Published in final edited form as:

Ann Epidemiol. 2008 March ; 18(3): 214–221.

Cutaneous melanoma and obesity in the Agricultural Health Study

Leslie K. Dennis, MS, PhD¹, John B. Lowe, DrPH, FAHPA, FAAHB², Charles F. Lynch, MD, PhD¹, and Michael C. R. Alavanja, DrPH³

¹Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA, USA

²Department of Community and Behavioral Health, College of Public Health, University of Iowa, Iowa City, IA, USA

³Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA

Abstract

Purpose—To describe the risk of cutaneous melanoma in the Agricultural Health Study (AHS), a cohort of pesticide applicators and their spouses, according to baseline characteristics related to obesity along with sun exposure, and sun sensitivity.

Methods—The AHS cohort was enrolled in Iowa and North Carolina during 1993–97 and followed through 2003 for cancer incidence. We identified 315 cases of cutaneous melanoma, which reduced to 168 incident cases among subjects reporting height, weight, sun sensitivity and sun exposure information (on the spouse questionnaire or take home applicator questionnaire; n=44,086). Unconditional multiple logistic regression models were used to obtain adjusted odds ratios (OR) and 95% confidence intervals (95% CI).

Results—The results were consistent with prior studies of melanoma that indicate an association with measures of sun sensitivity. The highest category of body surface area (BSA; OR=2.6; 95% CI of 1.5–4.4) and body mass index (BMI; OR=2.5; 95% CI of 1.5–4.3) at age 20 were significantly associated with melanoma. There was some evidence for an association with BSA, but not BMI, at enrollment.

Conclusions—Obesity was associated with an increased risk of melanoma, indicating strategies to control obesity may result in risk reduction for melanoma.

Keywords

melanoma; sun sensitivity; obesity; farmers; Body Mass Index; Body Surface Area; Lentigo Maligna; Agricultural Health Study

INTRODUCTION

Cutaneous melanoma has consistently been associated with intermittent sun exposure such as sunburns or sunny vacations.^{1,2} Occupational exposure to the sun tends to be of a chronic nature and its relationship to the development of cutaneous melanoma is not as clear.^{2–6} It is unclear if the conflicting associations may be due to uncontrolled confounding by skin sensitivity to the sun (fair skin color, light eye and hair color, or a tendency to burn easily).

Correspondence to: Leslie K. Dennis, Department of Epidemiology, College of Public Health, University of Iowa, 200 Hawkins Drive, C21H-GH, Iowa City, IA 52242, (319) 384-5010, Fax: (319) 384-5004, e-mail: leslie-dennis@uiowa.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Armstrong¹ suggested that the relationship is complex and may be best described by an inverse U-shaped curve for chronic sun exposure theoretically due to different rates of melanoma in untanned individuals and those who develop and maintain a tan.

While sun exposure and sun sensitivity are fairly well understood as related to melanoma, the relationship of skin surface area is less well understood. Melanoma studies have looked at weight or body mass index (BMI) calculated from weight and height, primarily as a measure of obesity. However, for melanoma such associations may be related to obesity or may be related to a larger skin surface area representing more skin cells that can convert to cancer. Thus, body surface area (BSA), also based on weight and height, may be more useful in quantifying melanoma risk than either weight alone or BMI. Either way, a better understanding of the association between melanoma and obesity will help in designing prevention efforts.

We conducted a study within an existing cohort of pesticide applicators (typically farmers) and their spouses in Iowa and North Carolina. The study objective was to describe the risk of cutaneous melanoma among pesticide applicators and their spouses according to baseline characteristics related to obesity, sun exposure, and sun sensitivity.

MATERIALS AND METHODS

The Agricultural Health Study is a prospective cohort study of private applicators and commercial applicators licensed to apply restricted use pesticides in Iowa and North Carolina, along with the spouses of private applicators.⁷ Among the applicators, 95% are private applicators or farmers. Less than 2% are non-white. Private applicators are typically farmers, while “commercial” applicators are employed by pest control companies or businesses that use pesticides.

In Iowa and North Carolina, individuals who want to apply restricted-use pesticides must undergo training or testing every few years to become licensed to purchase restricted-use pesticides.⁷ Pesticide applicators were enrolled in the Agricultural Health Study when they voluntarily completed an Enrollment Questionnaire in conjunction with seeking training or testing for pesticide applicator licensure. Private and commercial applicators were also asked to complete a “take-home” Applicator Questionnaire that sought more extensive information on occupational activities. Their spouses were asked to complete a Spouse Questionnaire (all questionnaires are at <http://www.aghealth.org/questionnaires.html>). Enrollment of applicators and their spouses began in December 1993 and continued until December 1997.

