of Keratinocyte Carcinoma** |
| **Key Warning Signs** |
| New growth |
| A lesion that is changing in size or shape |
| A sore that does not heal |
| **Nonspecific Features That May Be Seen in Keratinocyte Carcinoma** |
| Nodular growth |
| Irregular border |
| Elevation |
| Erosion, ulceration, crust |
| Bleeding |
| Erythema with sharp borders |
| **Features That May Be Seen in Basal Cell Carcinoma** |
| Translucent (pearly or waxy) appearance |
| Telangiectases (fine, tortuous vessels visible near the surface) |
| Raised (“rolled”) border |
| Pigment without a netlike pattern |
| Scarlike appearance |
| Erythema with pinpoint erosions |
| **Features That May Be Seen in Squamous Cell Carcinoma** |
| Adherent scale or crust |
| Cutaneous horn |
FIGURE 1 This BCC is slightly elevated and has an opalescent appearance and erythema.

FIGURE 2 This nodular BCC is well circumscribed with a rolled, pearly border.

FIGURE 3 This pigmented BCC is lobulated with "floating" pigment. This lesion could be misdiagnosed as a melanoma.

FIGURE 4 This nodular BCC of the nose has central ulceration.
FIGURE 5  This BCC is raised with a waxy and erythematous appearance and fine telangiectases.

FIGURE 6  This BCC is a well-demarcated erythematous papule.

FIGURE 7  This superficial BCC is erythematous with scale and a translucent border.

FIGURE 8  This SCC in situ (Bowen disease) is a well-defined, erythematous plaque with a keratotic surface. Adjacent seborrheic keratoses are seen; these common, benign lesions appear as well-demarcated, “stuck on” brown papules and plaques.
FIGURE 9  This SCC of the ear is an erythematous plaque with keratotic and crusted areas.

FIGURE 10  This SCC in situ (Bowen disease) is a well-defined, erythematous patch with scale, crust, and an irregular border.

FIGURE 11  This SCC of the temple has a hyperkeratotic center.

FIGURE 12  This SCC of the leg is a large, ulcerated nodule with an indurated border.
histologic evaluation. Other conditions in the differential diagnosis include pyogenic granuloma, verrucae, malignant melanoma, lupus erythematosus, and Merkel cell carcinoma.30

---

**BIOPSY AND PATHOLOGY FINDINGS**

The diagnosis of BCC or SCC can be confirmed by a punch or shave biopsy.37,38 These are relatively simple procedures that have a low risk for infection or bleeding. A shave biopsy often provides a sufficient tissue sample for the diagnosis of BCC, actinic keratosis, or SCC in situ. In performing this procedure, the biopsy area is first cleansed with alcohol or another antiseptic, and 1% lidocaine is injected locally using a 30 gauge needle. A sterile scalpel or razor blade is then used to cut along the base of the lesion with adequate depth for accurate pathologic diagnosis. The lesion may be stabilized during the biopsy with a needle tip or forceps. Sutures are not necessary, and hemostasis is achieved with electrocautery or the use of a chemical agent such as an aluminum chloride or ferric subsulfate solution applied with a cotton swab.

A punch biopsy provides a full-thickness skin specimen, which may aid in the histopathologic interpretation by revealing tumor depth and tissue architecture. A punch biopsy is indicated if invasive SCC or melanoma are included in the differential diagnosis. After the biopsy area is cleansed and infiltrated with local anesthesia, a cylindrical punch tool (typically 3 or 4 mm in diameter) is compressed into the lesion. A gentle rotating motion is used, and the surrounding skin is stretched, perpendicular to skin tension lines, with the free hand. After removing the punch tool, the specimen is grasped with a forceps and cut at the base with scissors. A 3 mm or larger punch generally requires closure with one or more nonabsorbable sutures that are left in place for 5 to 7 days on the face and 7 to 14 days elsewhere.38 Punch biopsies should be performed with care in areas with little soft tissue or overlying superficial arteries or nerves.38

