Precursors to Skin Cancer

Arthur J. Sober, M.D., and Jay M. Burstein, M.D.

Certain cutaneous lesions serve as both precursors of skin cancer and markers for increased risk. The solar or actinic keratosis serves such a role for the nonmelanoma (NMSC) forms of skin cancer (basal cell carcinoma and squamous cell carcinoma). Clinically, these keratoses manifest as rough, scaly, erythematous patches on chronically sun-exposed surfaces. Conversion to squamous cell carcinoma in an individual lesion is uncommon and has been estimated at 1 per 1000 per year. Individuals with actinic keratoses have had sufficient chronic photodamage to produce skin cancer, and regular surveillance is recommended. The second precursor for invasive NMSC is Bowen's disease (squamous cell carcinoma in situ). Invasion of the dermis results in frank squamous cell carcinoma. Some types of viral warts may develop into squamous cell carcinoma.

The most important precursor/marker for melanoma is the clinically atypical mole (CAM) or dysplastic nevus. CAMs occur in 5–10% of the U.S. population. CAMs, under photographic follow-up, have been observed to evolve into cutaneous melanoma. The frequency of conversion to melanoma of any single CAM is quite low; however, in melanoma-prone families, prospectively diagnosed melanomas arise in association with a histopathologically observed dysplastic nevus in more than 80% of the cases.

Giant congenital melanocytic nevi have an approximately 6% lifetime risk of melanoma development. The risk associated with small congenital nevi is uncertain.

Lentigo maligna develop into invasive melanoma with a frequency reported in the literature ranging from 5–50%. *Cancer* 1995;75:645–50.

Key words: actinic keratosis, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, dysplastic nevus, clinically atypical mole, congenital nevus, melanoma.

Certain cutaneous lesions serve as precursors of cutaneous malignancy, markers of increased risk, or both. Awareness of the clinical appearance and natural history of these lesions leads to the development of rational screening and follow-up strategies to deal with secondary prevention (early diagnosis) of skin cancers. Precursors exist for both the nonmelanoma skin cancer (NMSC) and cutaneous melanoma. These will be reviewed in turn.

Precursors to NMSC

Actinic Keratoses

The solar or actinic keratosis is both a precursor and mark of increased risk for NMSC. Clinically, these keratoses manifest as rough, scaly, erythematous patches on chronically sun-exposed surfaces. Frequency (prevalence) increases with age and is seen most often in persons with a history of extensive outdoor exposure, which may be occupational (e.g., farmer, sailor) or recreational.[1] Although usually asymptomatic, mild lesional tenderness is reported occasionally. Persons who burn easily, tan poorly, and freckle (Type I and Type II skin phototype) are at greatest risk of development of actinic keratoses.[2] Persons living at higher elevations have increased age-specific rates of solar keratoses compared with persons of similar skin type and similar latitude living at lower elevations (there is increased ultraviolet exposure at higher elevation).[3]

Persons may have a single solar keratosis or, more frequently, multiple lesions. Actinic keratosis may be discrete, with relatively sharp borders, or diffuse. The most common sites are those of greatest solar exposure (i.e., nose, cheeks, forehead, and, in men, the dorsa of the ears). However, an increasing frequency of actinic keratoses are being noted on the trunk. The presence of actinic keratoses indicates sufficient solar exposure to develop NMSC (both basal cell carcinoma and squamous cell carcinoma).[4] These persons should be monitored once or twice annually for the early detection of NMSC.

The conversion rate of any individual actinic kera-

Presented at the National Cancer Society's National Conference on Skin Cancers, Phoenix, Arizona, April 14–16, 1994.

From the Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Supported in part by the Marion Gardner Jackson Trust, Bank of Boston, trustee.

Address for reprints: Arthur J. Sober, M.D., Department of Dermatology, Bartlett 410, Massachusetts General Hospital, Boston, MA 02114.

