Análisis de Documentos sobre Melanoma

# Causas Identificadas

* Recently, we  
  examined a series of equivocal melanocytic lesions, includ-  
  ing 37 melanomas and 65 nevi, all excised because of  
  dermoscopic aspects suggestive of malignancy, and an  
  algorithm based on the detection of six features was  
  developed (Pellacani et al., 2005b).
* No lesions excised for  
  cosmetic reasons or solely due to a patient request were included.
* Due to this close connection between the immune sys-  
  tem and melanoma, we can expect that immunosuppres-  
  sive or immunomodulating drugs affect this balance.
* However, a conclusion   
  could not be drawn regarding the risk of melanoma in   
  patients treated with cyclophosphamide due to an insuf-  
  ficient number of cases.
* The association between immunomodulatory therapies   
  and melanoma is of particular interest due to the nature   
  of melanoma as an immunogenic tumor.
* Therefore, we   
  recommend all patients with a history of invasive mel-  
  anoma to avoid these agents due to their baseline high   
  risk of melanoma.
* It can occur because of more  
  sensitive or intensive screening or from changing the disease  
  classiﬁcation threshold or nomenclature (Brodersen et al.,  
  2018).
* Changes in the  
  incidence of regional and distant cases over time are most likely caused by differences in staging practices over time (that is, upstaging owing to increased use of  
  imaging and sentinel lymph node biopsy).
* Although an incongruent rise in incidence  
  versus mortality over time might be due to an increase in true  
  cancer occurrence plus effective secondary prevention miti-  
  gating the rise in observed mortality or causing lead time  
  bias, these factors appear unlikely.
* Melanoma Overdiagnosis in the United States  
  www.jidonline.org  
  1807  
  incidence of thicker melanomas because of earlier diagnoses.
* A decline in true occurrence risk could be  
  due to effective primary prevention and possibly the suc-  
  cessful removal of potential melanoma precursors (that is,  
  congenital and dysplastic nevi).
* Unique age-related differences in mel-  
  anoma risk by sex could be due to indoor tanning, which is  
  more prevalent in young females (Centers for Disease Control  
  and Prevention, 2012).
* It must be  
  distinguished from junctional nevi, “racial” melano-  
  sis, congenital ocular, or oculodermal melanosis, as  
  well as from pigmentation due to systemic diseases  
  (e.g., Addison’s disease) and deposits from mascara  
  and topically instilled drugs.148 The precancerous  
  variant of PAM cannot be separated from PAM with-  
  out atypia on the clinical appearance alone; this re-  
  quires cytologic or histopathologic examination  
  (Figs.
* This  
  condition is clinically bothersome, as the PAM can-  
  not be exactly delineated.149,226  
  In the late 1980s, Jakobiec and coworkers concep-  
  tualized the “in-transit” metastases of conjunctival  
  melanoma.147 These are small secondary nodules of  
  conjunctival melanoma growing beneath an intact  
  epithelium and believed to be caused by local lym-  
  phatic spread within the conjunctiva.
* In the Dutch survey, the median  
  age was 58 years and the youngest patient was 21  
  years old at the time of presentation.68 Calculations  
  of the age-specific incidence of conjunctival mela-  
  noma in Sweden concur with these findings (Table  
  2).267 The youngest patient ever to have had a con-  
  junctival melanoma appears to have been a 10-year-  
  old boy, who was included in the case series by Ber-  
  nardino and associates.31 Also, the histopathology  
  files of one center were reviewed for 71 conjunctival  
  melanocytic lesions in patients younger than 20  
  years of age.201 Only three of these specimens con-  
  tained conjunctival melanomas, including that of a  
  12-year-old boy with subsequently biopsy-proven  
  metastasis of an ipsilateral parotid lymph node.201  
  However, the youngest reported patient with dis-  
  seminated disease caused by a presumed conjuncti-  
  val melanoma was an 11-year-old boy who under-  
  went orbital exenteration.60  
  TABLE 1  
  Distribution of Noncutaneous Melanoma  
  Location   
  Number of   
  Patients  
  Percent of   
  Noncutaneous   
  Melanomas  
  Skin  
  2598  
  Uvea  
  250  
  58.1  
  Conjunctiva  
  7  
  1.6  
  Ocular site unknown  
  84  
  19.5  
  Vulva  
  31  
  7.2  
  Soft tissue  
  11  
  2.6  
  Rectum  
  10  
  2.3  
  Vagina  
  9  
  2.1  
  Upper respiratory tract  
  7  
  1.6  
  Gum and mouth  
  5  
  1.2  
  Gastrointestinal tract  
  3  
  0.7  
  Other sites  
  13  
  3.0  
  Total  
  3,028  
  100.0  
  Modified from Scotto et al.262  
  TABLE 2  
  Age-Specific Incidence of Conjunctival Melanoma  
  Age (y)  
  Cases   
  Observed  
  Incidence\*  
  , 30  
  0  
  0  
  30–49  
  12  
  0.027  
  50–69  
  24  
  0.055  
  .
* Gloor  
  and Alexandrakis recognized PAM in 36% of outpa-  
  tients visiting a corneal and external disease ser-  
  vice,107 but these data may be biased because of  
  CONJUNCTIVAL MELANOMA  
  331  
  patient selection (notably a large proportion of pa-  
  tients had southern European ancestry and 25% of  
  pigmented lesions were bilateral, which suggested  
  racial melanosis rather than PAM).
* An ab-  
  errant form of skin nevus, the so-called dysplastic ne-  
  vus, has raised considerable interest because of its as-  
  sociation with cutaneous melanoma.
* Based on the histopathologic findings and the set-  
  ting in a patient with numerous dysplastic skin nevi,  
  this lesion was interpreted as a dysplastic nevus of  
  the conjunctiva.150 Other rare variants of conjuncti-  
  val nevi include the spindle and epitheloid nevus of  
  Spitz (once referred to as “juvenile melanoma”).280  
  This is an infrequent entity of childhood,313 but the  
  Spitz nevus of the conjunctiva may extremely rarely  
  present in adults and then sometimes appear as a  
  pure epitheloid cell nevus.150 In contrast to the dys-  
  plastic nevus, the Spitz nevus is not believed to be as-  
  sociated with an increased risk of malignant transfor-  
  mation, but both these types of lesions may be  
  misdiagnosed as melanomas because of their un-  
  usual histopathologic features.88,150  
  D. PRESENTATION DE NOVO  
  Conjunctival melanomas occurring de novo are  
  probably far less common than melanomas deriving  
  from PAM or nevi.
* Some data suggest that conjunctival melanoma  
  arising from the caruncle has a particularly ominous  
  prognosis, possibly because the caruncle is a skin de-  
  rivative.231 Primary eyelid melanoma may secondarily  
  invade the conjunctiva,214 but on rare occasions, pri-  
  mary conjunctival melanoma may be present in con-  
  junction with a separate eyelid melanoma.104 The im-  
  plications of this dual appearance are unclear, but  
  data indicate that patients with conjunctival mela-  
  noma associated with ipsilateral pigmentation of the  
  eyelid margin do worse; in one study, 12 of 17 pa-  
  tients with conjunctival melanoma, including associ-  
  ated eyelid pigmentation ranging from increased  
  pigmentation of the melanocytes to invasive cutane-  
  ous melanoma, died of metastatic disease.246 How-  
  ever, recent findings from a series of 47 patients with  
  primary eyelid melanomas also indicate that patients  
  with tumors extending to the eyelid margin have a  
  worse prognosis than patients without lid margin in-  
  volvement.291 Even though these data are difficult to  
  interpret because of the small number of patients in-  
  volved, they may suggest an association between con-  
  junctival and skin melanoma.