The take-home Applicator Questionnaire and the Spouse Questionnaire included information on height and weight, hours in the sun during the growing season, type of sun protection, eye color, natural hair color, and tendency to burn. Tendency to sunburn was defined as the skin’s reaction the first time in strong sunlight for more than one hour each year. Skin phototype was not measured. Height and weight were self-reported by participants at enrollment along with reporting their weight at 20 years of age. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. BSA was calculated using Mosteller’s formula (square-root of height times weight in meters and kilograms, respectively).⁸ The take-home Applicator Questionnaire and Spouse Questionnaire were completed by 25,290 applicators and 32,347 spouses. Height and/or weight data were missing for 3,143 applicators and 10,289 spouses. Extreme outliers suggested some subjects who may have miss-checked their height or weight, producing a BMI < 15 (unlikely except in hospitalized anorexia patients). Thus, we excluded 119 subjects from analyses: 27 with height over 7’, 63 with height under 4’8” (most under 4’) and 29 additional subjects with a BMI < 15. Analyses were restricted to 22,101 applicators and 21,985 spouses with data on height and weight from AHS data release P1REL0506.02. No

difference in percentage of melanoma cases was seen between those included in this report and those excluded (chi square $p=0.94$).

Follow-up

Cohort members were matched to statewide cancer registry files in Iowa and North Carolina for case identification and to the state death registries and the National Death Index to ascertain vital status. The average follow-up time was 8.2 years. Study subjects alive but no longer residing in Iowa or North Carolina were identified through personal contacts with the study subject, motor vehicle records, pesticide registration records, and an Internal Revenue Service address database. Less than 2% ($n=827$) of applicators have moved out of either state.

Analyses—Descriptive statistics were used to compare overall cutaneous melanoma cases to this sub-cohort. Odds ratios (ORs) and 95 percent confidence intervals (CIs) were derived from unconditional multiple logistic regression. We examined the independent effect of obesity measured via weight, BMI, and BSA. We report both crude and adjusted associations between melanoma and measures of sun sensitivity (tendency to burn, hair color, and eye color), since debate remains regarding adjusting host factors. Other risk factors examined included sun protection while in the sun during the growing season, self-reported personal history of skin cancer, family history of skin cancer, and hours per day spent in the sun during the growing season at enrollment and 10 years prior to enrollment. Other items examined as potential measures of sun exposure in this group included years living on a farm, summer and winter hours per week spent exercising during leisure time, number of acres planted along with whether or not they planted crops, handpicked crops, tilled the soil or used a tractor with an enclosed cab. We examined each of these factors adjusted for the important confounders described as follows, but only report estimates adjusted for the factors that actually confounded the associations. Confounding by age, gender, tendency to burn, red hair color, personal or family history of skin cancer, hours in the sun (at enrollment and 10 years prior), sunscreen use, and sun protection use (sunscreen, a hat with a brim, or long sleeved shirt) was examined. Confounding was determined to be present by changes of 15% or more in the OR of interest after adjustment for a potential confounder. While a parsimonious model increases the precision of estimates, ORs more fully adjusted for factors confounding other items presented in tables were similar to individually adjusted ORs without appreciable loss of precision, thus the more fully adjusted ORs are presented in the tables. However, this is not true if all factors examined in any analyses were included in the models, so saturated models are not presented.

Trend p values are reported for ordered categorical variables. Trend ORs and 95 percent CIs comparing the highest category with the reference category are also presented. The trend OR fits a line to the β coefficients for each category, assuming an equal increase in the log (OR) for each category level. If a linear model did not fit, then a quadratic model was examined to determine the strength of the curvilinear model (inverse U-shaped in these data). Such estimates were compared to estimates using dummy variables. If similar, then the unconfined estimates based on dummy variables are presented for easier interpretation.

RESULTS

Among those completing the take-home or spouse questionnaire, 168 cases of cutaneous melanoma were reported after enrollment through December 31, 2003. Table 1 compares cutaneous melanoma characteristics in the overall enrolled cohort ($N=89,658$) to subjects included in this report ($N=44,086$). Similar distributions by histological type and location on the body were seen between subjects examined in this report and the entire cohort.

Table 2 compares cutaneous melanoma cases and non-cases by various demographic factors. Melanoma cases tended to be older and male. Other factors including ethnicity (white vs.

nonwhite), state of residence (Iowa, North Carolina), education, and marital status did not vary by case status. Commercial applicators did not differ significantly from private applicators in melanoma risk, nor did spouses after adjustment for age and sex.

The relationships between cutaneous melanoma and sun sensitivity and sun exposure in this population are described in Table 3. Among these applicators and their spouses, the strongest sun sensitivity factors related to melanoma were having red hair and tendency to burn (only marginally significant). Use of sun protection showed an increased risk of melanoma, however, this association was reduced after adjustment for age, gender, tendency to burn and hair color. An inverse U-shaped trend ($p=0.003$ for the quadratic model) was seen across categories of hours per day of sun exposure at enrollment (Table 3). When the highest category, more than 10 hours per day, was compared to 10 hours or less (all other categories), the apparent protective association with cutaneous melanoma strengthened ($OR=0.32$; 95% $CI=0.13-0.77$). However, these data are based on a limited number of cases. Among applicators, a crude association was seen with categorical data for years lived or worked on a farm (over 30 years vs. 30 years or less) and melanoma ($OR=2.80$; 95% $CI=1.50-5.22$), but this association reduced after adjustment for age ($OR=1.71$; 95% $CI=0.90-3.25$). For spouses, years living or working on a farm was measured continuously and the risk of melanoma increased with increasing number of decades on a farm with a significant risk for over 60 years (compared to under 60 years) even after adjustment for age ($OR=2.19$; 95% $CI=1.15-4.17$). No associations were seen for other variables that might be related to sun exposure or with self-reported family history of skin cancer. Skin cancer prior to AHS enrollment did not confound any of the associations reported here.