Received July 25, 1994; accepted September 16, 1994.

tosis to squamous cell carcinoma is relatively low. It has been estimated that one actinic keratosis per 1000 per year converts to squamous cell carcinoma.[5] Those lesions at greatest risk include those developing substantial thickness (cutaneous horn formation), induration of the base, or ulceration. These lesions should be biopsied and the base carefully examined for the presence of squamous cell carcinoma. In a histopathologic study of 643 cutaneous horns, 61% were benign; 23%, premalignant; and 16%, squamous cell carcinoma.[6]

Natural history. Many actinic keratoses spontaneously involute when patients have not received substantial solar exposure for a reasonable period of time (up to 25% within a 12-month period).[7] Recurrence at the same site after intense reexposure is often noted. Eventually, lesions become permanent and remain unless treated by some destructive modality. Of note, a recent sunscreen trial in Australia resulted in some decrease in actinic keratosis frequency in the sunscreen group compared with the control group.[8] This study is preliminary and awaits confirmation.

Histopathology. The actinic keratosis demonstrates alteration of the epidermal basal cell layer keratinocytes. These keratinocytes vary in size and shape and contain nuclei that may be enlarged with prominent nucleoli. Individual basal cells may keratinize. Stratum corneum may be thickened. The dermis shows basophilic solar changes. A mononuclear cell infiltrate is present. No invasion of the dermis by abnormal keratinocytes is noted, and keratinocytic atypia is usually limited to the base of the epidermis (nonfull thickness).

Treatment. There are several approaches to treatment. Gentle destruction with liquid nitrogen cryotherapy is a common approach to treatment of discrete lesions. Diffuse areas can be treated with topical chemotherapy. Either 5-fluorouracil cream twice daily for 2–4 weeks or 10% masoprocol cream twice daily for 4 weeks is used. The latter agent has only recently been approved in the United States, and its exact role in actinic keratosis treatment is undetermined.

Follow-up. Follow-up for monitoring any progression of actinic keratosis to skin cancer or for the development of NMSC elsewhere is recommended at 6- to 12-month intervals.

Bowen's Disease

Bowen's disease, or squamous cell carcinoma in situ, was named after Dr. John T. Bowen, a turn-of-the century dermatologist at the Massachusetts General Hospital.[9] This lesion is usually indolent and after a relatively long period of time may develop into invasive squamous cell carcinoma. Occasionally, more rapid progression can occur. Bowen's disease on the penis is termed erythroplasia of Queyrat. Bowen's disease primarily affects older persons. In one study, 80% of the patients were older than 60.[10]

Clinical presentation. Bowen's disease presents as a reddish, well defined, scaly, erythematous plaque that has usually been present for months to years and fails to respond to topical steroid applications, as will patches of psoriasis or nummular eczema, with which it may be confused. Bowen's disease patches may be multiple in about one fifth to one third of cases. In dark-complected persons, Bowen's disease may be pigmented, although this is uncommon.[11] In one large series of cases from Australia, three fourths of lesions developed on sun-exposed surfaces.[12] Bowen's disease developing in non-sun-exposed surfaces may indicate prior exposure to arsenic and may be associated with an increased frequency of internal malignancy. Bowen's disease developing on sun-exposed surfaces does not seem to be associated with an increased risk of associated internal malignancy.

Histopathology. Bowen's disease demonstrates full thickness, intraepidermal keratinocytic atypia. No invasion into the dermis by atypical keratinocytes is present. The upper dermis shows a mononuclear cell inflammatory infiltrate.

Natural history. Although progression to squamous cell carcinoma is typically slow, at least 5% may undergo invasion of the dermis, in which case the result is squamous cell carcinoma. Once invasion has occurred, at least one third have metastatic capacity. Forty-two percent of patients with Bowen's disease will develop other premalignant or malignant cutaneous and/or mucosal lesions within 7 years of follow-up.[13]

Treatment. Bowen's disease can be treated by a variety of approaches, including destructive modalities (cryosurgery or electrodesiccation and curettage) and surgical excision. Extensive lesions, especially those near vital organs, may be best handled by Mohs' micrographic surgery, which is both tissue sparing and has the highest overall cure rate of available techniques.

Follow-up. An annual checkup after removal is reasonable for the detection of recurrence or the development of NMSC at another site. Screening for internal malignancy may be reasonable for Bowen's disease occurring on non-sun-exposed surfaces, especially if a history of arsenic exposure is found.

Human Papillomavirus

Most warts are not precursors to cutaneous cancers. The earliest linkage between warts and skin cancer was noted for the rare genetic disorder epidermodysplasia verruciformis. It is transmitted as an autosomal recessive disorder, and persons afflicted with this condition

develop numerous warts with squamous cell carcinomas associated. Human papillomavirus, especially types 5 and 8, has been found most commonly in epidermodysplasia verruciformis.[14] Patient education and frequent examination are necessary in these patients.

