JNCI Cancer Spectrum, 2025, **9(1)**, pkaf005
https://doi.org/10.1093/jncics/pkaf005
Advance Access Publication Date: January 12, 2025
Brief Communications

Sex differences in melanoma survival—a GEM study

Tharani Murali, MHS[1], Matthew Schwartz, PhD[2], Adam Z. Reynolds, PhD[3], Li Luo, PhD[3], Grace Ridgeway, BS[1], Klaus J. Busam, MD[4], Anne E. Cust, PhD[5], Hoda Anton-Culver, PhD[6], Richard P. Gallagher, MA[7], Roberto Zanetti, MD[8], Stefano Rosso, PhD[8], Lidia Sacchetto, PhD[9], Colin B. Begg, PhD[10], Irene Orlow, DSc[10], Nancy E. Thomas, MD, PhD[11], Marianne Berwick, PhD, MPH[3,*]; for the GEM Study Team

[1]Department of Internal Medicine, School of Medicine, University of New Mexico, Albuquerque, NM 87131, United States
[2]College of Population Health, University of New Mexico, Albuquerque, NM 87131, United States
[3]University of New Mexico Comprehensive Cancer Center, Division of Epidemiology, Biostatistics and Preventive Medicine, Albuquerque, NM 87131, United States
[4]Department of Pathology, New York, NY 10065, United States
[5]The Daffodil Center and the Melanoma Institute of Australia, School of Public Health, University of Sydney, Sydney, NSW 2050, Australia
[6]Division of General Internal Medicine and Primary Care, Medicine, University of California at Irvine, Irvine, CA 92697, United States
[7]British Columbia Cancer Research Center, University of British Columbia, Vancouver, BC V6T 1Z3, Canada
[8]Piedmont Cancer Registry, CPO, Turin 2015, Italy
[9]Bayer AG, Berlin 13353, Germany
[10]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY 10065, United States
[11]Department of Dermatology and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC 27514, United States

*Corresponding author: Marianne Berwick, PhD, MPH, School of Medicine, University of New Mexico, 2325 Camino de Salud, CRF G39, Albuquerque, NM 87131, United States (mberwick@salud.unm.edu)

Author Contributions: T. Murali, M. Schwartz, A.Z. Reynolds, and L. Luo contributed equally to the paper.

Abstract

Sex differences in melanoma are prominent, with female having a significant survival advantage. However, it is unclear why we see this survival advantage. Here, we investigate the relationship between sex, clinicopathologic variables, and melanoma specific survival in 1753 single primary melanomas from patients in the GEM (Genes, Environment, and Melanoma) study. Using Cox proportional hazard models and formal mediation analysis, the effect of sex on survival is explained largely by differences in the clinicopathologic features of tumors at diagnosis. Specifically, we find evidence that 86.5% of the effect of sex on melanoma survival is mediated by differences in age at diagnosis, Breslow thickness, ulceration, mitoses, and site (hazard ratio [HR] = 1.85, $P < .001$). This analysis indicates that the female survival advantage in melanoma is not primarily due to a direct effect of sex (HR = 1.19, $P = .42$) but is largely a result of an indirect effect of sex mediated by clinicopathologic features.

Sex differences in melanoma are prominent. In general, incidence is higher in women at young ages but men gradually predominate as age increases.[1,2] However, we consistently see women having a significant survival advantage compared with men.[3-8] The current determinants of melanoma stage and prognostic factors include tumor characteristics such as Breslow thickness, ulceration, and nodal metastasis; however, several studies have also shown sex to be an independent prognostic factor after adjusting for these known tumor characteristics.[3-9] It is not yet fully understood why women have a survival advantage. Several mechanisms including behavioral differences, biological processes, and histopathologic variables have been speculated to explain the sex-specific differences we see in melanoma survival.[10]