Table 4 describes the relationship between cutaneous melanoma and weight at enrollment (1994-1997) and at age 20, along with BMI and BSA based on these two reported weights and heights. Height alone was not associated with risk of melanoma. The data suggest an increased risk with increased weight at age 20. No association was seen with BMI at enrollment, however, risk increased with increasing BMI at age 20. The associations with BSA were stronger. Cutaneous melanoma was significantly associated with BSA at age 20, with some evidence for an association at enrollment.

DISCUSSION

Our data, among pesticide applicators and their spouses in Iowa and North Carolina, support an association between melanoma and increased BSA and BMI at age 20. There is a marginal risk of melanoma seen with BSA at enrollment. The stronger association with BSA at age 20 may reflect a latency period needed for development of melanoma. Obesity is difficult to quantify based on weight alone. BMI is a measure that attempts to adjust an individual's weight for their height, whereas BSA attempts to estimate the skin surface area of an individual based on their height and weight. Since both measures are based on height and weight, they are two different mathematical representations of the same data. However, they are conceptually different. BMI is more commonly reported, however, BSA is conceptually more important for skin cancer since the association with melanoma could be related to obesity or may be related to a larger skin surface area with more skin cells and consequently a greater opportunity for skin cancer development. Thus we reported both. BSA and BMI based on recalled weight at age 20, each showed an increased risk of cutaneous melanoma as they increased, suggesting a latency affect. These associations increased after adjustment for confounding factors (age, gender, and tendency to burn). We also found a suggested association with BSA at enrollment but not BMI. However, our data are limited since height and weight are recalled, not measured. A case-control study of Italian women found an increased risk of melanoma with increasing BMI and with BSA >1.7 after adjustment, suggesting that BSA is independent of nevi.⁹ However, nevi are typically considered to be precursor lesions to cutaneous melanoma, thus

adjustment for nevi would dilute the real association. Thus while we could not adjust for number of nevi in our study, we believe that such adjustment is inappropriate. Other studies reporting on anthropometric associations have varied with reports of an increased risk of melanoma with increased BMI,¹⁰ increased BSA,¹¹ increased BSA but not BMI,^{12,13} increased with both BMI and BSA,¹⁴ while another study found no association.¹⁵ Our data support some of these prior reports, showing an association with BSA particularly at age 20 among this cohort of agricultural workers and their spouses. Whether this risk is related to “fat” or a larger surface area for skin lesions to develop, it is related to obesity. Thus efforts to reduce obesity may assist skin cancer prevention efforts.

Our data also support prior studies that have shown cutaneous melanoma risk to increase with a tendency to sunburn,^{12,16-22} and natural red hair color,^{11,12,16-20,23,24} and with age^{12,23,24} along with increased melanoma rates among males.²⁵ Although this population is predominant white (98%), only 29% of the cohort reported experiencing a severe or painful sunburn when first exposed to the sun in the summer. Among these applicators and their spouses, tendency to burn and having red hair are good markers of sun sensitivity showing an increased risk of cutaneous melanoma. As with several other populations in the United States^{23,26-28} and Canada,²⁹ eye color does not appear to be a good marker of melanoma risk. There was some evidence of an inverse U-shaped association between hours in the sun and melanoma, with a protective risk at the highest level of exposure.

While our data are limited, we saw an inverse U-shaped risk of cutaneous melanoma among farmers and their spouses with four categories of hours per day in the sun during the growing season. Armstrong¹ suggested a peak in melanoma incidence produced by intermittent intense sun exposure of untanned skin, followed by a fall in incidence presumed to be due to the development and maintenance of a protective tan. However, few studies have shown supporting evidence of this theoretical model. Prior studies have had conflicting reports about chronic sun exposure and risk of melanoma.^{21,30-32} While some of these studies adjusted for confounding by sun sensitivity, those working long hours outdoors may be more likely to be less sensitive to the sun reducing their risk of melanoma based on their darker complexion (as Armstrong suggests). Among our farmers and their spouses, we saw an inverse U-shaped association with melanoma. This may reflect both intermittent sun exposure mainly among spouses and more chronic exposure among applicators creating a complex relationship with melanoma as described by Armstrong.¹ One other study found an inverse U-shaped association with estimated occupational hours of sun exposure,³³ while several others found no clear association.³⁴⁻³⁷ An increased risk of melanoma was seen in two studies that adjusted for skin color and skin type,^{38,39} however, no clear association was seen for hours working outdoors in the summer as an adult adjusted for age, gender and skin type in another study³⁰ or cumulative occupational sun exposure adjusted for burn reaction to the sun in males.⁴⁰

Long-term cumulative sun exposure is believed to induce lentigo maligna (LM), a specific histological type of melanoma as seen with high rates in places like Australia.⁴¹ The distribution of histological types of cutaneous melanomas in our study found 46% of in-situ cases to be lentigo maligna compared to 7% of malignant cases. This is slightly higher than the 35% of in-situ cases reported as lentigo maligna in the national SEER data but similar to the 48% seen in SEER data restricted to Iowa.⁴² Compared to other studies with cases diagnosed prior to 1990,^{31,43-45} we found a higher percentage of melanomas of the head (33%). Analyses of risk factors for lentigo maligna and cutaneous melanomas of the head showed similar or stronger associations compared with all melanomas for tendency to burn and for natural red hair color. However, as expected they were more common after age 50 and increased with 3+ hours per day in the sun during growing season at enrollment and 10 years prior. These data are not presented due to the small number of cases (38 lentigo malignas and 52 cutaneous melanomas of the head).