* However, this study was  
  challenged because of its choice of controls and be-  
  cause the investigator was unmasked.162 Recently,  
  the respective prevalence of PAM and nevi of the  
  uvea and choroid in 119 individuals with DNS D2  
  phenotype was compared with controls, matched for  
  sex and age, but otherwise randomly selected from a  
  census file.269 In contrast to previous reports, data in-  
  dicated that individuals with this high-risk variant of  
  DNS did not have PAM or uveal or conjunctival nevi  
  more often than controls.
* Also, excisional biopsies  
  of four conjunctival lesions of the DNS D2 group re-  
  vealed only PAM without atypia, suggesting that  
  these particular lesions would have been unlikely to  
  progress to melanoma even if surgery had not been  
  performed.269  
  In conclusion, there is yet no definite evidence of  
  an association between cutaneous and conjunctival  
  melanoma, and because of the low incidence of  
  both conjunctival and uveal melanoma, new tumors  
  will probably rarely be detected by repeat examina-  
  tions.
* This creates  
  an absorptive barrier that will minimize the risk for  
  damage to the globe.145 It is currently suggested that  
  cryotherapy is applied to the margins of exposed  
  conjunctiva after tumor excision, but not to the  
  scleral bed because of risks for damage to the under-  
  lying retina, uveitis, cataract formation, and ciliary  
  body shutdown with hypotony.275d Heavy cryotherapy  
  to the scleral bed after tumor excision may on rare  
  occasions cause scleral melt.305b While earlier reports  
  suggest that 2158 to 2208 C is adequate for the treat-  
  ment of intraepithelial growth,145 more recent data  
  indicate that the application of a double freeze-thaw  
  cycle at 2708 to 2808 C will destroy the epithelium  
  without causing serious side effects.13 Cryotherapy en-  
  ables the potential destruction of clinically invisible  
  PAM, i.e., PAM sine pigmento, which may be present  
  beyond the surgical margin.149 This may in part ex-  
  plain why patients treated with tumor excision alone  
  appear to have a higher recurrence rate than those  
  treated initially with excision and supplemental cryo-  
  therapy.67 Adjunctive cryotherapy is possibly of less  
  338  
  Surv Ophthalmol 42 (4) January–February 1998  
  SEREGARD  
  value when margins are monitored by microscopi-  
  cally controlled surgery.
* Rarely, obstruction of the nasolacrimal duct is  
  caused by a local tumor recurrence.
* Therefore,  
  it is currently advised that surface cytology should be  
  used judiciously and not replace biopsy for sus-  
  pected neoplastic conditions.84,120  
  H. RECURRENT DISEASE  
  Recent data from a case series comprising 68 indi-  
  viduals with malignant melanoma of the conjunctiva  
  showed that 56% of patients develop one or more re-  
  currences and that 32% eventually experience multi-  
  ple recurrences.67 Similarly, population-based data  
  suggest that recurrences take place in 56–62% of pa-  
  tients.68,270 The mean interval between the first treat-  
  ment and the first recurrence ranges from 0.4 to 14  
  years, with a mean time interval of 2.5 years.67  
  Whereas some data suggest that recurrent disease is  
  associated with the development of metastases,67  
  other reports are conflicting.272 Patients receiving  
  cryotherapy after surgery seem to have fewer recur-  
  rences than those treated by surgery alone.67 More-  
  over, patients with multifocal conjunctival disease  
  are more likely to have recurrences than patients  
  with unifocal nodules,149 and orbital exenteration is  
  more often performed because of recurrent disease  
  than as a primary procedure.230 Some data suggest  
  that recurrent disease is more common in conjuncti-  
  val melanoma associated with PAM, but also that tu-  
  mors that histologically appear incompletely excised  
  may not necessarily recur.68 A number of adjuvant  
  treatments have been suggested to reduce the risk of  
  local tumor recurrence.
* At a median follow-up of 10 years, no differences   
  were seen in local recurrence and disease-free and   
  overall survivals.39,40 Prospective randomized trials   
  from Sweden have confirmed that satisfactory local   
  control and melanoma-specific survival are not com­  
  promised by narrower margins.41,42   
  In a more recent prospective randomized trial   
  comparing 1.0- versus 3.0-cm margins for melanomas   
  thicker than 2.0 mm, wider margins were associated   
  with a slightly lower rate of combined local/regional/  
  nodal recurrence, but not improvement in local re­  
  currence alone or melanoma-specific survival.43 A   
  systematic review and meta-analysis also reported   
  that surgical excision margins no more than 2.0 cm   
  are adequate, and that surgical margins should not be   
  less than 1.0 cm around primary melanoma.44  
  Management of lentigo maligna and in situ mel­  
  anoma may present unique problems because of the   
  characteristic, yet unpredictable, subclinical exten­  
  sion of atypical junctional melanocytic hyperplasia,   
  which may extend several centimeters beyond the   
  visible margins.
* Although surgical excision remains the standard   
  of care for in situ melanoma, it is sometimes not fea­  
  sible because of comorbidity or cosmetically sensi­  
  tive tumor location.
* However, an improvement was seen in the esti­  
  mated 5-year disease-free survival rate in the SLNB   
  group (78% after SLNB vs. 73% after observation;   
  P = .009), at least partly because of the higher nodal   
  relapse rate in the observation group.
* The randomized phase   
  III trial of adjuvant GM2-KLH21 in 1314 patients   
  with stage II melanoma (EORTC 18961) was closed   
  early by the data monitoring committee because of   
  inferior survival in the vaccine arm.79  
  A recent retrospective review of 200 patients   
  with melanoma (stage IIB, IIC, or III) reported that   
  those who had autoantibodies or clinical manifesta­  
  tions of autoimmunity after treatment with high-  
  NCCN Clinical Practice Guidelines in Oncology  
  Melanoma  
  © JNCCN–Journal of the National Comprehensive Cancer Network  |  Volume 10 Number 3  |  March 2012  
  388  
  dose interferon alfa-2b had improved relapse-free   
  and overall survivals compared with patients who   
  did not show manifestation of autoimmunity.80   
  Review of data combined from the randomized   
  controlled trials found that adjuvant interferon alfa   
  was not associated with improved overall survival in   
  patients with melanoma who were at increased risk   
  for recurrence.81 A pooled analysis of E1684, E1690,   
  and E1694 confirmed an improvement in relapse-  
  free survival in patients with high-risk resected mel­  
  anoma (2-sided log-rank P value = .006) but found   
  no significant improvement in overall survival.82  
  The ECOG studies included patients with stage   
  IIB (≥ 4.0 mm with no evidence of lymph node in­  
  volvement) and III melanomas with either regional   
  lymph node disease or in-transit metastases.
* Treatment with adjuvant high-dose or pegylated   
  interferon alfa is currently a category 2B recommen­  
  dation in all of the cases described because of low   
  benefit-to-risk ratio.
* Overall, 38% of patients receiving vemu­  
  rafenib required dose modification because of adverse   
  events.
* LM also represents a therapeutic  
  challenge because of its usual size as well as location and  
  propensity to locally recur, estimated to be between 8 and  
  31% after conventional surgery (Agarwal-Antal et al., 2002;  
  Osborne and Hutchinson, 2002; McKenna et al., 2006).
* It is  
  noteworthy that the improved sensitivity and specificity found  
  in the test set may be due to the incorporation of additional  
  cases by the Florida group, not found in the training set.
* It is noteworthy that keratoses were less easy to differentiate  
  from LMs than other BMs of the face, perhaps due to the  
  distortion of pigmented keratinocytes that had a similar  
  reflectance signal under RCM to atypical melanocytes.