There are behavioral and biological differences between men and women that may contribute to the differences in survival. First, women are more likely to go to the doctor, which may result in earlier detection of melanoma.[11] Additionally, women are more likely to possess "skin awareness," which is associated with a decreased risk of melanoma death.[12,13] Also, men have been shown to have higher UV exposure than women, another explanation for the differences in melanoma-specific survival.[14] Several biological factors such as hormone milieu, oxidative stress response, vitamin D levels, and differences in gene expression have also been postulated to explain the difference.[15,16] Melanoma is an immunogenic disease, and there are innate immunological differences between men and women such that women may exhibit a stronger immune response compared with men.[17-20] Overall, there is no clear consensus on why women have improved melanoma-specific survival compared with men. The goal of our study is to further examine the relationship between sex and melanoma-specific survival and determine whether sex differences in survival are mediated by established prognostic factors.

The Genes, Environment, and Melanoma (GEM) study consists of 3579 patients with incident primary cutaneous melanoma from 1998 to 2003 (2373 single primary melanomas and 1206 multiple primary melanomas) at 8 population-based cancer registries in Australia, Canada, United States, and Italy and at 1 hospital-based institution in Michigan.[21] The Institutional Review Board at each center reviewed and approved the study

Received: September 20, 2024. **Revised:** December 23, 2024. **Accepted:** January 6, 2025

protocol. In this analysis, we included 1753 patients. We excluded non-Caucasian patients, patients with multiple primary melanomas, and those with missing values in the analytic variables. These variables included sex, melanoma-specific survival, Breslow thickness, ulceration, mitoses, tumor infiltrating lymphocyte (TIL) grade, solar elastosis, histological subtype, anatomic site of melanoma, skin type, educational level, erythemal ultraviolet radiation (UVE) dose, and age at diagnosis. All pathology was reviewed by expert dermatopathologists. Erythemally weighted UVE[22] and dose were calculated.[23]

A descriptive analysis comparing men with women in our sample was performed. A bivariate Cox proportional hazards model was used to calculate a hazard ratio (HR) for association between sex and melanoma-specific survival controlling for age and center. Then a multivariable Cox proportional hazards model was used to determine the association between survival and the selected variables associated with melanoma, adjusting for age and center (Table 1). Mediation analysis was then used to decompose the direct effect of sex from the indirect effects operating through clinicopathologic variables that were associated with survival.

The indirect effects were estimated from the coefficients of 2 regression models: a model regressing the survival outcome on the mediator, sex, and center, and a model regressing the mediator variable on sex and center. We conducted an initial mediation analysis examining 1 mediator variable at a time, and a multiple mediation analysis investigating the combined indirect effects of multiple clinicopathological variables. All analyses were performed using the *survival* package (for Cox models) and *CMAverse* (for mediation analysis) in *R Statistical Software*. A *P* value of less than .05 was considered significant for all analyses, and all tests of statistical significance are 2-sided.

Of the 1753 patients included in our sample, 836 (47.7%) were women and 917 (52.3%) were men. There were 34 women (4.1%) and 74 men (8.1%) who died within 7.4 years, the follow-up time for this cohort. Controlling for only age and center, men are more likely to die of melanoma (HR = 1.81, $P = .005$). After adjusting for the clinicopathological variables, there is no longer a statistically significant association between sex and survival (HR = 1.19, $P = .47$). However, individuals with thicker tumors (HR = 1.14, $P < .001$), mitoses (HR = 4.52, $P < .001$), and ulceration (HR = 3.11, $P < .001$) had a higher risk of dying of melanoma. Older patients (HR = 1.02, $P = .02$) were also more likely to die of melanoma. Individuals with brisk TILs (HR = 0.23, $P = .008$), marked solar elastosis (HR = 0.33, $P = .004$), tumors on trunk/pelvis (HR = 0.48, $P = .02$) and extremities (HR = 0.35, $P < .001$) had a lower risk of dying of melanoma. College graduates were also less likely to die of melanoma (HR = 0.50, $P = .01$).