This population has several strengths. Overall the Agricultural Health Study has had high participation rates. Although it had a longer enrollment questionnaire (17 pages) than the British Doctors Study, the Nurse's health Study, the Lutheran Brotherhood Study or the Radiologic technologist Study, the Agricultural Health Study had a higher enrollment rate than any of these studies.⁴⁶ Previous analyses have shown that Agricultural Health Study applicators completing the take-home questionnaire were similar to those who only completed the enrollment questionnaire with the exception that those completing the take-home questionnaire tended to be older.⁴⁶ Little or no difference was seen by years of education, marital status, smoking status, frequency of alcohol consumption, or previous disease diagnoses. Only minor differences in a few cell frequencies were seen by various farming activities. The lack of evidence for selection bias is reassuring. This suggests restricting applicators to those completing the take-home questionnaire (sun sensitivity, sun exposure, height and weight) is unlikely to bias exposure estimates. A comparison of the incident cutaneous melanoma cases seen in the overall cohort compared to the take-home questionnaire showed similar distributions by histological site and body site. Additionally in sub-analyses, we found ORs similar to other studies for known sun sensitivity risk factors for melanoma.

Conclusions

These data support an association between obesity at age 20 and melanoma and also support prior associations between melanoma and sun sensitivity factors. While height and weight data were only available on the sub-cohort who completed the take-home questionnaires, comparisons between subjects included in these analyses and the overall cohort (described above) suggest that the results we present are not biased by who completed the take-home questionnaire. Relevant to public health, we observed that obesity at a young age increases the risk of cutaneous melanoma later in life, and our data suggest the development of cutaneous melanoma may not be effected by changing lifestyles later in life. The need for obesity prevention programs directed at youth may be critical to reduce a number of health concerns including cutaneous melanoma.

Acknowledgments

This research was supported in part by the National Cancer Institute, grant number 5K07CA104556.

Abbreviations

CI, confidence interval.
OR, odds ratio..

REFERENCES

1. Armstrong BK. Epidemiology of malignant melanoma: intermittent or total accumulated exposure to the sun? *J Dermatol Surg Oncol* 1988;14(8):835–49. [PubMed: 3397443]
2. Armstrong BK, Krickler A, English DR. Sun exposure and skin cancer. *Australas J Dermatol* 1997;38 (Suppl 1):S1-6. [PubMed: 10994463]
3. Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. *Int J Cancer* 1997;73(2):198–203. [PubMed: 9335442]
4. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, Melchi CF. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer* 2005;41(1):45–60. [PubMed: 15617990]
5. Hakansson N, Floderus B, Gustavsson P, Feychting M, Hallin N. Occupational sunlight exposure and cancer incidence among Swedish construction workers. *Epidemiology* 2001;12(5):552–7. [PubMed: 11505175]