* In Vivo Reflectance Confocal Microscopy  
  K  
  Epidermal shadow (Supplementary Figure S4 online),  
  defined as large featureless area with blurred border  
  disrupting the normal epidermis and corresponding to the  
  horizontal clefting (due to hyporeflective stroma, Ulrich  
  et al., 2011) is also a useful feature  
  There were three negative features useful for the diagnosis  
  of BCCs:  
  K  
  Disarray of the honeycomb epidermal layer is more  
  specific of MMs (Pellacani et al., 2007), and the  
  honeycomb pattern was recognized in more than 90%  
  of the BCCs of this series  
  K  
  Papillae were ‘‘non-visible,’’ meaning that BCC structures  
  altered the normal junction organization.
* In this regard, although RCM and  
  dermoscopy have the same sensitivity for the diagnosis of  
  MMs (91%, 95% CI: 84.6–95.5 for RCM, and 88%, 95% CI:  
  80.7–92.6 for dermoscopy), the sensitivity increases drama-  
  tically to 98% when lesions are excised, because of either the  
  RCM or dermoscopy evidence of MMs.
* In part because of the  
  lack of uniformity of definition, however, the reports of histologic  
  melanocytic dysplasia in association with melanoma range from 5 to  
  36% [11,17–20].
* Because of the characteristic pattern of epidermal ridge  
  pattern and junctional nest cross-bridging in dysplastic nevi, the  
  junctional changes were considered an integral part of the diagnosis.
* Whether  
  the thicker tumors develop with a similar proportion of nevi and the  
  tumor growth over-rides the nevus, or whether thicker tumors develop  
  less frequently in nevi and attain a greater thickness because of some  
  other mechanism, is not known.
* Recently, we  
  examined a series of equivocal melanocytic lesions, includ-  
  ing 37 melanomas and 65 nevi, all excised because of  
  dermoscopic aspects suggestive of malignancy, and an  
  algorithm based on the detection of six features was  
  developed (Pellacani et al., 2005b).
* No lesions excised for  
  cosmetic reasons or solely due to a patient request were included.
* Because of the difficulty of exploring sun exposure during  
  childhood with the same indicators used for assessing sun exposure  
  during adulthood, combining data on sun exposure that took place  
  during different periods of life has been impossible, and the joint  
  effect on melanoma risk of sun exposure at different moments of  
  life has seldom been examined.
* The observed estimated risk was  
  4.2, suggesting a relative excess risk due to interaction of 4.2 2  
  2.4 5 1.8 (Rothman, 1986).
* A relative excess risk due to interaction  
  was also found for the other levels of increased child and adult sun  
  exposure in Table IV.
* If this were the case, the melanoma risk associated  
  with sun exposure during childhood and during adulthood would  
  simply add their effects, and there would not be a relative excess  
  risk due to interaction.
* However, because of the above-mentioned  
  limitations, the type of interaction found in these data is difficult to  
  deﬁne, and at this stage, we cannot assert whether additive or  
  multiplicative models would be more appropriate.
* The important contribution of sun exposure during childhood  
  has remained underestimated in many epidemiological studies  
  because of the difficulties in assessing sun exposure during that  
  period of life.
* As a result, and  
  because of the difficulty in assessing sun exposure during early life,  
  in Australia, the melanoma risk associated with intermittent sun  
  exposure during adulthood may have appeared as relatively low,  
  whereas it was found to be higher in Northern Europe or Canada.
* Only recently, a  
  further meta-analysis involving 4579 patients’ data from  
  seven randomized clinical trials revealed no signiﬁcant  
  difference between narrow (1e2 cm) and wide (3e5 cm)  
  excision margins in locoregional or distant recurrence,  
  metastasis, death, or death due to melanoma [15].
* Because of unpredictable subclinical  
  extension of the adjacent intraepidermal component, the  
  management of lentigo maligna melanoma may range  
  from a 5 mm margin to wider margins (up to 10 mm).
* Grade 3, 4, or 5 AE occurred  
  in 14.7% of the patients in the pembrolizumab arm and  
  in 3.4% in the placebo arm, with one death in the  
  pembrolizumab arm due to myositis.
* The rates of grade 3 or 4 AE were 33% with the com-  
  bination vs. 13% with nivolumab; 19% of the patients in  
  the combination arm discontinued therapy due to AE  
  compared to 6% in the nivolumab arm.
* Although the median time on treatment was only 6.5  
  weeks in the ipilimumab and nivolumab arm, with  
  treatment discontinuation being mostly due to high-  
  grade toxicity, RFS after 24 months was 70% for nivo-  
  lumab plus ipilimumab, compared to 42% for nivolu-  
  mab and 14% for placebo, resulting in a HR of 0.23 for  
  nivolumab plus ipilimumab over placebo [80].
* In the  
  nivolumab plus ipilimumab arm, 71% of patients expe-  
  rienced treatment-related grade 3e4 AEs compared to  
  27% in the nivolumab arm; 62% of the patients dis-  
  continued treatment due to AE in the combination arm,  
  compared to 13% in the nivolumab arm and there were  
  no treatment-related deaths.
* Using AJCC as a criterion of  
  entry for adjuvant therapy results in two important  
  limitations: (1) a number of so-called high-risk patients  
  with stage III, or IIB-C disease are exposed to a  
  treatment, although they do not require it and (2)  
  AJCC low-risk stage I and IIA account for most of the  
  deaths in the end, because of their very high number.
* This is probably due to the signiﬁcant  
  number of different c-Kit mutations and the lack of  
  consistency of response even when the same mutation is  
  present.
* Cutaneous melanoma is induced by UV radiation and  
  therefore carries a high number of mutations leading to  
  an excellent response to immunotherapies.
* Because of the preferential metastasis to the liver,  
  patients with ocular melanoma and liver metastases may  
  be candidates for local-regional therapeutic measures,  
  such as surgery, chemoablation, chemoembolization,  
  radiofrequency ablation, or STR.
* This publication was conceptu-  
  alized mainly due to advances in the medical treatment  
  of patients with cutaneous melanoma, which justify a  
  newer multidisciplinary therapeutic strategy.

# Consecuencias Identificadas

* Comparing equal or thinner than 1 mm melanomas and  
  thicker ones, epidermal disarray, cells in sheet-like structures,  
  cerebriform nests and nucleated cells within dermal papilla  
  were significantly associated with thick melanomas.
* However, immunosuppressant drugs   
  are associated with an increased risk of certain cancers.
* Increased   
  production of transforming growth factor beta-1 also   
  contributes to immunosuppression [34–38].
* This suggests that natali-  
  zumab exposure could be associated with the develop-  
  ment of melanoma.
* Animal models demonstrate that IL-12 defi-  
  ciency is associated with a higher risk of skin tumors   
  [57].
* On the other hand, IL-23 is associated with a Th17   
  response and has pro-tumorigenic effects of decreasing   
  CD8+ T-cell infiltration and increasing angiogenesis   
  [58,59].
* The following immunomodulating agents have been   
  found to be associated with an increased risk of melanoma   
  or to have an inconclusive association with melanoma:   
  cyclosporine, sirolimus, natalizumab, IL-6 inhibitors,   
  cyclophosphamide, methotrexate and the TNF-alpha   
  inhibitors infliximab and etanercept.
* There appears   
  to be epidemiologic evidence that some immunosup-  
  pressive drugs, including cyclosporine, natalizumab   
  and sirolimus are associated with melanoma.
* Malignancies associated with tumour necrosis factor   
  inhibitors in registries and prospective observational studies: a systematic   
  review and meta-analysis.
* This has also led to a re-evaluation of  
  the potential causes of the increase in melanoma incidence  
  as well as the efﬁcacy of prevention efforts on mortality  
  (Welch et al., 2021).
* These lesions are most prevalent in younger  
  females, present as dermal nodules, and are associated with  
  false-positive melanoma diagnoses  
  (Dika  
  et  
  al.,  
  2017;  
  Orchard et al., 1997).