In multivariable analyses, Breslow thickness, ulceration, mitoses, TIL grade, solar elastosis, and anatomic site were found to be statistically significantly associated with melanoma-specific survival. An interaction analysis showed no interactions between age and sex. A mediation analysis conducted on these variables found that age, Breslow thickness, ulceration, and mitoses significantly mediated the effect of sex on melanoma-specific survival (Table 2). Overall, 86.5% of the effect of sex on melanoma-specific survival can be explained by age, Breslow thickness, ulceration, mitoses, and anatomic site (HR = 1.85, $P < .001$).

Table 1. Multivariable analysis of melanoma-specific survival.[a]

	n			
Variable	**Female**	**Male**	**HR (95% CI)**	***P***
Sex	836	917	1.19 (0.75 to 1.89)	.47
Median Breslow thickness (mm)[b]	0.70	0.83	1.14 (1.09 to 1.21)[b]	<.001
Ulceration				
Absent	786	825	Referent	
Present	50	92	3.11 (1.96 to 4.95)	<.001
Mitoses				
Absent	517	487	Referent	
Present	319	430	4.52 (2.50 to 8.18)	<.001
TIL grade				
Absent	184	180	Referent	
Non-brisk	536	593	0.65 (0.41 to 1.02)	.06
Brisk	116	144	0.23 (0.08 to 0.68)	.008
Solar elastosis				
Absent	331	293	Referent	
Mild/moderate	387	470	0.69 (0.43 to 1.10)	.12
Marked	118	154	0.33 (0.15 to 0.70)	.004
Histology				
Superficial spreading melanoma	642	638	Referent	
Nodular melanoma	60	99	1.38 (0.83 to 2.30)	.22
Other	134	180	0.97 (0.52 to 1.82)	.93
Anatomic site				
Head/neck	93	166	Referent	
Trunk/pelvis	250	539	0.48 (0.26 to 0.87)	.02
Extremities	493	212	0.35 (0.19 to 0.63)	<.001
Skin type				
Freckle/occasionally tan	406	309	Referent	
Deeply/moderately tan	430	608	1.31 (0.86 to 2.00)	.21
Education level				
≤High school	597	618	Referent	
>High school	239	299	0.5 (0.29 to 0.87)	.01
UVE dose (z-scaled)			1.02 (0.81 to 1.28)	.86

Abbreviations: CI = confidence interval; HR = hazard ratio; mm = millimeters; TIL = tumor infiltrating lymphocyte; UVE = erythemal ultraviolet radiation.
[a] Controlled for age and center.
[b] Breslow thickness was log transformed for analyses.

Table 2. Mediation analyses of age and clinicopathologic variables on the effect of sex on melanoma survival.

	HR (95% CI)	P	Proportion mediated
Indirect effects			
Age	1.18 (1.07 to 1.30)	<.001	29.0%
Breslow—mm	1.37 (1.17 to 1.59)	<.001	52.0%
Ulceration	1.19 (1.05 to 1.34)	.01	28.6%
Mitoses	1.17 (1.07 to 1.28)	<.001	27.8%
Solar elastosis	1.00 (0.97 to 1.04)	.97	0.1%
TILs	0.98 (0.94 to 1.02)	.26	−4.5%
Site	1.12 (0.96 to 1.29)	.15	19.8%
Joint effects[a]			
Indirect	1.85 (1.43 to 2.58)	<.001	86.50%
Direct	1.15 (0.72 to 1.92)	.54	
Total	2.13 (1.39 to 3.68)	.002	

Abbreviations: CI = confidence interval; HR = hazard ratio; mm = millimeters; TILs = tumor infiltrating lymphocytes.
[a] Center is included as a covariate. Multiple mediators include age, ulceration, Breslow thickness (log), presence of mitoses, and anatomic site.

Several studies in the literature show sex to be an independent prognostic factor for melanoma.[3-9] However, the results of this study show that the effect of sex on melanoma-specific survival sex is largely mediated by clinicopathologic features of the tumors at time of diagnosis, with 86.5% of the effect of sex explained by age, Breslow, ulceration, mitoses, and anatomic site. It is unclear if the remaining 13.5%, although not statistically significant, represents an independent effect of sex, or if it captures the effect of other unmeasured variables. Regardless, an overwhelming majority of sex's effect on survival is explained through other variables, which suggests that the female survival advantage may be due to differences in tumor characteristics present at time of diagnosis.