6. Espinosa Arranz J, Sanchez Hernandez JJ, Bravo Fernandez P, Gonzalez-Baron M, Zamora Aunon P, Espinosa Arranz E, Jalon Lopez JJ, Ordonez Gallego A. Cutaneous malignant melanoma and sun exposure in Spain. *Melanoma Res* 1999;9(2):199–205. [PubMed: 10380943]
7. Alavanja MC, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, Pennybacker M, Rothman N, Dosemeci M, Bond AE, Blair A. The Agricultural Health Study. *Environ Health Perspect* 1996;104(4):362–9. [PubMed: 8732939]
8. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987;317(17):1098. [PubMed: 3657876]
9. Naldi L, Altieri A, Imberti GL, Giordano L, Gallus S, La Vecchia C. Cutaneous malignant melanoma in women. Phenotypic characteristics, sun exposure, and hormonal factors: a case-control study from Italy. *Ann Epidemiol* 2005;15(7):545–50. [PubMed: 16029848]
10. Kirkpatrick CS, White E, Lee JA. Case-control study of malignant melanoma in Washington State. II. Diet, alcohol, and obesity. *Am J Epidemiol* 1994;139(9):869–80. [PubMed: 8166137]
11. Veierod MB, Weiderpass E, Thorn M, Hansson J, Lund E, Armstrong B, Adami HO. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. *J Natl Cancer Inst* 2003;95(20):1530–8. [PubMed: 14559875]
12. Shors AR, Solomon C, McTiernan A, White E. Melanoma risk in relation to height, weight, and exercise (United States). *Cancer Causes & Control* 2001;12(7):599–606. [PubMed: 11552707]
13. Thune I, Olsen A, Albrektsen G, Tretli S. Cutaneous malignant melanoma: association with height, weight and body-surface area. a prospective study in Norway. *Int J Cancer* 1993;55(4):555–61. [PubMed: 8406981]
14. Gallus S, Naldi L, Martin L, Martinelli M, La Vecchia C. Anthropometric measures and risk of cutaneous malignant melanoma: a case-control study from Italy. *Melanoma Res* 2006;16(1):83–7. [PubMed: 16432461]
15. Freedman DM, Sigurdson A, Rao RS, Hauptmann M, Alexander B, Mohan A, Morin Doody M, Linet MS. Risk of melanoma among radiologic technologists in the United States. *Int J Cancer* 2003;103(4):556–62. [PubMed: 12478675]
16. Han J, Colditz GA, Hunter DJ. Risk factors for skin cancers: a nested case-control study within the Nurses' Health Study. *Int J Epidemiol* 2006;35(6):1514–21. [PubMed: 16943234]
17. Youl P, Aitken J, Hayward N, Hogg D, Liu L, Lassam N, Martin N, Green A. Melanoma in adolescents: a case-control study of risk factors in Queensland, Australia. *Int J Cancer* 2002;98(1):92–8. [PubMed: 11857391]
18. Osterlind A, Tucker MA, Hou-Jensen K, Stone BJ, Engholm G, Jensen OM. The Danish case-control study of cutaneous malignant melanoma. I. Importance of host factors. *Int J Cancer* 1988;42(2):200–6. [PubMed: 3403065]
19. Naldi L, Lorenzo Imberti G, Parazzini F, Gallus S, La Vecchia C. Pigmentary traits, modalities of sun reaction, history of sunburns, and melanocytic nevi as risk factors for cutaneous malignant melanoma in the Italian population: results of a collaborative case-control study. *Cancer* 2000;88(12):2703–10. [PubMed: 10870052]
20. Kaskel P, Sander S, Kron M, Kind P, Peter RU, Krahn G. Outdoor activities in childhood: a protective factor for cutaneous melanoma? Results of a case-control study in 271 matched pairs. *British Journal of Dermatology* 2001;145(4):602–9. [PubMed: 11703287]
21. White E, Kirkpatrick CS, Lee JA. Case-control study of malignant melanoma in Washington State. I. Constitutional factors and sun exposure. *Am J Epidemiol* 1994;139(9):857–68. [PubMed: 8166136]
22. Beane Freeman LE, Dennis LK, Lynch CF, Thorne PS, Just CL. Toenail arsenic content and cutaneous melanoma in Iowa. *Am J Epidemiol* 2004;160(7):679–87. [PubMed: 15383412]
23. Cho E, Rosner BA, Feskanich D, Colditz GA. Risk factors and individual probabilities of melanoma for whites. *J Clin Oncol* 2005;23(12):2669–75. [PubMed: 15837981]
24. Solomon CC, White E, Kristal AR, Vaughan T. Melanoma and lifetime UV radiation. *Cancer Causes Control* 2004;15(9):893–902. [PubMed: 15577291]
25. Ries, LAG.; Melbert, D.; Krapcho, M.; Mariotto, A.; Miller, BA.; Feuer, EJ.; Clegg, L.; Horner, MJ.; Howlander, N.; Eisner, MP.; Reichman, M.; Edwards, BK. SEER Cancer Statistics Review,