* Second,  
  population-based  
  ecological  
  studies  
  have  
  shown  
  that  
  increased skin biopsies are associated with increased di-  
  agnoses of in situ, but not invasive, melanoma (Weinstock  
  et al., 2017; Welch et al., 2005).
* Compared with clinician-led surveillance,  
  patient-led surveillance was associated with increased SSE frequency (odds ratio [OR], 3.5;  
  95% CI, 0.9 to 14.0) and thoroughness (OR, 2.2; 95% CI, 0.8 to 5.7), had no detectable  
  adverse effect on psychological outcomes (fear of cancer recurrence subscale score; mean  
  difference, −1.3; 95% CI, −3.1 to 0.5), and increased clinic visits (risk ratio [RR], 1.5; 95% CI,  
  1.1 to 2.1), skin lesion excisions (RR, 1.1; 95% CI, 0.6 to 2.0), and subsequent melanoma  
  diagnoses and subsequent melanoma diagnoses (risk difference, 10%; 95% CI, −2% to 23%).
* Downloaded from jamanetwork.com by Universidad Nacional Autonoma de Mexico (UNAM) user on 05/06/2025  
  C  
  utaneous melanoma is associated with high morbidity  
  and mortality burden in populations of European  
  ancestry.1,2 In Australia, the incidence has been increas-  
  ing since the 1980s, largely driven by increased diagnoses of  
  localized melanoma before it has spread from the primary site  
  on the skin (>95% of all new melanoma diagnoses in Australia  
  in2011).3Aftersurgicalexcisionofalocalizedmelanoma,patients  
  are recommended to undergo long-term follow-up at routinely  
  scheduledclinicvisits(clinician-ledsurveillance).4However,the  
  frequency and duration of clinician surveillance varies widely,  
  leading to substantial differences in health care utilization and  
  costsandunclearclinicalbenefitsforhigherutilizationpatterns  
  ofcare.5Somepatientsexperiencepsychologicalharms(eg,anxi-  
  ety)leadinguptoeachvisit,6-8andmanydonotadheretofollow-  
  up schedules recommended by physicians.9 Clinician-led sur-  
  veillance can also incur considerable financial and opportunity  
  coststoboththepatientandthehealthcaresystem,whichmay  
  not be sustainable if melanoma incidence continues to rise.10  
  Patient-ledsurveillanceisanalternativemodeloffollow-up  
  after treatment of localized melanoma, based on evidence that  
  patientsandtheirpartnersdetectmanysubsequentnewprimary  
  or recurrent melanomas ahead of a routinely scheduled clinic  
  visit.11,12Althoughskinself-examination(SSE)bypatientsisuni-  
  versallyrecommendedinclinicalguidelines,itisoftenperformed  
  inadequately.13,14Thepatient-ledmodelmayincludethefollow-  
  ing interventions: training in SSE (delivered face-to-face or via  
  internetplatformand/orsmartphoneapplications),digitaltech-  
  nologies to record and take images of concerning lesions (eg,  
  smartphone applications, mobile dermatoscopes), online sys-  
  tems for submitting images for remote review by a dermatolo-  
  gist,andadviceonwhetherurgentclinicalreviewmaybeneeded  
  (teledermatology).13Previously,manyphysicianswerereluctant  
  to use telehealth methods, eg, teledermatology15,16; however,  
  these methods have become more accepted during the COVID-  
  19 pandemic as an alternative to traditional face-to-face  
  consultations.17Thismodelofcarecouldaddressthecurrentin-  
  equityofaccesstodermatologistsandothermelanomaspecial-  
  ists where populations are geographically dispersed, such as in  
  Australia where 29% of residents live outside of major cities.18  
  To assess whether patient-led surveillance may be recom-  
  mended as an alternative model of care in clinical practice, ro-  
  bust evidence is needed of its effects on health, psychologi-  
  cal, and resource use outcomes compared with those of  
  clinician-led surveillance.
* In addition, the intervention was associated with  
  improvements in SSE knowledge, attitudes, and practices  
  without any adverse psychological outcomes.
* We are collecting more detailed information on re-  
  cruitment processes in a larger ongoing trial of the same  
  intervention.39  
  The increased detection of melanoma observed in the in-  
  tervention group raises the possibility of overdiagnosis, that  
  is, the detection of indolent lesions that would not cause harm  
  if left untreated.40,41 Melanoma overdiagnosis may produce  
  substantial financial and opportunity costs to the health care  
  system,4,10,42 as well as psychological distress.7,8 We note that,  
  unlike increased detection associated with screening asymp-  
  tomatic people at lower risk for melanoma,43,44 the patients  
  in the present study population were clinically considered to  
  beathighriskofamelanoma.Allhadahistoryofatleast1mela-  
  noma and were in long-term regular clinical surveillance (at  
  intervalsrangingfromevery3monthstoevery12months).Evi-  
  dence of their high-risk status is shown by the 6% annual in-  
  cidence rate observed in the control arm.
* Nevertheless, long-term  
  follow-up after the pilot trial and after the larger ongoing trial  
  are needed to better determine the extent of overdiagnosis  
  associated with patient-led surveillance.46-48  
  The difficulties that were encountered have provided  
  important information for refining the design and conduct of  
  a larger ongoing RCT of patient-led surveillance.39 Improve-  
  ments to address the patient burden include the introduc-  
  tion of an active run-in phase prior to randomization to  
  ensure participants are able to adhere to the protocol and  
  use of a “target lesion” (chosen by the treating physician)  
  that the patient will monitor via teledermoscopy along with  
  any other suggestive lesions they identify.
* The concept of  
  in-transit metastases could in part explain the occur-  
  rence of multifocal conjunctival melanoma; how-  
  ever, multifocal disease will most often appear as  
  new primary tumors associated with pigmented or  
  Fig.
* There are a few reports of corneal or  
  conjunctival melanoma occurring in black individu-  
  als,49,161,206,261,318 and occasionally conjunctival mela-  
  noma may present in the caruncle in blacks.158 How-  
  ever, the overall white-to-black ocular melanoma risk  
  ratio is believed to be at least 8:1.113 Grossniklaus and  
  colleagues included five additional cases of conjunc-  
  tival melanoma of black patients, indicating a white-  
  to-black ratio of 13.6:1.0 in their series.121 Two  
  reports from Egypt and Thailand suggest that con-  
  junctival melanoma is an extreme rarity in these  
  nonwhite populations.75,238  
  D. CONJUNCTIVAL MELANOMA IN ANIMALS  
  Even though Cotchin found one limbal mela-  
  noma in his summary of 1,150 canine neoplasms,58  
  this was not mentioned by Morgan in his review on  
  ocular tumors in animals.211 However, later reports  
  confirm that conjunctival melanoma is an occasional  
  tumor not only of dogs,29,179,197,235 but of cats.57,235 Pos-  
  sibly, melanoma associated with PAM may present in  
  the canine conjunctiva.235  
  V. Etiology  
  A. ULTRAVIOLET RADIATION  
  Massive data now clearly indicate that high doses  
  of ultraviolet radiation (UVR) may cause skin mela-  
  noma.289,290 It would be tempting to conclude that  
  UVR also may induce malignant melanocytic trans-  
  formation in other sites, and most conjunctival mela-  
  nomas appear to arise from the UVR-exposed bulbar  
  surface.
* Previous data suggest  
  that as many as 28% of Hispanics, 36% of Orientals,  
  and 92% of blacks feature grossly visible conjunctival  
  pigmentation.128 This condition is associated with  
  darker skin types, being more common in heavily  
  pigmented individuals, and is usually bilateral.88 It is  
  recognized as complexion-associated pigmentation  
  or racial pigmentation by some88 and as benign epi-  
  thelial melanosis or racial melanosis by others.56  
  However, the equivalent of racial melanosis exists  
  among whites, and approximately 5% of a white  
  population will feature grossly visible, small, pig-  
  mented patches in the interpalpebral conjunctiva  
  (Fig.