Biopsy specimens are placed in formalin and sent for pathologic evaluation. A biopsy positive for BCC reveals nests of atypical basaloid cells invading the dermis that are characterized by peripheral palisading and mucin deposition in the surrounding stroma.29 Morpheaform BCC has a dense fibrous stroma and narrow cords of infiltrating tumor cells. Histopathologic findings in SCC are a proliferation of squamous cells into the dermis with atypia that includes variation in the size and shape of cells, enlargement and hyperchromasia of the nuclei, and atypical mitotic figures.39 Other features that may be observed histologically are “horn pearls” of keratin and a marked inflammatory reaction in the dermis. SCC may be cytologically graded as well differentiated, moderately differentiated, or poorly differentiated, or a numeric grade may be given.40

---

**PREVENTION AND EARLY DIAGNOSIS**

Ultraviolet avoidance and protection constitute the mainstay of primary prevention of KC.41 Recommendations include avoiding strong sunlight exposure, particularly during the mid-day hours. Protective clothing includes a wide-brimmed hat, a tightly woven long-sleeved shirt and pants, and sunglasses. Vigilant sun protection is most important for those at greatest risk for KC, such as light-skinned and immunosuppressed persons. Although patients should be encouraged to avoid intense exposure and to use protection, they should also understand that such recommendations are not meant to discourage physical activity. In addition, because ultraviolet light plays a role in vitamin D synthesis in the skin, dietary supplementation should be considered for those at risk for vitamin D insufficiency.42

The efficacy of sunscreens in preventing some skin cancers (particularly melanoma) is a matter of controversy, although sunscreen use is considered a helpful protective measure.43 Application of a sunscreen with a sun protection factor (SPF) of 30 or higher is recommended. Two randomized trials have provided evidence that sunscreens can protect against actinic keratosis formation.44,45 One study followed 588 Australians who were 40 years or older and who applied either sunscreen (SPF
17) or base cream without sunscreen during a 6-month period. The mean number of actinic keratoses increased by 1.0 in the control group and decreased by 0.6 in the sunscreen group. A recent randomized trial also suggests that sunscreen may protect against SCC formation. Persons were assigned to daily sunscreen or no sunscreen and followed more than 4.5 years; no effect on the incidence of BCC was observed, but the incidence of SCC was significantly less in the sunscreen group.

The effectiveness of sunscreens may be compromised by their improper use. Sunscreens should be applied liberally 15 to 30 minutes before sun exposure and then reapplied regularly, particularly after sweating or bathing. It has been argued that sunscreen should be reapplied 15 to 30 minutes after exposure begins because it is frequently applied nonuniformly and in insufficient amounts to achieve the rated SPF. Previously, sunscreens with an SPF of 15 were considered acceptable; however, because consumers typically apply sunscreens thinly, and because sunscreens with an SPF of 30 or higher are now widely available, their use is recommended. It is important that sunscreen be considered only part of an overall sun protection strategy, because users are still susceptible to the deleterious effects of excessive sunlight exposure.

Counseling of patients should address favorable popular attitudes toward suntanning. A 1996 telephone survey of 1,000 adults by the American Academy of Dermatology showed that 56% of respondents believed that persons looked more healthy when they had a suntan, and 25% reported that they “intentionally worked on a tan.” The indoor tanning industry in the United States has an estimated one million patrons a day, the majority of whom are women aged 16 to 30 years. A recent survey indicated that 10% of US youth, ages 11 to 18 years, had used indoor tanning lamps in the previous year, whereas fewer than one third used effective sun protection. The avoidance of deliberate tanning should be emphasized because of the role UVA plays in photoaging of the skin and its potential carcinogenicity. A case-control study suggested that tanning devices may contribute to the incidence of KC. Although investigations also have suggested a positive association between tanning lamp use and melanoma, a review of the epidemiologic literature indicated that published data are as yet insufficient to conclude that there is a proven causal relation.

Regular self-examination is an important secondary prevention method for the early detection of skin cancer. Patients should be made aware of warning signs and symptoms for cancerous skin lesions: change in size, shape, or color; irregular margins; crusting, ulceration, or bleeding; sores that do not heal; and new growths. Self-examination is best performed in a methodical fashion for the entire skin surface using a full-length mirror and a handheld mirror. A family member can assist the patient in examining difficult areas, such as the scalp, back, and buttocks.