Several different hypotheses explain the sex differences in melanoma survival, which include both behavioral and biological differences. Many studies postulate that the differences in survival cannot fully be explained by behavioral differences, as the female survival advantage persists even in advanced stages and metastatic melanoma.[6,7,24,25] One study showed that mitotic rate is not an effect modifier or confounder of the relationship between sex and survival, indicating that biological or host-related factors may explain the survival advantage we see in women.[26]

In the present study, we see the effect of sex on survival is significantly mediated through age, Breslow thickness, ulceration, mitoses, and anatomic site. The mediating effects of Breslow thickness and ulceration are suggestive that sex differences in melanoma progression and survival may be related to behavioral differences between men and women. Men tend to have deeper lesions at time of diagnosis, possibly because they are less likely to visit the doctor and to perform skin self-examinations, which may contribute to later stage at diagnosis in men.[11-13,27,28]

Mitoses are also a significant mediator of the effect of sex on survival, which may be explained by both behavioral and biological differences between men and women. Given that women mount more robust immune responses than men, they may be better at slowing down melanoma progression. This may result in men having more aggressive tumors with higher mitotic rates at time of diagnosis.[20] Mitotic rate has also been shown to be associated with vitamin D levels and reactive oxygen species.[15,29,30] In some studies, women have been shown to have higher vitamin D plasma levels. Vitamin D has been shown to have an anti-tumor effect, inhibiting DNA synthesis and melanoma cell doubling time, which may contribute to the higher mitotic rates we see in men.[15,31-34] Melanoma is characterized by high reactive oxygen species levels, which promote growth and metastasis, and men have been shown to have lower levels of antioxidant enzymes, possibly explaining why mitoses are a mediator of the effect of sex on survival.[30,35-37]

Other researchers have argued that evolved differences in immunity for men and women may contribute to differences in immune responses in melanoma. Thus, we may have expected to see immunological variables such as TILs to differ significantly between men and women.[17-20] In our sample, only 1 woman with brisk TILs died. This could show a protective effect of TILs that differ by sex, but our statistical ability to detect TILs as a mediating variable is limited, given that only 1 woman with brisk TILs died.

Another limitation of this study is that our sample is population based and thus has substantially thinner tumors, which may have influenced the significance of the relationship we see between sex and Breslow thickness.

In summary, this study shows that the effect of sex on melanoma-specific survival is mediated through age, Breslow thickness, mitoses, and ulceration. Previous literature suggests that sex is an independent prognostic factor for melanoma.[3-9] However, our results indicate that the female survival advantage in melanoma is largely due to mediating effects of clinicopathologic features of male and female tumors at the time of diagnosis.