* Some data suggest that conjunctival melanoma  
  arising from the caruncle has a particularly ominous  
  prognosis, possibly because the caruncle is a skin de-  
  rivative.231 Primary eyelid melanoma may secondarily  
  invade the conjunctiva,214 but on rare occasions, pri-  
  mary conjunctival melanoma may be present in con-  
  junction with a separate eyelid melanoma.104 The im-  
  plications of this dual appearance are unclear, but  
  data indicate that patients with conjunctival mela-  
  noma associated with ipsilateral pigmentation of the  
  eyelid margin do worse; in one study, 12 of 17 pa-  
  tients with conjunctival melanoma, including associ-  
  ated eyelid pigmentation ranging from increased  
  pigmentation of the melanocytes to invasive cutane-  
  ous melanoma, died of metastatic disease.246 How-  
  ever, recent findings from a series of 47 patients with  
  primary eyelid melanomas also indicate that patients  
  with tumors extending to the eyelid margin have a  
  worse prognosis than patients without lid margin in-  
  volvement.291 Even though these data are difficult to  
  interpret because of the small number of patients in-  
  volved, they may suggest an association between con-  
  junctival and skin melanoma.
* A fourth case comprised sporadic dys-  
  plastic nevi and a conjunctival melanoma occurring  
  in the same individual.200 The same year, Bataille  
  and associates listed three patients with PAM of the  
  conjunctiva in conjunction with the DNS.24 Two pa-  
  tients had the D1 phenotype; one of these had a con-  
  junctival melanoma associated with PAM, and the  
  other had PAM without atypia.
* H. ASSOCIATION WITH OTHER ENTITIES   
  OR CONDITIONS  
  Similar to malignant melanoma in other locations,  
  conjunctival melanoma appears to be associated with  
  neural crest disorders like neurofibromatosis.297,303 In  
  contrast to the uveal tract, ocular and oculodermal  
  melanocytosis are not associated with malignant  
  melanocytic transformation of the conjunctiva.88 Sin-  
  gle case reports indicate that tumor progression of  
  conjunctival melanoma may occur during preg-  
  nancy,151,175,213 suggesting a possible hormonal influ-  
  ence.
* Relative contraindi-  
  cations for any radiation therapy include bulky  
  tumors in the fornix, tumor involvement of the  
  palpebral conjunctiva, and recurrent melanoma pre-  
  viously treated with radiation.46  
  D. CRYOTHERAPY  
  Cryotherapy is used in combination with surgery  
  and never as the sole primary treatment of conjunc-  
  tival melanoma.146 It has been advocated as an adju-  
  vant treatment after surgery, both for PAM and con-  
  junctival melanoma.41,145,146,149,172 Results indicate that  
  this technique may be of value for local tumor con-  
  trol, but it appears to have no additive effect in pre-  
  venting metastatic disease.149 A double freeze-thaw  
  cycle is preferred, in which the cryoprobe remains in  
  place for 10–20 seconds until an ice ball forms.145  
  The epibulbar conjunctiva may be ballooned by the  
  subconjunctival injection of anesthetic.
* Charged particle irradiation using helium ions and  
  proton beam radiotherapy for uveal melanoma may  
  cause anterior segment complications such as dry  
  eye, eye lash loss, and neovascular glaucoma in some  
  20–30% of patients.48,110,112 However, data on side ef-  
  fects related to proton beam treatment for conjunc-  
  tival melanoma are minimal, but some of the com-  
  plications associated with proton beam therapy for  
  uveal melanoma can arise with the addition of cor-  
  neal melting.39  
  G. MONITORING THE PATIENT AFTER   
  PRIMARY TREATMENT  
  There are two main reasons for monitoring pa-  
  tients after primary treatment of conjunctival mela-  
  noma.
* Therefore,  
  it is currently advised that surface cytology should be  
  used judiciously and not replace biopsy for sus-  
  pected neoplastic conditions.84,120  
  H. RECURRENT DISEASE  
  Recent data from a case series comprising 68 indi-  
  viduals with malignant melanoma of the conjunctiva  
  showed that 56% of patients develop one or more re-  
  currences and that 32% eventually experience multi-  
  ple recurrences.67 Similarly, population-based data  
  suggest that recurrences take place in 56–62% of pa-  
  tients.68,270 The mean interval between the first treat-  
  ment and the first recurrence ranges from 0.4 to 14  
  years, with a mean time interval of 2.5 years.67  
  Whereas some data suggest that recurrent disease is  
  associated with the development of metastases,67  
  other reports are conflicting.272 Patients receiving  
  cryotherapy after surgery seem to have fewer recur-  
  rences than those treated by surgery alone.67 More-  
  over, patients with multifocal conjunctival disease  
  are more likely to have recurrences than patients  
  with unifocal nodules,149 and orbital exenteration is  
  more often performed because of recurrent disease  
  than as a primary procedure.230 Some data suggest  
  that recurrent disease is more common in conjuncti-  
  val melanoma associated with PAM, but also that tu-  
  mors that histologically appear incompletely excised  
  may not necessarily recur.68 A number of adjuvant  
  treatments have been suggested to reduce the risk of  
  local tumor recurrence.
* Loss to follow-up should be eliminated, or at  
  least minimized, as no method can adjust for the  
  bias of failure to obtain complete follow-up.132 In  
  Sweden, all causes of death are filed with the Na-  
  tional Causes of Death Registry, which is linked to  
  the National Cancer Registry.
* Prognostic Factors  
  A. TUMOR DEPTH AND SIZE  
  The prognosis for cutaneous melanomas is inti-  
  mately associated with tumor thickness37 and grade  
  TABLE 4  
  Summary of Prognostic Studies 1950 Through 1996 Comprising Patients With Conjunctival Melanoma  
  Author(s)  
  Year  
  Reference #  
  Study Design  
  Patients  
  Mortality  
  (%)  
  Comments  
  Ash  
  1950  
  14  
  Case series  
  60  
  9  
  Survival data on 45 patients.
* Size also has prognostic implica-  
  tions, and patients with tumors larger than 10 mm  
  appear to do worse.272 Similarly, Lommatzsch and  
  colleagues used the TNM classification and showed  
  that large (pT3) tumors had a worse prognosis than  
  small tumors (pT1).188  
  B. TUMOR LOCATION  
  Involvement of the palpebral or caruncular con-  
  junctiva has been regarded by many as heralding a  
  poor prognosis.59,98,151,154,231,278,282 Caruncular melano-  
  mas seem to have a particularly ominous prognosis,  
  irrespective of treatment modality.230 Recently, Pa-  
  ridaens and associates used a large data set for multi-  
  variate analysis and concluded that tumors in pre-  
  sumed unfavorable locations, i.e., those involving  
  the palpebral conjunctiva, fornices, plica, caruncle,  
  and lid margins were associated with 2.2 times  
  greater mortality than melanomas confined to the  
  bulbar conjunctiva.231 Furthermore, tumor thickness  
  only carried prognostic significance in melanomas  
  in “unfavorable” locations.
* In contrast, multifocality  
  only had a poor prognostic value in melanomas in  
  “favorable” sites.231  
  C. HISTOPATHOLOGIC FEATURES  
  Folberg and associates reported that the outcome  
  in patients with conjunctival melanoma was similar  
  regardless of the presence of PAM.92 The presence  
  of pagetoid spread predicted adverse prognosis,92  
  patients with mixed cell tumors had about three  
  times greater mortality than patients with spindle  
  cell melanomas, and histologic evidence of lym-  
  phatic invasion carried a fourfold increase in the  
  death rate.92 Clinical origin of tumor (PAM, pre-  
  existing nevi, or de novo) were not useful prognostic  
  indicators.92  
  D. TUMOR CELL PROLIFERATION  
  A high capacity for growth is reflected in the rela-  
  tive or total number of tumor cells that feature mi-  
  totic figures and in conjunctival melanoma; a high  
  mitotic rate is associated with an adverse progno-  
  sis.30,59,92,272,283 It has been suggested that the mitotic  
  rate and tumor depth should be combined for a  
  prognostic index.283 However, only a small propor-  
  tion of cycling cells are in mitosis, but most cells in  
  late G1 and S phases show immunoreactivity for the  
  proliferating cell nuclear antigen.