Human papillomavirus has also been found in association with lesions of Bowen's disease.[15] Viral transformation to squamous cell carcinoma has also been noted for the giant condyloma accuminata of Buschke-Löwenstein, which affects anogenital areas.[16,17]

Human papillomavirus has been identified in association with NMSC in immunosuppressed transplant patients. Because warts commonly occur in this group and risk of NMSC is elevated, the transplant group should be aggressively monitored for skin cancer development.[18,19] NMSCs in this group are often numerous, making treatment strategies problematic. Good solar protection practices should be instituted, because most of these cancers will develop in sun-exposed sites.

Rare Precursor Lesions

Congenital Jadassohn's sebaceous nevus, which presents as a yellowish plaque on the head and neck (usually scalp), develops into basal cell carcinoma in 5–7% of cases.[20] Some large epidermal nevi have developed associated basal cell carcinoma in later life.[21]

Melanoma

Dysplastic Nevi or Clinically Atypical Moles

The most important precursor/marker for melanoma is the CAM or dysplastic nevus. Numerous reviews are available that explore the relationship of CAMs and melanoma.[22–24] CAMs occur in 5–10% of the U.S. population. Clinically, CAMs, under photographic follow-up, have been observed to evolve into cutaneous melanoma. The frequency of conversion to melanoma of any single CAM is quite low; however, in melanoma-prone families, prospectively diagnosed melanomas arise in association with a histopathologically associated dysplastic nevus in more than 80% of cases. It has been estimated that persons who have CAM and lack a family history of melanoma have an approximately 6% lifetime risk of melanoma.[25]

The CAM was first described in the late 1970s as a precursor/marker for melanoma in hereditary melanoma-prone families.[26,27] In these families, melanoma risk appeared to be transmitted in an autosomal dominant fashion. The dysplastic nevus trait in these families recently has been associated with a region on the short arm of chromosome 9.[28] Persons with CAM and two family members with cutaneous melanoma have a lifetime risk of melanoma development greater than 50%.[29] In prospectively diagnosed melanomas in these families, an associated histopathologic dysplastic nevus was identified in the melanoma specimen in greater than 80% of cases.

Table 1. Clinical Features of Clinically Atypical Moles[32]

Feature	Clinically atypical mole
Age at onset	After 6–12 mo; usually evident by puberty
Anatomic sites	Any site, may involve scalp, breasts, buttocks
Number	One or many
Size	Usually ≥ 5 mm in diameter
Coloration	Disorderly, often two or more shades of brown, may be very darkly pigmented, pink hue may be present
Shape	Round, oval, or irregular
Outline	Irregular, may have fuzzy border

Many terminologic disputes have arisen in the past decade over the nomenclature, diagnostic characteristics, and significance of CAM. Two National Institutes of Health Consensus Conferences (1983, 1991) have concerned themselves with this issue.[30,31] At the most recent conference, the following conclusions were reached:

1. CAM can be suspected in individuals with large, variegated, and/or numerous nevi. The histopathology may vary and overlap with normal nevi.
2. Individuals with CAM and family members with melanoma have substantially increased risk of melanoma development and should be monitored prospectively.
3. Individuals with CAM and no family history of melanoma (perhaps 2–10% of the population) also have increased risk of melanoma over the population at large and should be monitored prospectively.[31]

Clinical and histopathologic features are summarized in Tables 1 and 2.[32,33]

Management. Those nevi that have features suggestive of melanoma should be removed for histopathologic examination. Review by a dermatopathologist may sometimes be needed to distinguish some dysplastic nevi from cutaneous melanoma. Photographic follow-up of select lesions, although not the standard of care, may be helpful.