- 1975-2004. National Cancer Institute; Bethesda, MD: 2007. http://seer.cancer.gov/csr/1975_2004/, based on November 2006 SEER data submission, posted to the SEER web site, 2007
26. Wei Q, Lee JE, Gershenwald JE, Ross MI, Mansfield PF, Strom SS, Wang LE, Guo Z, Qiao Y, Amos CI, Spitz MR, Duvic M. Repair of UV light-induced DNA damage and risk of cutaneous malignant melanoma. *J Natl Cancer Inst* 2003;95(4):308–15. [PubMed: 12591987]
 27. Moore DH 2nd, Patterson HW, Hatch F, Discher D, Schneider JS, Bennett D, Mendelsohn ML. Case-control study of malignant melanoma among employees of the Lawrence Livermore National Laboratory. *Am J Ind Med* 1997;32(4):377–91. [PubMed: 9258392]
 28. Cockburn M, Black W, McKelvey W, Mack T. Determinants of melanoma in a case-control study of twins (United States). *Cancer Causes & Control* 2001;12(7):615–25. [PubMed: 11552709]
 29. Gallagher RP, Elwood JM, Hill GB. Risk factors for cutaneous malignant melanoma: the Western Canada Melanoma Study. *Recent Results Cancer Res* 1986;102:38–55. [PubMed: 3738186]
 30. Bataille V, Winnett A, Sasieni P, Newton Bishop JA, Cuzick J. Exposure to the sun and sunbeds and the risk of cutaneous melanoma in the UK: a case-control study. *Eur J Cancer* 2004;40(3):429–35. [PubMed: 14746862]
 31. Walter SD, King WD, Marrett LD. Association of cutaneous malignant melanoma with intermittent exposure to ultraviolet radiation: results of a case-control study in Ontario, Canada. *International Journal of Epidemiology* 1999;28(3):418–27. [PubMed: 10405843]
 32. Holman CD, Armstrong BK, Heenan PJ. Relationship of cutaneous malignant melanoma to individual sunlight-exposure habits. *J Natl Cancer Inst* 1986;76(3):403–14. [PubMed: 3456458]
 33. Elwood JM, Gallagher RP, Hill GB, Pearson JC. Cutaneous melanoma in relation to intermittent and constant sun exposure--the Western Canada Melanoma Study. *Int J Cancer* 1985;35(4):427–33. [PubMed: 3988369]
 34. Rosso S, Zanetti R, Pippione M, Sancho-Garnier H. Parallel risk assessment of melanoma and basal cell carcinoma: skin characteristics and sun exposure. *Melanoma Res* 1998;8(6):573–83. [PubMed: 9918420]
 35. Elwood JM, Williamson C, Stapleton PJ. Malignant melanoma in relation to moles, pigmentation, and exposure to fluorescent and other lighting sources. *Br J Cancer* 1986;53(1):65–74. [PubMed: 3947517]
 36. Loria D, Matos E. Risk factors for cutaneous melanoma: a case-control study in Argentina. *Int J Dermatol* 2001;40(2):108–14. [PubMed: 11328391]
 37. Landi MT, Baccarelli A, Calista D, Pesatori A, Fears T, Tucker MA, Landi G. Combined risk factors for melanoma in a Mediterranean population. *British Journal of Cancer* 2001;85(9):1304–10. [PubMed: 11720465]
 38. Rodenas JM, Delgado-Rodriguez M, Herranz MT, Tercedor J, Serrano S. Sun exposure, pigmentary traits, and risk of cutaneous malignant melanoma: a case-control study in a Mediterranean population. *Cancer Causes Control* 1996;7(2):275–83. [PubMed: 8740740]
 39. Beane Freeman, LE. Arsenic exposure, artificial tanning and melanoma in Iowa [dissertation]. Univ. of Iowa; 2003.
 40. Graham S, Marshall J, Haughey B, Stoll H, Zielezny M, Brasure J, West D. An inquiry into the epidemiology of melanoma. *Am J Epidemiol* 1985;122(4):606–19. [PubMed: 4025303]
 41. Holman CD, Armstrong BK. Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: an analysis separating histogenetic types. *J Natl Cancer Inst* 1984;73(1):75–82. [PubMed: 6588237]
 42. Surveillance, Epidemiology, and End Results (SEER). National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; Program(www.seer.cancer.gov). SEER*Stat Database: Incidence-SEER 17 Regs Public-Use, Nov 2005 Sub (1973-2003 varying)-Linked to County Attributes-Total U.S., 1969-2003 Counties released April 2006, based on the November 2005 submission
 43. Dubin N, Moseson M, Pasternack BS. Epidemiology of malignant melanoma: pigmentary traits, ultraviolet radiation, and the identification of high-risk populations. *Recent Results Cancer Res* 1986;102:56–75. [PubMed: 3738187]

44. Cress RD, Holly EA, Ahn DK, LeBoit PE, Sagebiel RW. Cutaneous melanoma in women: anatomic distribution in relation to sun exposure and phenotype. *Cancer Epidemiol Biomarkers Prev* 1995;4(8):831–6. [PubMed: 8634653]
45. Chen YT, Dubrow R, Holford TR, Zheng T, Barnhill RL, Fine J, Berwick M. Malignant melanoma risk factors by anatomic site: a case-control study and polychotomous logistic regression analysis. *Int J Cancer* 1996;67(5):636–43. [PubMed: 8782651]
46. Tarone RE, Alavanja MC, Zahm SH, Lubin JH, Sandler DP, McMaster SB, Rothman N, Blair A. The Agricultural Health Study: factors affecting completion and return of self-administered questionnaires in a large prospective cohort study of pesticide applicators. *Am J Ind Med* 1997;31(2):233–42. [PubMed: 9028440]

Table 1

Cutaneous melanoma characteristics diagnosed 1994-2003 in the Agricultural Health Study cohort

	Incident Cutaneous Melanoma	
	Cases among Enrolled Cohort (n=315) N (%)	Cases presented in analyses (n=168) N (%)
<u>Malignant cutaneous melanomas</u>	203 (64.4%)	108 (64.3%)
<u>In-situ cutaneous melanomas</u>	112 (35.6%)	60 (35.7%)
	Chi Square P-value [†]	p=0.95
<u>Histological type</u> [*]		
<u>In situ (n=112)</u>		
SSM	6 (5.4%)	2 (3.3%)
LM	51 (45.5%)	30 (50.0%)
NM	0 (0.0%)	0 (0.0%)
NOS	55 (49.1%)	28 (46.7%)
Other	0 (0.0%)	0 (0.0%)
	Chi Square P-value [†]	p=0.43
<u>Malignant (n=203)</u>		
SSM	95 (46.8%)	53 (49.1%)
LM	14 (6.9%)	8 (7.4%)
NM	23 (11.3%)	12 (11.1%)
NOS	64 (31.5%)	34 (31.5%)
Other	7 (3.4%)	1 (0.9%)
	Chi Square P-value [†]	p=0.33
<u>Body site location</u>		
Head and neck	105 (33.3%)	52 (31.0%)
Trunk	87 (27.6%)	40 (23.8%)
Upper limbs (arms, shoulders and hands)	56 (17.8%)	34 (20.2%)
Lower limbs (legs, hips and feet)	53 (16.8%)	35 (20.8%)
NOS	14 (4.4%)	7 (4.2%)
	Chi Square P-value [†]	p=0.12