* This nuclear pro-  
  tein may be used to enhance the sensitivity in detect-  
  ing cycling cells and the total number of tumor cells  
  per square millimeter featuring immunoreactivity is  
  strongly associated with a poor prognosis, even after  
  adjusting for possible confounding factors.265 The  
  proliferating cell nuclear antigen may also be used  
  for grading of conjunctival melanocytic lesions.43,64  
  and will predict which lesions featuring PAM with  
  atypia may progress to melanoma.266  
  E. NUCLEOLAR ORGANIZER REGIONS  
  In eukaryotic genomes, hundreds or thousands of  
  ribosomal RNA repeats are clustered at sites on sev-  
  eral chromosomes.
* Poor prognosis is associated with thick tu-  
  mors and tumors arising from the palpebral or  
  caruncular conjunctiva.
* Giblin ME, Shields JA, Shields CL, Eagle RC Jr: Primary eyelid  
  malignant melanoma associated with primary conjunctival ma-  
  lignant melanoma.
* Adjuvant interferon has been associated with improved disease-free survival, but its impact on overall survival is unclear.
* Adjuvant interferon has been associated with improved disease-free survival, but its impact on overall survival is unclear.
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  t  
  Adjuvant interferon has been associated with improved disease-free survival, but its impact on overall survival is unclear.
* A higher radiotherapy dose is associated with more durable palliation and longer survival  
  in patients with metastatic melanoma.
* 7Administration of multiagent regimens and high-dose interleukin-2 is complex and associated with significant toxicities.
* Sev­  
  eral other studies have also confirmed the prognostic   
  importance of mitotic rate in patients with primary   
  cutaneous melanoma.10–12 In the evidence-based   
  derivation of the 2010 AJCC staging system, mitotic   
  rate greater than or equal to 1 per mm2 was inde­  
  pendently associated with worse disease-specific sur­  
  vival, especially in patients with melanoma less than   
  or equal to 1.0-mm thick.
* The randomized phase   
  III trial of adjuvant GM2-KLH21 in 1314 patients   
  with stage II melanoma (EORTC 18961) was closed   
  early by the data monitoring committee because of   
  inferior survival in the vaccine arm.79  
  A recent retrospective review of 200 patients   
  with melanoma (stage IIB, IIC, or III) reported that   
  those who had autoantibodies or clinical manifesta­  
  tions of autoimmunity after treatment with high-  
  NCCN Clinical Practice Guidelines in Oncology  
  Melanoma  
  © JNCCN–Journal of the National Comprehensive Cancer Network  |  Volume 10 Number 3  |  March 2012  
  388  
  dose interferon alfa-2b had improved relapse-free   
  and overall survivals compared with patients who   
  did not show manifestation of autoimmunity.80   
  Review of data combined from the randomized   
  controlled trials found that adjuvant interferon alfa   
  was not associated with improved overall survival in   
  patients with melanoma who were at increased risk   
  for recurrence.81 A pooled analysis of E1684, E1690,   
  and E1694 confirmed an improvement in relapse-  
  free survival in patients with high-risk resected mel­  
  anoma (2-sided log-rank P value = .006) but found   
  no significant improvement in overall survival.82  
  The ECOG studies included patients with stage   
  IIB (≥ 4.0 mm with no evidence of lymph node in­  
  volvement) and III melanomas with either regional   
  lymph node disease or in-transit metastases.
* A recent study of isolated limb infu­  
  sion in 128 patients showed a complete response rate   
  of 31%.96 However, a modified hyperthermic iso­  
  lated limb perfusion procedure was associated with   
  a higher complete response rate of 63%, with 5-year   
  survival observed in 38% of patients.97   
  Other therapies include intralesional local in­  
  jections with bacillus Calmette-Guérin (BCG)98 or   
  interferon alfa, laser ablation, and topical imiqui­  
  mod.99 Imiquimod may have some activity for small   
  superficial dermal lesions but not for subcutaneous   
  disease.100 RT is sometimes used; however, patients   
  with satellitosis are at risk for recurrence in the ra­  
  diated field.
* In a series of high-risk patients who   
  received adjuvant radiation, the only risk factor as­  
  sociated with in-field locoregional recurrence was   
  satellitosis.90  
  Systemic Therapy  
  Traditional Chemotherapy: Metastatic melanoma   
  is associated with a poor prognosis.
* Vemurafenib is a   
  specific inhibitor of signaling by mutated BRAF.116 A   
  randomized phase III trial compared vemurafenib with   
  dacarbazine in 675 patients with previously untreated   
  metastatic melanoma containing a V600 mutation of   
  BRAF.117 Vemurafenib was associated with improved   
  overall and progression-free survival (relative risk   
  [RR] of death, 0.37; RR of death or progression, 0.26;   
  P < .001).
* Ipilimumab is associated with   
  the potential for serious autoimmune toxicity, clini­  
  cal responses may take months to become apparent,   
  and the overall response rate is less than 20%.
* Vemurafenib, on the other hand, is associated with a   
  40% to 50% response rate in patients with a V600-  
  mutated BRAF gene, and responses may be seen days   
  to weeks after starting the drug.
* Additional   
  attempts to decrease toxicity of biochemotherapy   
  through administering subcutaneous outpatient   
  interleukin-2 did not show a substantial benefit of   
  biochemotherapy versus chemotherapy alone.123–125   
  A recent meta-analysis also showed that although   
  biochemotherapy improved overall response rates,   
  it was not associated with a survival benefit in pa­  
  tients with metastatic melanoma.126   
  Palliative Radiation Therapy: Contrary to common   
  perception that melanoma is radioresistant, RT often   
  achieves good palliation of symptomatic metastatic   
  disease.
* However, increasing   
  risk of systemic or brain relapse was associated with   
  higher substage, with stage IIIC having a 48% risk of   
  nonbrain recurrence and a 13% risk of brain involve­  
  ment.
* A higher radiotherapy   
  dose is associated with more durable palliation and longer survival   
  in patients with metastatic melanoma.
* In contrast,  
  the atypical cobblestone pattern, particularly when com-  
  posed of small nucleated cells (Figure 2), was strongly  
  associated with LM (OR of 13.3) but was uncommon  
  (6% of LM).
* When the pagetoid  
  cells were widespread, pleomorphic, in clusters of three, or  
  numerous (three or more pagetoid cells found on five images  
  of 0.5 0.5 mm2), they were strongly associated with LM,  
  with ORs 47.
* Dermal nests were very  
  rare (7 out of 81 LMs) and more associated with LM (OR of  
  4.7).
* Plump bright cells, particularly sparse within the  
  papillary dermis, were strongly associated with the LMs (OR  
  of 5.3).
* Broadened reticulated collagen fibers were mostly  
  associated with BMs of the face (58%), whereas collagen  
  bundles were mostly associated with LM but were present in  
  only 14% of biopsies.
* Some other pathology components of classical LM such as  
  thin epidermis, solar elastosis (corresponding to collagen  
  bundles), and melanophages (corresponding to plump bright  
  cells) were also found to be more closely associated with LM,  
  but were less significant than the aforementioned criteria.