Follow-up. Follow-up frequency depends on family history of melanoma, personal history of melanoma, and the number and clinical degree of atypia. Table 3 shows a recommended follow-up schedule. Patients with one melanoma are at increased risk of development of subsequent melanomas. In familial melanoma,

Table 2. Histopathologic Features of Dysplastic Nevi[33]

Atypical nevomelanocytes in a basilar location
Extension of epidermal proliferation at least three rete ridges beyond a dermal nevic component, if present (shoulder effect)
Intraepidermal proliferation of the above cells is either lentiginous or epitheloid in pattern
Presence of papillary dermal fibrosis (lamellar and/or concentric eosinophilic)
Rete ridges are fused (bridging)
Neovascularization
A dermal inflammatory cell infiltrate

more than 30% of melanoma patients will have two or more primary tumors.[29] Screening of family members is recommended, because melanoma may occur with increased frequency in family members of patients with CAM.[34]

Giant Congenital Nevi

The giant congenital nevus is an established precursor for cutaneous melanoma. Fortunately, this is a rare lesion affecting fewer than 1 of 20,000 births. Melanoma development in giant congenital nevi is usually in the deep dermal or subcutaneous regions of the skin, unlike most cutaneous melanomas, whose origins are at the dermoepidermal junction. This finding plus the irregular shape, coloration, and variability of texture of these large nevi make early diagnosis problematic.

The exact risk of malignant transformation is unknown. Estimates range from 2–40%. Rhodes et al. estimated the lifetime risk to be in the 6% range, based on extrapolation of Danish registry data of Lorentzen et al.[35,36] Greatest risk appears to occur before age 5 and the next greatest risk before age 10, although melanoma transformation can occur in later life.

Management recommendations are controversial and range from serial excision with grafting early in life to observation. Complete risk cannot be eliminated by surgical removal, because the nevus cells may penetrate into underlying muscle and into the linings of the central nervous system if the nevus overlies the midline posteriorly.

Small Congenital Nevi

One child in 100 is born with a small congenital melanocytic nevus. No consensus exists regarding either increased risk of melanoma development in small congenital nevi or their management. The 1983 National Institutes of Health Consensus Conference concluded that no consensus could be reached as to whether the small congenital nevus is a precursor to melanoma.[30] Nonetheless, melanomas have been seen clinically arising within small congenital nevi. Whether this is coincidental has not been established. However, based on body surface area considerations and probability, it would seem that small congenital nevi have some increased risk of melanoma development.[37,38] Prepubertal risk appears to be quite low with small congenital nevi. Centers recommending consideration of prophylactic excision usually do so for persons older than age 10, at which time local anesthesia can be used in a cooperative patient. Conversely, some melanoma centers believe that the small congenital nevus has no increased risk.

Lentigo Maligna

The lentigo maligna is the known precursor of the least common type of melanoma, the lentigo maligna melanoma, which accounts for 5% of all melanomas.

Clinical presentation. Lentigo maligna lesions are completely flat, tan-brown macules occurring on chronically sun-damaged surfaces. Most common locations are the cheeks and nose. Ninety percent occur on the head and neck.[39] Typically, the lesion grows slowly in diameter. Borders become increasingly irregular and pigment pattern varies. A portion of the lentigo maligna may undergo spontaneous regression and appear to disappear.

Natural history. Lentigo malignas have been reputed to evolve into invasive melanoma over a 5–50-year period. Not all lentigo malignas develop into invasive melanoma. Textbooks suggest that perhaps one third progress. In an epidemiologic study by Weinstock and Sober, the conversion rate was estimated to be as low as 5%.[40] Nonetheless, once diagnosed, a lentigo maligna must be either followed or removed.

Diagnosis. Histopathologic changes are relatively characteristic. In an atrophic epidermis, increased numbers of large and bizarrely shaped basalar layer melanocytes are seen. Extension down rete ridges and appendageal structures is characteristic. Solar elastotic changes are noted in the dermis, but invasive tumor cells are absent.

Treatment. Surgical excision is the treatment of

Table 3. Follow-Up of Patients With Dysplastic Nevi

Past history of melanoma	Family history of melanoma	Frequency of follow-up
–	–	6–12 mo
+	–	Depends on thickness of the melanoma
–	+	6–12 mo
+	+	6 mo

choice. Recurrence is common. Some of these lesions are multifocal. Superficial electron beam therapy is also effective. A variety of superficial approaches have been recommended. So far, none have passed the test of time. Mohs' micrographic surgery has been used for the treatment of large lentigo maligna in an attempt to decrease local recurrence rates. Its role requires longer follow-up and a study of larger numbers of patients.