The value of early detection has not been quantified, and recommendations vary regarding routine full skin examination by a clinician. The American Academy of Dermatology and the Skin Cancer Foundation recommend an annual full skin examination for all patients; the American Cancer Society recommends full skin examination every 3 years for all persons 20 to 40 years old and annually for all persons older than 40 years; the US Preventive Services Task Force and American College of Preventive Medicine do not recommend routine screening except in persons at high risk. Public health efforts are aimed at both primary and secondary prevention. These include efforts by national organizations such as the American Academy of Dermatology, the American Cancer Society, and the Skin Cancer Foundation to educate the public about the risk of excessive exposure to sunlight and to provide guidelines that can be followed. Australia, which has the highest incidence of melanoma and KC in the world, has had widespread public health campaigns for two decades that have led to changes in the public’s knowledge and behavior regarding sun protection. There is evidence that incidence rates of BCC and melanoma in younger Australian cohorts are leveling off or decreasing, and it is possible that this is related to behavioral changes. However, these trends must be inter-
interpreted with caution because they may also reflect the changing racial composition of Australia. Recently, the American Cancer Society adopted the Slip! Slop! Slap!® slogan used successfully in Australia, which reminds the public to slip on a shirt, slop on sunscreen, and slap on a hat. Other prevention efforts have included school-based education projects and interventions at beaches and swimming pools. Public health programs have also combined screenings with patient education about skin cancer and sun protection. The American Academy of Dermatology has sponsored free skin cancer education and skin cancer examinations in the United States annually since 1985.

TREATMENT

Several treatment methods are available to cure KC. Surgical excision is commonly used and has the advantage of allowing histologic examination for tumor-free margins. Typically, an elliptical excision around the tumor is made with clinical margins of 3 to 5 mm for BCC and 4 to 6 mm for SCC. If residual tumor is observed histologically, repeated excision is usually indicated because of the high rate of recurrence. Reported cure rates for surgical excision of primary KC are frequently 90% to 95%. A specialized type of surgery, called Mohs micrographic surgery, uses examination of surgical margins by frozen section. This allows for the removal of the residual tumor in stages and is associated with a cure rate for primary BCC and well-differentiated SCC that is better than 97%. Referral for Mohs surgery should be considered for patients who have recurrent KC, high-risk SCC, morpheaform BCC, tumors larger than 2 cm, or tumors located in difficult areas such as the eyelid, nose, and ears.

Electrodesiccation and curettage is another treatment method that is particularly useful for small, well-defined primary BCCs and SCCs in situ of the neck, trunk, or extremities. The tumor is scraped off with a curette and the base is electrodesiccated along with a 2 mm rim of surrounding tissue. This is repeated for a total of two to three cycles. This technique does not provide histologic information about the margins, so it should not be used for high-risk lesions. A recent systemic review indicated that recurrence rates after electrodesiccation and curettage of primary BCC ranged from 6% to 19%.

Other therapies include cryotherapy with liquid nitrogen (-196°C), applied by probe or spray, which causes local tissue destruction. Cryotherapy is a standard treatment for actinic keratoses. Radiation is used infrequently today for KC but remains a treatment option, particularly for patients who cannot tolerate surgery. Topical chemotherapy with fluorouracil is most useful for treating widespread actinic keratoses, but this has also been used to treat BCC and SCC in situ. More recently, topical 5% imiquimod, an immune-response modifier, has been reported to show efficacy in treating BCC, especially the superficial subtype. Photodynamic therapy, which is laser treatment after the application of a photosensitizing drug such as 5-aminolevulinic acid, is a treatment for actinic keratoses and an investigational therapy for KC.

After treatment, patients with KC should receive regular follow-up examinations. SCC recurrence or metastasis usually occurs within the first 3 years, so they should be followed particularly carefully during this time. In addition to the possibility of recurrence, patients are at high risk for the development of a second skin cancer. A literature review indicated the mean 3-year cumulative risk for the development of a subsequent SCC after a first one was 18%, whereas the mean 3-year cumulative risk for the development of a subsequent BCC after a first one was 44%. In addition, patients with KC have been reported to have an increased risk for melanoma.

CONCLUSIONS

KC represents a major public health problem that appears to be increasing. Because of its high prevalence, all health care providers should be familiar with the diagnosis and clinical management of KC. Primary prevention
efforts continue to focus on reducing ultraviolet light exposure, particularly in those persons at greatest risk for the development of KC. Early detection of KC can be achieved through patient education about the warning signs of skin cancer, self-examination, and physical examination by a clinician. Such strategies may ultimately decrease the morbidity and mortality rates for KC.