* In  
  order of importance, these features were: cerebriform nests,  
  atypical cobblestone pattern with small nucleated cells in the  
  epidermis, marked cytological atypia, and pagetoid cells, and  
  disarranged epidermal layer with no honey comb recognized  
  in some areas were associated with the MM diagnosis.
* Large  
  inter-papillae spaces filled with honeycomb or cobblestone  
  aspect was negatively associated with MMs.
* Pathology review showed that three were  
  ‘‘early-stage’’ lentigo maligna, three were classic lentigo maligna,  
  two were in situ MMs of superficial spreading type associated  
  with nevi, three were thin (o1.0mm Breslow thickness)  
  superficial spreading MMs (associated with nevi in two cases),  
  and one was a superficial spreading MM associated with nevus  
  (2mm Breslow thickness).
* Overall, dermal melanocytic nevi were found  
  associated with 1126 of 1954 primary SSM/NM (57.6%).
* When the melanomas were stratified by tumor thickness, an inverse  
  relationship between the presence of benign nevus cells and tumor thickness was found: 64.9% of tumors less than 0.76 mm  
  and 64.5% of those between 0.76 and 1.69 mm were associated with dermal nevi, whereas in the thickness range  
  1.70–3.60 mm, there were 45.6% associated nevi, and in melanomas greater than 3.60 mm, there were only 32.0% noted to  
  have nevus cells.
* When melanomas were separated by nevus type, it was found that 41% were associated with an acquired  
  pattern nevus, 38% with congenital pattern nevus, and 21% with dysplastic nevus.
* 2) The congenital pattern nevus extends between  
  reticular dermal collagen bundles and is closely associated with  
  appendages, especially pilosebaceous units.
* By the preceding  
  definitions of melanocytic nevus, 42% of the SSM type were associ-  
  ated with acquired pattern nevi, 35% were found to have a congenital  
  pattern nevus, and 24% were associated with a nevus showing features  
  of dysplasia.
* Of the 94 NM tumors, 38% were associated with acquired pattern  
  nevi, 60% with congenital pattern nevi, and only 2% with dysplastic  
  nevi.
* Histologic dermal nevus associated with the melanoma was  
  found in 57.6% of 1954 patients with primary cutaneous malignant  
  melanomas.
* Numbers of Melanoma Cases Associated with  
  Dermal Melanocytic Nevi as a Function of Tumor  
  Thickness  
  Tumor Thickness  
  (mm)a  
  Total Cases of  
  Melanomab  
  Cases Associated with  
  Nevus (%)  
  o0.76  
  696  
  452 (64.9)  
  0.76–1.69  
  659  
  425 (64.5)  
  1.70–3.60  
  421  
  192 (45.6)  
  43.60  
  178  
  57 (32.0)  
  Total  
  1954  
  1126 (57.6)  
  aMillimeters by ocular microscopic on slide.
* Correlation of Melanocytic Nevus Type  
  Associated with Histogenetic Types of Melanoma  
  Nevus Type  
  SSM (%)  
  NM (%)  
  Total (%)  
  Acquired  
  298 (42)  
  36 (38)  
  333 (41)  
  Congenital  
  248 (35)  
  56 (60)  
  304 (38)  
  Dysplastic  
  168 (24)  
  2 (2)  
  171 (21)  
  Total  
  714  
  94  
  808  
  VOL.
* Other types, such as acral  
  lentiginous melanoma or those arising in lentigo maligna, were  
  seldom found associated with nevi in a preliminary search of  
  the data base, and they would only account for a maximum  
  10–15% dilution.
* Friedman et al [30], who studied 557 patients with  
  primary malignant melanoma, specifically excluded ‘‘melano-  
  mas associated with histologic evidence of congenital as  
  opposed to acquired melanocytic nevi’’; they also found that  
  23% of their series had histologic evidence of an acquired  
  melanocytic nevus in association with the melanoma.
* In an  
  earlier study using the same criteria and the same pathologist  
  [31], it was shown that 50% of in situ and 53% of thin  
  melanomas less than 0.76 mm were associated with precursor  
  nevi.
* Incidence by Tumor Thickness The results indicate a clear decrease in  
  the numbers of associated dermal nevi in contiguity with primary  
  melanoma of increasing tumor thickness.
* The contribution of Friedman et al [30] suggests a more favorable  
  prognosis in those melanomas associated with acquired melanocytic  
  nevi.
* Incidence of Nevus Type and Histogenetic Type In SSM associated with  
  nevi, 42% are of the acquired type; 35% are congenital nevi, and 24%  
  show features of dysplasia.
* In the case of NM, 38% were associated with acquired pattern nevi  
  and 60% were associated with congenital pattern nevi.
* Only two cases (2%) of NM were found to be associated with  
  dysplastic nevi.
* Although  
  this is somewhat higher than the present study, which found 24% of SSM  
  excisions associated with dysplastic nevi, Black also found only 9.8% of  
  nevi in SSM excisions without dysplasia (compared with 42% of SSM in  
  the present study).
* The overall  
  frequency of 57.6% of these tumors associated with nevi may be  
  somewhat elevated by the proportion of thin tumors in this series, but the  
  frequency of almost two-thirds of melanoma with thicknesses less than  
  1.70 mm associated with dermal nevi indicates that the majority of  
  melanomas may be associated with precursor nevi.
* Swerdlow AJ, English J, MacKie RM, et al Benign naevi associated with  
  high risk of melanoma.
* Friedman RJ, Rigel DS, Kopf AW, Leiblich L, Lew R, Harris MN,  
  Roses DF, Gumport SL, Ragaz A, Waldo E, Levine J, Levenstein M,  
  Koenig R, Bart RS, Trau H: Favorable prognosis for malignant melanomas  
  associated with acquired melanocytic nevi.
* Comparing equal or thinner than 1 mm melanomas and  
  thicker ones, epidermal disarray, cells in sheet-like structures,  
  cerebriform nests and nucleated cells within dermal papilla  
  were significantly associated with thick melanomas.
* We therefore  
  constructed composite indices of sun exposure during child-  
  hood and during adulthood, assuming additive combinations  
  of melanoma risk associated with each indicator of sun  
  exposure.
* Logistic regression modeling showed that the  
  melanoma risk associated with a given level of sun exposure  
  during adulthood increased with higher sun exposure during  
  childhood, but the increase in risk was higher than the simple  
  addition of melanoma risk associated with sun exposure  
  during childhood or adulthood.
* Table I lists the indicators relating to sun exposure that  
  emerged as associated with an increased melanoma risk at the p 5  
  0.10 level in a logistic model, as recommended when proceeding to  
  stepwise multivariate analysis (Kleinbaum et al., 1982).
* History of non-malignant skin  
  disease that lasted for 1 year or more was associated with a reduced  
  risk of melanoma, probably because subjects who suffered from  
  serious skin disease were generally more inclined to adopt sun  
  protection behavior patterns.
* For instance, the increase in melanoma risk associated with  
  Grant sponsor: Commission of the European Union; Grant number:  
  91CVV01177-0; Grant sponsor: Conseil Ge´ne´ral du Rhoˆne, France.
* Another example was the addition of the risk associated  
  with sunscreen use to the risk associated with duration of holidays  
  in sunny areas (Autier et al., 1996).
* The indicator ‘‘sunscreen  
  use’’ comprised 2 levels of risk because psoralen sunscreens  
  were a mixture of regular sunscreen and 5-methoxypsoralen,  
  and thus the melanoma risk associated with the presence of  
  5-methoxypsoralen had to be considered supplementary to  
  the risk associated with the use of regular sunscreens (Autier  
  et al., 1995).
* These relationships  
  were more pronounced among skin phototype I–II subjects (i.e.,  
  subjects with poor tanning ability), but were nonetheless present  
  among skin phototype III–IV subjects (i.e., subjects with good  
  TABLE I – MELANOMA RISK ASSOCIATED WITH SUN EXPOSURE INDICATORS  
  IN BELGIUM, FRANCE AND GERMANY (1991–1992)1  
  Sun exposure risk factors  
  Adjusted  
  OR  
  95% CI  
  Risk factors during childhood (0–14 years  
  old)2  
  1.