* SSM= superficial spreading melanoma; LM=lentigo melanoma; NM= nodular melanoma; NOS= not otherwise specified; Other includes amelanotic melanomas, acral lentiginous melanomas, desmoplastic/neurotropic melanomas and spindle cell, NOS.

[†] Comparing those in the analyses(n=168) to those not in the analyses (n=147).

Table 2
Risk of cutaneous melanoma for demographic characteristics in the Agricultural Health Study*

	Melanoma Cases (n=168) N (%)	Non-cases (n=43,918) N (%)	Chi-square	Crude OR (95% CI)	Adjusted # OR (95% CI)
Age					
12-39	22 (13%)	12,920 (30%)			ref [#]
40-49	35 (21%)	11,897 (27%)		1.73 (1.01-2.95)	1.72 (1.01-2.94)
50-59	38 (23%)	10,278 (23%)		2.17 (1.28-3.67)	2.17 (1.28-3.68)
60-93	73 (43%)	8,823 (20%)	<0.001	4.86 (3.01-7.83)	4.82 (2.97-7.82)
Trend OR age 60-93 vs. 12-39				Trend OR=4.8 (3.1-7.4)	Trend OR=4.7 (3.0-7.3)
Gender					
Females	72 (43%)	22,337 (51%)			ref [#]
Males	96 (57%)	21,581 (49%)	0.04	1.38 (1.02-1.87)	1.83 (0.54-6.25)
Cohort group					
Applicators					
Commercial	6 (3%)	2,317 (5%)		0.57 (0.25-1.30)	0.79 (0.34-1.83)
Private	90 (54%)	19,688 (45%)		ref	ref [#]
Spouses	72 (43%)	21,913 (50%)	0.07	0.72 (0.53-0.98)	1.42 (0.42-4.84)

* Analyses are restricted to applicators returning the take home questionnaire & spouses returning the mailed spouse questionnaire

adjusted for age at enrollment, gender, cohort group (commercial, spouse), state of residence

Table 3
Risk of cutaneous melanoma for sun sensitivity and sun exposure factors in the Agricultural Health Study*

	Melanoma Cases (n=168) N (%)	Non-cases (n=43,918) N (%)	Crude OR (95% CI)	Adjusted OR [‡] (95% CI)
<u>Sun Sensitivity Factors</u>				
Tendency to burn				
No or mild sunburn	107 (64%)	31,306 (71%)	ref	ref
Blistering or painful sunburn	61 (36%)	12,434 (28%)	1.44 (1.05-1.97)	1.34 (0.96-1.86)
(missing)	0 (0%)	178 (0.4%)		
Hair color				
Black/brown/blonde	147 (88%)	41,850 (95%)	ref	ref
Red	17 (10%)	1,489 (3%)	3.25 (1.96-5.38)	2.93 (1.74-4.95)
(missing)	4 (2%)	579 (1%)		
Eye color				
Brown/green/hazel	92 (55%)	24,664 (56%)	ref	ref
Blue/gray	74 (44%)	18,914 (43%)	1.05 (0.77-1.42)	0.92 (0.67-1.26)
(missing)	2 (1%)	340 (1%)		
Sun protection while in the sun during the growing season				
Do not use anything [‡]	60 (36%)	19,844 (45%)	ref	ref
Use sun protection [‡]	108 (64%)	24,074 (55%)	1.48 (1.08-2.04)	1.40 (1.00-1.96)
<u>Sun Exposure</u>				
Hours per day spent in the sun during growing season...				
... at enrollment (1993-97)				
<2 hours/day	52 (31%)	14,890 (34%)	ref [§]	ref [§]
3-5 hours/day	54 (32%)	12,122 (28%)	1.28 (0.87-1.87)	1.25 (0.82-1.89)
6-10 hours/day	55 (33%)	12,249 (28%)	1.29 (0.88-1.88)	1.16 (0.73-1.85)
>10 hours per day	5 (3%)	3,865 (9%)	0.37 (0.15-0.93)	0.37 (0.14-0.97)
(missing)	2 (1%)	792 (2%)		
... 10 years ago				
<2 hours/day	36 (21%)	9,946 (23%)	ref	ref
3-5 hours/day	38 (23%)	10,834 (25%)	0.97 (0.61-1.53)	1.03 (0.64-1.66)
6-10 hours/day	62 (37%)	14,153 (32%)	1.21 (0.80-1.83)	1.10 (0.67-1.80)
>10 hours per day	21 (12%)	5,498 (12%)	1.06 (0.62-1.81)	0.94 (0.51-1.74)
(missing)	11 (7%)	3,487 (8%)		

* Analyses are restricted to applicators returning the take home questionnaire and spouses returning the mailed spouse questionnaire and those who provided information on height and weight at study enrollment 1993-97 (n=44,086)

[‡] Sun protection includes the use of sunscreen, a hat with a brim, or a long sleeved shirt

[‡] Adjusted for age at enrollment, gender, tendency to burn and red hair

[§] Linear modeling of this trend was non-significant, but quadratic modeling was significant (p=0.003 and 0.008, respectively) for an inverse U-shaped curve.