Acknowledgments

We are indebted to the GEM Study Group: Coordinating Center, Memorial Sloan Kettering Cancer Center, New York, NY (USA): Marianne Berwick, MPH, PhD (principal investigator [PI], University of New Mexico, Albuquerque, NM), Colin Begg, PhD (co-PI), Irene Orlow, DSc, MS (co-investigator), Klaus J. Busam, MD (dermatopathologist); Study centers: University of New Mexico, Albuquerque, NM: Marianne Berwick, MPH, PhD (PI), Li Luo, PhD (biostatistician), Tawny W. Boyce, MPH (data manager); University of Sydney and the Cancer Council New South Wales, Sydney, Australia: Anne E. Cust, PhD (PI), Bruce K. Armstrong, MD, PhD (former PI), Anne Kricker, PhD, (former co-PI); Menzies Institute for Medical Research University of Tasmania, Australia: Alison Venn, PhD (former PI), Terence Dwyer, MD (PI, currently at the University of Oxford, United Kingdom), Paul Tucker (dermatopathologist); BC Cancer Research Centre, Vancouver, Canada: Richard P. Gallagher, MA (PI); Cancer Care Ontario, Toronto, Canada: Loraine D. Marrett, PhD (PI); CPO, Center for Cancer Prevention, Torino, Italy: Roberto Zanetti, MD (PI), Stefano Rosso, MD, MSc (co-PI), Lidia Sacchetto, PhD (biostatistician); University of California, Irvine, CA: Hoda Anton-Culver, PhD (PI); University of Michigan, Ann Arbor, MI: Stephen B. Gruber, MD, MPH, PhD (PI, currently at City of Hope National Medical Center, Duarte, CA), Shu-Chen Huang, MS, MBA (coinvestigator, joint at USC-University of Michigan); University of North Carolina, Chapel Hill, NC: Nancy E. Thomas, MD, PhD (PI), Kathleen Conway, PhD (coinvestigator), David W. Ollila, MD (coinvestigator), Paul B. Googe, MD (dermatopathologist), Sharon N. Edmiston, BA (research analyst), Honglin Hao (laboratory specialist), Eloise Parrish, MSPH (laboratory specialist), David C. Gibbs, MD, PhD (currently a resident physician at Emory University, Atlanta, GA); University of Pennsylvania, Philadelphia, PA: Timothy R. Rebbeck, PhD (former PI), Peter A. Kanetsky, MPH, PhD (PI, currently at Moffitt Cancer Center & Research Institute, Tampa, FL);

Ultraviolet radiation data consultants: Julia Lee Taylor, PhD, and Sasha Madronich, PhD, National Centre for Atmospheric Research, Boulder, CO. The following laboratory members were key contributors to early stages of the study: at MSK, Pampa Roy, PhD and Rebecca Canchola (procurement of specimens and genotyping), Emily LaPilla, MS, Sarah Yoo, MS, Ajay Sharma, MS, and Javier Cotignola, MS (genotyping); at UNC, Alison Eaton (genotyping), Pamela Groben (dermatopathology); at UNM: Kirsten White, PhD (laboratory supervisor); at the University of Pennsylvania: Amy Walker and Saarene Panossian (genotyping).

Author contributions

Tharani Murali, MHS (Writing—original draft; Writing—review & editing), Matthew Schwartz, PhD (Conceptualization; Formal analysis; Writing—original draft; Writing—review & editing), Adam Z. Reynolds, PhD (Formal analysis; Methodology; Supervision; Writing—original draft; Writing—review & editing), Li Luo, PhD (Formal analysis; Methodology; Supervision; Writing—original draft; Writing—review & editing), Grace Ridgeway, BA (Writing—original draft; Writing—review & editing), Klaus J. Busam, MD (Data curation; Funding acquisition; Writing—review & editing), Anne E. Cust, PhD (Data curation; Investigation; Project administration; Writing—review & editing), Hoda Anton-Culver, PhD (Conceptualization; Data curation; Funding acquisition; Investigation; Writing—review & editing), Richard P. Gallagher, MA (Data curation; Funding acquisition; Investigation; Project administration; Writing—review & editing), Roberto Zanetti, MD (Conceptualization; Data curation; Funding acquisition; Investigation; Project administration; Writing—review & editing), Stefano Rosso, PhD (Conceptualization; Data curation; Funding acquisition; Investigation; Project administration; Writing—review & editing), Lidia Sacchetto, PhD (Investigation; Writing—review & editing), Colin B. Begg, PhD (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Resources; Supervision; Writing—original draft; Writing—review & editing), Irene Orlow, DSc (Data curation; Funding acquisition; Investigation; Project administration; Writing—original draft; Writing—review & editing), Nancy E. Thomas, MD, PhD (Investigation; Project administration; Writing—original draft; Writing—review & editing), and Marianne Berwick, PhD, MPH (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing—original draft; Writing—review & editing)

Funding

This work was supported by the National Cancer Institute of the National Institutes of Health grant numbers P01 CA206980 to M. B. (contact PI) and N.E.T.; NCI R01 CA233524 to N.E.T., M.B., C.B. B., and H. A.-C.; U01 CA 83101, R01 CA112524, R01 CA 112524-05S2, K05 CA13165 to M.B.; NCI R21CA134368, NCI R33CA160138, and NCI R03CA199487 to K.C. and N.E.T.; The University of New Mexico Comprehensive Cancer Center (NCI 5P30CA118100-15); The UNC Lineberger Comprehensive Cancer Center (NCIP30CA016086), Memorial Sloan Kettering Cancer Center (P30 CA0008748); NHMR Investigator Fellowship (2008454) to A.C.