* The most  
  probable explanation for these observations is that sun protection  
  during childhood induced a better awareness of the dangers  
  associated with exaggerated exposure to sunlight (Autier et al.,  
  1994a).
* TABLE II – MELANOMA RISK ASSOCIATED WITH INDICES OF SUN EXPOSURE DURING CHILDHOOD  
  AND DURING ADULTHOOD  
  Indices added to basic model1  
  All subjects  
  Skin phototype III–IV  
  Skin phototype I–II  
  Adjusted  
  OR  
  95% CI  
  Adjusted  
  OR  
  95% CI  
  Adjusted  
  OR  
  95% CI  
  Sun exposure during childhood  
  Low (no risk factor)3  
  1.02  
  —  
  1.02  
  —  
  1.02  
  —  
  Medium (1 risk factor)  
  1.5  
  1.1–2.2  
  1.2  
  0.7–1.9  
  2.3  
  1.3–4.1  
  High (2 risk factors)  
  2.5  
  1.4–4.3  
  2.4  
  1.1–5.0  
  2.8  
  1.3–6.2  
  Sun exposure during adulthood  
  Low (no or 1 risk factor)  
  1.02  
  —  
  1.02  
  —  
  1.02  
  —  
  Moderate (2 risk factors)  
  1.5  
  1.0–2.5  
  1.5  
  0.8–2.7  
  1.7  
  0.8–3.7  
  High (3 risk factors)  
  3.4  
  2.0–5.5  
  2.9  
  1.6–5.3  
  4.2  
  2.0–9.1  
  Very high (4 risk factors)  
  3.4  
  2.1–5.4  
  3.0  
  1.6–5.6  
  4.0  
  1.8–8.9  
  Extreme (5–7 risk factors)  
  6.9  
  3.3–14.2  
  5.7  
  2.4–13.8  
  9.2  
  2.5–34.4  
  Sun exposure during childhood and  
  during adulthood  
  During childhood  
  Low (no risk factor)  
  1.02  
  —  
  1.02  
  —  
  1.02  
  —  
  Medium (1 risk factor)  
  1.8  
  1.2–2.5  
  1.3  
  0.8–2.1  
  2.9  
  1.6–5.5  
  High (2 risk factors)  
  2.5  
  1.4–4.2  
  2.3  
  1.1–4.9  
  3.0  
  1.3–6.9  
  During adulthood  
  Low (no or 1 risk factor)  
  1.02  
  —  
  1.02  
  —  
  1.02  
  —  
  Moderate (2 risk factors)  
  1.6  
  1.0–2.5  
  1.4  
  0.8–2.6  
  1.9  
  0.9–4.1  
  High (3 risk factors)  
  3.5  
  2.2–5.6  
  2.8  
  1.6–5.1  
  5.0  
  2.3–11.0  
  Very high (4 risk factors)  
  3.5  
  2.1–5.8  
  3.0  
  1.6–5.7  
  4.6  
  2.0–10.3  
  Extreme (5–7 risk factors)  
  7.4  
  3.6–15.5  
  5.7  
  2.4–13.9  
  12.1  
  3.1–47.5  
  1Basic model for all subjects includes exact age, gender, skin phototype and hair color.
* Our index of sun exposure during childhood was based on  
  broader data, and thus, probably that lesser recall bias was  
  associated with that index than when relying only upon the sunburn  
  experience.
* Results in Table IV are not an expression of lifetime exposure to  
  solar radiation.
* For instance, some studies done in  
  countries with year-round high ambient ultraviolet irradiation and  
  high melanoma incidence, such as Australia, found low melanoma  
  risk associated with sun exposure, with risk levels situated between  
  1.0 and 2.0 (Elwood and Jopson, 1997).
* In contrast, melanoma risk  
  associated with sun exposure was often found to be above 2.0 in  
  countries with less sunny weather year-round, e.g., Canada or  
  Northern Europe (Elwood and Jopson, 1997).
* As a result, and  
  because of the difficulty in assessing sun exposure during early life,  
  in Australia, the melanoma risk associated with intermittent sun  
  exposure during adulthood may have appeared as relatively low,  
  whereas it was found to be higher in Northern Europe or Canada.
* Cancer Causes Control, 2,  
  401–411 (1991).
* WEINSTOCK, M.A., COLDITZ, G.A., WILLET, W.C., STAMPFER, M.J., BRON-  
  STEIN, B.R., MIHN, M.C., JR. and SPEIZER, F.E., Nonfamilial cutaneous  
  melanoma incidence in women associated with sun exposure before 20  
  years of age.
* Adjuvant ipilimumab 10 mg/kg was associated with  
  immune-related adverse events (irAEs) in 94% of the  
  patients, and 5 patients died.
* The combination therapy was  
  associated with more toxicity than nivolumab alone.
* The D þ T combination was associated with pyrexia  
  grade 1e2 in 97% with chills in 37% and grade 3e4  
  pyrexia in 5%.
* The high rate of pyrexia associated with D þ T  
  can be reduced by using the management algorithm  
  investigated in the COMBI-Aplus trial.
* Treatment discontinuation associated with AE  
  was seen in 15.3% and 2.5% of the patients, respectively.
* Using AJCC as a criterion of  
  entry for adjuvant therapy results in two important  
  limitations: (1) a number of so-called high-risk patients  
  with stage III, or IIB-C disease are exposed to a  
  treatment, although they do not require it and (2)  
  AJCC low-risk stage I and IIA account for most of the  
  deaths in the end, because of their very high number.
* This  
  study addresses whether recurrence can be detected  
  earlier with ctDNA monitoring than with standard  
  clinical follow-up, and whether early treatment of  
  molecular recurrence with immunotherapy results in a  
  survival beneﬁt.
* Systemic therapy for metastatic disease  
  In the last decade, the increased knowledge about  
  signaling pathways associated with tumor development  
  and progression, and the molecular mechanisms of  
  signaling and controlling of the immune system trans-  
  formed the survival outcomes of melanoma patients  
  [110,111].
* Monotherapy with anti-CTLA-4 and anti-PD-1  
  Blockade of immune checkpoint mechanisms with an-  
  tibodies to CTLA-4 and PD-1 expressed by lymphocytes  
  abrogates down-regulation of immune responses and  
  leads to continued activation of lymphocytes, enabling  
  killing of tumor cells.
* This  
  exploratory analysis showed that pembrolizumab was  
  associated with improved clinical outcomes regardless of  
  BRAF status, prior BRAF/MEK inhibitors therapy,  
  high LDH level, larger tumor size, or presence of brain  
  metastases.
* Local therapy  
  Melanoma often metastasizes to the brain, which is  
  associated with a worse prognosis.
* In the CheckMate 067 trial, 91 patients in the nivo-  
  lumab arm received subsequent systemic therapy with  
  ipilimumab, but the survival beneﬁt associated with this  
  second line was not reported.
* The process of producing TILs is technically chal-  
  lenging, and concomitant administration of IL-2 is  
  associated with signiﬁcant toxicity.
* In  
  acral melanoma, treatment with anti-PD-1 (n Z 330)  
  was associated with signiﬁcantly better OS at 12 months  
  (53%) than patients treated with anti-CTLA-4 therapies  
  (n Z 94) (34% survival at 12 months, P < 0.001) [192].
* A  
  higher radiotherapy dose is associated with more durable palli-  
  ation and longer survival in patients with metastatic melanoma.

# Conclusión General

Los documentos revisados sugieren que los melanomas son peligrosos y deben tratarse con cuidado médico.