Table 4
Risk of cutaneous melanoma for body size-related variables in the Agricultural Health Cohort Study*

	Melanoma Cases (n=168) N (%)	Non-cases (n=43,918) N (%)	Crude OR (95% CI)	Adjusted OR [§] (95% CI)
Based on weight recorded at enrollment:				
Weight				
75 to 150 pounds	34 (20.2%)	11,298 (25.7%)	ref	ref
151 to 200 pounds	82 (48.8%)	21,586 (49.2%)	1.26 (0.85-1.88)	1.05 (0.68-1.62)
201 to 499 pounds	52 (31.0%)	11,034 (25.1%)	1.57 (1.02-2.41)	1.34 (0.81-2.22)
Trend OR weight 201+ vs. <151 lbs			trend 1.6(1.0-2.4) trend p=0.04	trend 1.4(0.8-2.3) trend p=0.20
BMI at enrollment [†]				
< 25 kg/m ²	67 (39.9%)	16,912 (38.5%)	ref	ref
25-26.99 kg/m ²	28 (16.7%)	8,547 (19.5%)	0.83 (0.53-1.29)	0.69 (0.44-1.08)
27+ kg/m ²	73 (43.4%)	18,459 (42.0%)	1.00 (0.72-1.39)	0.85 (0.61-1.20)
Trend OR BMI 27+ vs. <25			trend 1.0(0.7-1.4) trend p=0.99	trend 0.9(0.6-1.2) trend p=0.40
BSA at enrollment [‡]				
< 1.81	44 (26.2%)	14,634 (33.3%)	ref	ref
1.81-2.03	54 (31.1%)	14,586 (33.2%)	1.23 (0.83-1.84)	1.09 (0.70-1.68)
2.04+	70 (41.7%)	14,698 (33.5%)	1.58 (1.09-2.31)	1.49 (0.92-2.39)
Trend OR BSA 2.04+ vs. <1.81			trend 1.6(1.1-2.3) trend p=0.02	trend 1.5(1.0-2.5) trend p=0.09
Based on weight recorded at age 20:				
Weight at age 20				
75 to 150 pounds	82 (48.8%)	24,416 (55.6%)	ref	ref
151 to 200 pounds	73 (43.4%)	16,085 (36.6%)	1.35 (0.98-1.85)	1.41 (0.95-2.10)
201 to 478 pounds (missing)	13 (7.7%) 0 (0%)	2,900 (6.6%) 517 (1.2%)	1.34 (0.74-2.40)	1.74 (0.90-3.35)
Trend OR weight at 20, 201+ vs. <151 lbs			trend 1.5(1.0-2.4) trend p=0.08	trend 1.8(1.0-3.3) trend p=0.05
BMI at age 20				
< 20 kg/m ²	26 (15.5%)	11,478 (26.1%)	ref	ref
20-24.99 kg/m ²	101 (60.1%)	23,800 (54.2%)	1.87 (1.22-2.88)	1.90 (1.22-2.94)
25+ kg/m ² (missing)	41 (24.4%) 0 (0%)	8,121 (18.5%) 519 (1.2%)	2.23 (1.36-3.65)	2.55 (1.52-4.30)
Trend OR BMI 25+ vs. <20			trend 2.1(1.3-3.3) trend p=0.001	trend 2.4(1.5-4.0) trend p=0.0004
BSA at age 20				
<1.64	41 (24.4%)	14,426 (32.9%)	ref	ref
1.64-1.86	55 (32.7%)	14,537 (33.1%)	1.33 (0.89-2.00)	1.47 (0.93-2.30)
1.87+ (missing)	72 (42.9%) 0 (0%)	14,438 (32.9%) 517 (1.2%)	1.76 (1.20-2.58)	2.41 (1.41-4.13)
Trend OR BSA 1.87+ vs. <1.64			trend 1.8(1.2-2.6) trend p=0.004	trend 2.4(1.4-4.2) trend p=0.001

OR= odds ratio; CI=confidence interval; BMI=body mass index; BSA= body surface area

* Analyses are restricted to applicators returning the take home questionnaire and spouses returning the mailed spouse questionnaire and those who provided information on height and weight at study enrollment 1993-97 (n=44,086)

[†] BMI= body mass index, measured as weight over height (at enrollment) squared in kg/m², where a BMI > 25 is considered overweight and a BMI >27 is considered obese.

[‡] BSA= body surface area, measured as square-root of height in meters (at enrollment) times weight in kilograms

[§] Adjusted for age at enrollment, gender, and tendency to burn