The funders had no role in the design of the study, the collection, analysis, and interpretation of the data, the writing of the manuscript and the decision to submit the manuscript for publication.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Data availability

Data are available by contacting Dr Marianne Berwick at mberwick@salud.unm.edu or Dr Irene Orlow at orlowi@mskcc.org.

References

1. Arnold M, Singh D, Laversanne M, et al. Global burden of cutaneous melanoma in 2020 and projections to 2040. *JAMA Dermatol*. 2022;158:495-503.
2. Olsen CM, Thompson JF, Pandeya N, Whiteman DC. Evaluation of sex-specific incidence of melanoma. *JAMA Dermatol*. 2020; 156:553-560.
3. Stidham KR, Johnson JL, Seigler HF. Survival superiority of females with melanoma: a multivariate analysis of 6383 patients exploring the significance of gender in prognostic outcome. *Arch Surg*. 1994;129:316-324.
4. de Vries E, Nijsten TEC, Visser O, et al. Superior survival of females among 1538 Dutch melanoma patients is independent of Breslow thickness, histologic type and tumor site. *Ann Oncol*. 2008;19:583-589.
5. Morgese F, Berardi R, Sampaolesi C, et al. Gender differences and outcome of melanoma patients. *J Transl Med*. 2015;13:P13.
6. Joosse A, Collette S, Suciu SO, et al. Sex is an independent prognostic indicator for survival and relapse/progression-free survival in metastasized stage III to IV melanoma: a pooled analysis of five European organisation for research and treatment of cancer randomized controlled trials. *J Clin Oncol*. 2013; 31:2337-2346.
7. Joosse A, Collette S, Suciu S, et al. Superior outcome of women with stage I/II cutaneous melanoma: pooled analysis of four European Organisations for Research and Treatment of Cancer phase III Trials. *J Clin Oncol*. 2012;30:2240-2247.
8. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol*. 2001;19:3622-3634.
9. Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol*. 2001;19:3635-3648.
10. Schwartz MR, Luo L, Berwick M. Sex differences in melanoma. *Curr Epidemiol Rep*. 2019;6:112-118.
11. Cleary PD, Mechanic D, Greenley JR. Sex differences in medical care utilization: an empirical investigation. *J Health Soc Behav*. 1982;23:106-119.
12. Paddock LE, Lu SE, Bandera EV, et al. Skin self-examination and long-term melanoma survival. *Melanoma Res*. 2016;26:401-408.
13. Berwick M, Armstrong BK, Ben-Porat L, et al. Sun exposure and mortality from melanoma. *J Natl Cancer Inst*. 2005;97:195-199.
14. Gordon D, Gillgren P, Eloranta S, et al. Time trends in incidence of cutaneous melanoma by detailed anatomical location and patterns of ultraviolet radiation exposure: a retrospective population-based study. *Melanoma Res*. 2015;25:348-356.
15. Nosrati A, Wei ML. Sex disparities in melanoma outcomes: the role of biology. *Arch Biochem Biophys*. 2014;563:42-50.
16. Bellenghi M, Puglisi R, Pontecorvi G, De Feo A, Carè A, Mattia G. Sex and gender disparities in melanoma. *Cancers (Basel)*. 2020; 12:1819.