REFERENCES

1. Weinstock MA. Epidemiology of nonmelanoma skin cancer: Clinical issues, definitions, and classification. J Invest Dermatol 1994;102(Suppl):4s–8s.
2. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: Incidence. J Am Acad Dermatol 1994;30:774–778.
3. Weinstock MA, Bogaars HA, Ashley M, et al. Nonmelanoma skin cancer mortality: A population-based study. Arch Dermatol 1991;127:1194–1197.
4. Jemal A, Murray T, Samuels A. CA Cancer J Clin 2003;53:5–26.
5. Weinstock MA. Death from skin cancer among the elderly: Epidemiological patterns. Arch Dermatol 1997;133:1207–1209.
6. Weinstock MA. Nonmelanoma skin cancer mortality in the United States, 1969 through 1988. Arch Dermatol 1993;129:1286–1290.
7. Glass AG, Hoover RN. The emerging epidemic of melanoma and squamous cell skin cancer. JAMA 1989;262:2097–2100.
8. Karagas MR, Greenberg ER, Spencer SK, et al. for the New Hampshire Skin Cancer Study Group. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. Int J Cancer 1999;81:555–559.
9. Harris RB, Griffith K, Moon TE. Trends in the incidence of nonmelanoma skin cancers in southeastern Arizona, 1985–1996. J Am Acad Dermatol 2001;45:528–536.
10. Strom SS, Yamamura Y. Epidemiology of nonmelanoma skin cancer. Clin Plast Surg 1997;24:627–636.
11. Staples M, Marks R, Giles G. Trends in the incidence of non-melanocytic skin cancer (NMSC) treated in Australia 1985–1995: Are primary prevention programs starting to have an effect? Int J Cancer 1998;78:144–148.
12. Lloyd SA. Stratospheric ozone depletion. Lancet 1993;342:1156–1158.
13. Albert MR, Osterheimer KG. The evolution of current medical and popular attitudes toward ultraviolet light exposure: Part I. J Am Acad Dermatol 2002;47:930–937.
14. Koh HK, Geller AC, Miller DR, et al.: Prevention and early detection strategies for melanoma and skin cancer. Arch Dermatol 1996;132:436–443.
15. Blum HF. Carcinogenesis by ultraviolet light. Princeton: Princeton University Press;1959.
16. de Grujir FR, Sterenberg HJ, Forbes PD, et al. Wavelength dependence of skin cancer induction by ultraviolet irradiation of albino mice. Cancer Res 1993;53:53–60.
17. Marks R. An overview of skin cancers: Incidence and causation. Cancer 1995;75(Suppl):607–612.
18. Harteveld MM, Barvick JNB, Koote AM, et al. Incidence of skin cancer after renal transplantation in the Netherlands. Transplantation 1990;49:506–509.
42. Gesensway D. Vitamin D and sunshine. Ann Intern Med 2000;133:319–320.

43. Weinstock MA. Sunscreens for melanoma prevention. Photodermatol Photoimmunol Photomed 1999;15:209–211.

44. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med 1993;329:1147–1151.

45. Naylor MF, Boyd A, Smith DW, et al. High sun protection factor sunscreens in the suppression of actinic neoplasia. Arch Dermatol 1995;131:170–175.

46. Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: A randomised controlled trial. Lancet 1999;354:723–729.

47. Diffey BL. When should sunscreen be reapplied? J Am Acad Dermatol 2001;45:882–885.

48. Stokes R, Diffey B. How well are sunscreen users protected? Photodermatol Photoimmunol Photomed 1997;13:186–188.

49. Weinstock MA. Updated sunscreen advice: SPF 30 [Letter]. J Am Acad Dermatol 2000;43:154.

50. Robinson JK, Rigel DS, Amonette RA. Trends in sun exposure knowledge, attitudes, and behaviors: 1986 to 1996. J Am Acad Dermatol 1997;33:288–298.

51. Spencer JM, Amonette RA. Indoor tanning: risks, benefits and future trends. J Am Acad Dermatol 1995;33:288–298.

52. Cokkinides VE, Johnston-Davis K, Weinstock M, et al. Sun exposure and sun-protection behaviors and attitudes among U. S. youth 11 to 18 years of age. Prev Med 2001;33:141–151.