Follow-up. Patients with lentigo maligna being monitored clinically should be seen at 6- to 12-month intervals. Patients should be instructed to return immediately if any palpable areas develop or if substantial darkening occurs. After removal of lentigo maligna, patients should be followed every 6–12 months for recurrence or the development of new lesions.

Summary

Awareness of these precursors and their management should lead to decreased mortality from melanoma by allowing earlier diagnosis. Educational, screening, and monitoring strategies are based on the frequency, clinical appearance, and natural history of these lesions.

References

1. Vitasa BC, Taylor HR, Strickland PT, Rosenthal FS, West S, Abbey H, et al. Association of non-melanoma skin cancer and actinic keratosis with cumulative solar exposure in Maryland watermen. *Cancer* 1990;65:2811–7.
2. Marks R, Ponsford MW, Selwood TS, Goodman G, Mason G. Non-melanotic skin cancer and solar keratoses in Victoria. *Med J Aust* 1983;2:619–22.
3. Marks R, Selwood TS. Solar keratoses: the association with erythemal ultraviolet radiation in Australia. *Cancer* 1985;56:2332–6.
4. Marks R, Rennie G, Selwood TS. The relationship of basal cell carcinomas and squamous cell carcinomas to solar keratoses. *Arch Dermatol* 1988;124:1039–42.
5. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma in the skin: a prospective study. *Lancet* 1988;1:795–7.
6. Yu RCH, Pryce DW, MacFarlane AW, Stewart TW. A histopathological study of 643 cutaneous horns. *Br J Dermatol* 1991;124:449–52.
7. Marks R, Foley P, Goodman G, Hage BH, Selwood TS. Spontaneous remission of solar keratoses: the case for conservative management. *Br J Dermatol* 1986;115:649–55.
8. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med* 1993;329:1147–51.
9. Bowen JT. Precancerous dermatoses: a study of two cases of chronic atypical epithelial proliferation. *J Cutan Dis* 1912;30:241–55.
10. Thestrup-Pedersen K, Ravnborg L, Reymann F. Morbus Bowen: a description of the disease in 617 patients. *Acta Derm Venereol (Stockh)* 1988;68:236–9.
11. Ragi G, Turner MS, Klein LE, Stoll HL Jr. Pigmented Bowen's disease and review of 420 Bowen's disease lesions. *J Dermatol Surg Oncol* 1988;14:765–9.
12. Kossard S, Rosen R. Cutaneous Bowen's disease: an analysis of 1001 cases according to age, sex, and site. *J Am Acad Dermatol* 1992;27:406–10.
13. Schwartz RA, Stoll HL Jr. Epithelial precancerous lesions. In: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, editors. Dermatology in general medicine. 4th ed. New York: McGraw-Hill, 1993: 804–21.
14. Orth G, Jablonska S, Favre M, Croissant O, Jarzabek-Chorzelska M, Rzesa G. Characterization of two types of human papillomavirus in lesions of epidermodysplasia verruciformis. *Proc Natl Acad Sci USA* 1978;75:1537–41.
15. Eliezri YD, Silverman SJ, Nuovo GJ. Occurrence of human papillomavirus type 16 DNA in cutaneous squamous and basal cell neoplasms. *J Am Acad Dermatol* 1990;23:836–42.
16. Schwartz RA. Buschke-Loewenstein tumor: verrucous carcinoma of the penis. *J Am Acad Dermatol* 1990;23:723–7.
17. Bogomoletz WV, Potet F, Molas G. Condylomata accuminata, giant condyloma accuminatum (Buschke-Loewenstein Tumor) and verrucous squamous cell carcinoma of the perianal and anogenital region: a continuous precancerous spectrum? *Histopathology* 1985;9:1155–69.
18. Gassenmaier A, Fuchs P, Schell H, Pfister H. Papillomavirus DNA in warts of immunosuppressed renal allograft recipients. *Arch Dermatol Res* 1986;278:219–23.
19. Barr BBB, Benton EC, McLaren K, Bunney MH, Smith IW, Blessing K, et al. Human papilloma virus infection and skin cancer in renal allograft recipients. *Lancet* 1989;1:124–8.
20. Lever WF, Schaumburg-Lever G. Histopathology of skin. 7th ed. Philadelphia: Lippincott, 1990: 595–7.
21. Solomon LM, Esterly NB. Epidermal and other organoid nevi. *Curr Probl Pediatr* 1975;6:1–56.
22. Greene MH, Clark WH Jr., Tucker MA, Kraemer KH, Elder DE, Fraser MC. High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. *Ann Intern Med* 1985;102:458–65.
23. Grob JJ, Andrac L, Romano MH, Davin D, Collet-Villette AM, Munoz MH, et al. Dysplastic naevus in non-familial melanoma: a clinicopathological study of 101 cases. *Br J Dermatol* 1988;118:745–52.
24. Elder DE, Goldman LI, Goldman SC, Greene WH, Clark WH Jr. The dysplastic nevus syndrome: a phenotypic association of sporadic cutaneous melanoma. *Cancer* 1980;46:1787–94.
25. Kraemer KH, Tucker MA, Tarone R, Elder DE, Clark WH Jr. Risk of cutaneous melanoma in dysplastic nevus syndrome types A and B. *N Engl J Med* 1986;315:1615–6.
26. Clark WH Jr., Reimer RR, Greene WH, Ainsworth A, Mastrangelo MJ. Origin of familial melanomas from heritable melanocytic lesions: the "B-K" syndrome. *Arch Dermatol* 1978;114:732–8.
27. Lynch HT, Frichot BC, Lynch JF. Familial atypical multiple mole-melanoma syndrome. *J Med Genet* 1978;15:352–6.
28. Cannon-Albright LA, Goldgar DE, Meyer LJ, Lewis CM, Anderson DE, Fountain JW, et al. Assignment of a locus for familial melanoma, MLM, to chromosome 9p13-p22. *Science* 1992;258:1148–52.
29. Tucker MA, Fraser MC, Goldstein AM, Elder DE, Guerry D IV, Organic SM. Risk of melanoma and other cancers in melanoma-prone families. *J Invest Dermatol* 1993;100:350S–5S.
30. Consensus Conference: precursors to malignant melanoma. *JAMA* 1984;251:1864–6.
31. Sober AJ. Diagnosis and management of early melanoma: a consensus view. *Semin Surg Oncol* 1993;9:194–7.
32. Rhodes AR. Neoplasms: benign neoplasias, hyperplasias, and dysplasias of melanocytes. In: Fitzpatrick TB, Eisen AZ, Wolff K,