17. Passarelli A, Mannavola F, Stucci LS, Tucci M, Silvestris F. Immune system and melanoma biology: a balance between immunosurveillance and immune escape. *Oncotarget*. 2017;8:106132-106142.
18. Kalaora S, Nagler A, Wargo JA, et al. Mechanisms of immune activation and regulation: lessons from melanoma. *Nat Rev Cancer*. 2022;22:195-207.
19. Bouman A, Schipper M, Heineman MJ, Faas MM. Gender difference in the non-specific and specific immune response in humans. *Am J Reprod Immunol*. 2004;52:19-26.
20. Klein SL, Flanagan KL. Sex differences in immune responses. *Nature Rev Immunol*. 2016;16:626-638.
21. Begg CB, Hummer AJ, Mujumdar U, et al.; GEM Study Group. A design for cancer case-control studies using only incident cases: experience with the GEM study of melanoma. *Int J Epidemiol*. 2006;35:756-764.
22. Thomas NE, Kricker A, From L, et al.; Genes, Environment, and Melanoma Study Group. Associations of cumulative sun exposure and phenotypic characteristics with histologic solar elastosis. *Cancer Epidemiol Biomarkers Prev*. 2010;19:2932-2941.
23. Berwick M, Reiner AS, Paine S, et al.; GEM Study Group. Sun exposure and melanoma survival: a GEM study. *Cancer Epidemiol Biomarkers Prev*. 2014;23:2145-2152.
24. Enninga EAL, Moser JC, Weaver AL, et al. Survival of cutaneous melanoma based on sex, age, and stage in the United States, 1992-2011. *Cancer Med*. 2017;6:2203-2212.
25. Joosse A, de Vries E, Eckel R, et al.; Munich Melanoma Group. Gender differences in melanoma survival: female patients have a decreased risk of metastasis. *J Invest Dermatol*. 2011;131:719-726.
26. Joosse A, van der Ploeg AP, Haydu LE, et al. Sex differences in melanoma survival are not related to mitotic rate of the primary tumor. *Ann Surg Oncol*. 2015;22:1598-1603.
27. Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. *J Adv Nurs*. 2005;49:616-623.
28. Brady MS, Oliveria SA, Christos PJ, et al. Patterns of detection in patients with cutaneous melanoma. *Cancer*. 2000;89:342-347.
29. Moreno-Arrones OM, Zegeer J, Gerbo M, et al. Decreased vitamin D serum levels at melanoma diagnosis are associated with tumor ulceration and high tumor mitotic rate. *Melanoma Res*. 2019;29:664-667.
30. Joosse A, De Vries E, van Eijck CH, Eggermont AM, Nijsten T, Coebergh JW. Reactive oxygen species and melanoma: an explanation for gender differences in survival? *Pigment Cell Melanoma Res*. 2010;23:352-364.
31. Johnson JA, Beckman MJ, Pansini-Porta A, et al. Age and gender effects on 1,25-dihydroxyvitamin D3-regulated gene expression. *Exp Gerontol*. 1995;30:631-643.
32. Ziyab AH, Mohammad A, Almousa Z, Mohammad T. Sex differences in the association between vitamin D and prediabetes in adults: a cross-sectional study. *Nutr Diabetes*. 2024;14:49.
33. Colston K, Colston MJ, Feldman D. 1,25-dihydroxyvitamin D3 and malignant melanoma: the presence of receptors and inhibition of cell growth in culture. *Endocrinology*. 1981;108:1083-1086.
34. Evans SR, Houghton AM, Schumaker L, et al. Vitamin D receptor and growth inhibition by 1,25-dihydroxyvitamin D3 in human malignant melanoma cell lines. *J Surg Res*. 1996;61:127-133.
35. Sander CS, Hamm F, Elsner P, Thiele JJ. Oxidative stress in malignant melanoma and non-melanoma skin cancer. *Br J Dermatol*. 2003;148:913-922.
36. Malorni W, Straface E, Matarrese P, et al. Redox state and gender differences in vascular smooth muscle cells. *FEBS Lett*. 2008;582:635-642.
37. Miller AA, De Silva TM, Jackman KA, Sobey CG. Effect of gender and sex hormones on vascular oxidative stress. *Clin Exp Pharmacol Physiol*. 2007;34:1037-1043.

JNCI Cancer Spectrum, 2025, 9, 1–5
https://doi.org/10.1093/jncics/pkaf005
Brief Communications