53. Cokkinides VE, Weinstock MA, O’Connell MC, et al. Use of indoor tanning sunlamps by U. S. youth, ages 11–18 years, and by their parent or guardian caregivers: Prevalence and correlates. Pediatrics 2002;109:1124–1130.

54. Karagas MR, Stannard VA, Mott LA, et al. Use of tanning devices and risk of basal cell and squamous cell skin cancers. J Natl Cancer Inst 2002;94:224–226.

55. Swerdlow AJ, Weinstock MA. Do tanning lamps cause melanoma? An epidemiologic assessment. J Am Acad Dermatol 1998;38:89–98.

56. Rigel DS, Cartucci JA. Malignant melanoma: Prevention, early detection and treatment in the 21st century. CA Cancer J Clin 2000;50:215–236.

57. Jerant AF, Johnson JT, Sheridan CD, Caffrey TJ. Early detection and treatment of skin cancer. Am Fam Physician 2000;62:357–368, 375–376, 381–382.

58. Can nonmelanoma skin cancer be found early? Accessed February 8, 2003, from American Cancer Society Web site: http://www.cancer.org

59. U. S. Preventive Services Task Force. Screening for skin cancer: recommendations and rationale. Am J Prev Med 2001;20(3S):44–46.

60. Hill D, Boulter J. Sun protection behaviour: Determinants and trends. Cancer Forum 1996;20:204–211.

61. Naylor MF, Boyd A, Smith DW, et al. High sun protection factor sunscreens in the suppression of actinic neoplasia. Arch Dermatol 1995;131:170–175.

62. Geller AC, Zhang Z, Sober AJ, et al. The first 15 years of the American Academy of Dermatology Skin Cancer Screening Programs: 1985–1999. J Am Acad Dermatol 2003;48:34–41.

63. Phelps R, Meehan CJ. Is the incidence of malignant melanoma decreasing in young Australians? J Am Acad Dermatol 2000;42:672–674.

64. Hill D, Boulter J. Sun protection behaviour: Determinants and trends. Cancer Forum 1996;20:204–211.

65. Marks R. Two decades of the public health approach to skin cancer control in Australia. Why, how and where are we now? Australas J Dermatol 1999;40:1–5.

66. Geller AC, Zhang Z, Sober AJ, et al. The first 15 years of the American Academy of Dermatology Skin Cancer Screening Programs: 1985–1999. J Am Acad Dermatol 2003;48:34–41.

67. An KP, Ratner D. Surgical management of cutaneous malignancies. Clin Dermatol 2001;19:309–320.

68. Thissen MRTM, Neumann MHA, Schouten IJ. A systematic review of treatment modalities for primary basal cell carcinoma. Arch Dermatol 1999;135:1177–1183.

69. Gibbs P, Gonzalez R, Lee LA, Wahl P. Medical management of cutaneous malignancies. Clin Dermatol 2001;19:298–304.

70. Can nonmelanoma skin cancer be found early? Accessed February 8, 2003, from American Cancer Society Web site: http://www.cancer.org

71. U. S. Preventive Services Task Force. Screening for skin cancer: recommendations and rationale. Am J Prev Med 2001;20(3S):44–46.

72. Hill D, Boulter J. Sun protection behaviour: Determinants and trends. Cancer Forum 1996;20:204–211.

73. Marks R. Two decades of the public health approach to skin cancer control in Australia. Why, how and where are we now? Australas J Dermatol 1999;40:1–5.

74. Geller AC, Zhang Z, Sober AJ, et al. The first 15 years of the American Academy of Dermatology Skin Cancer Screening Programs: 1985–1999. J Am Acad Dermatol 2003;48:34–41.

75. Naylor MF, Boyd A, Smith DW, et al. High sun protection factor sunscreens in the suppression of actinic neoplasia. Arch Dermatol 1995;131:170–175.

76. Geller AC, Zhang Z, Sober AJ, et al. The first 15 years of the American Academy of Dermatology Skin Cancer Screening Programs: 1985–1999. J Am Acad Dermatol 2003;48:34–41.

77. Hill D, Boulter J. Sun protection behaviour: Determinants and trends. Cancer Forum 1996;20:204–211.

78. Marks R. Two decades of the public health approach to skin cancer control in Australia. Why, how and where are we now? Australas J Dermatol 1999;40:1–5.