Freedberg IM, Austen KF, editors. Dermatology in general medicine. 4th ed. New York: McGraw-Hill, 1993: 996–1077.
33. Clemente C, Cochran A, Elder DE, Levene A, MacKie RM, Mihm MC Jr., et al. Histopathologic correlation in the diagnosis of dysplastic nevi: a concordance study. *Hum Pathol* 1991;22:313–9.
34. Albert LS, Rhodes AR, Sober AJ. Dysplastic melanocytic nevi and cutaneous melanoma: markers of increased melanoma risk for affected persons and blood relatives. *J Am Acad Dermatol* 1990;22:69–75.
35. Rhodes AR, Weinstock MA, Fitzpatrick TB, Mihm MC Jr., Sober AJ. Risk factors for cutaneous melanoma: a practical method of recognizing high risk individuals. *JAMA* 1987;258:3146–54.
36. Lorentzen M, Pers M, Bretteville-Jensen G. The incidence of malignant transformation in giant pigmented nevi. *Scand J Plast Reconstr Surg* 1977;11:163–7.
37. Rhodes AR, Sober AJ, Day CL Jr., Melski JW, Harrist TJ, Mihm MC Jr., et al. The malignant potential of small congenital nevocellular nevi: an estimate of association based in a histologic study of 234 primary cutaneous melanomas. *J Am Acad Dermatol* 1982;6:230–41.
38. Rhodes AR, Melski JW. Small congenital nevocellular nevi and the risk of cutaneous melanoma. *J Pediatr* 1982;100:219–24.
39. Koh HK, Michalik E, Sober AJ, Lew RA, Day CL Jr., Clark WH Jr., et al. Lentigo maligna melanoma has no better prognosis than other types of melanoma. *J Clin Oncol* 1984;2:994–1001.
40. Weinstock MA, Sober AJ. The risk of progression of lentigo maligna to lentigo maligna melanoma. *Br J Dermatol* 1987;116:303–10.