# Cutaneous melanoma in women###

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ABSTRACT

*Background:* Gender disparity in melanoma outcome is consistently observed, suggesting that gender is as an important prognostic factor. However, the source of this gender disparity in melanoma remains unclear.
*Objective:* This article reviews advances in our understanding of gender differences in melanoma and how such differences may contribute to outcomes.
*Methods:* A broad literature search was conducted using the PubMed database, with search terms such as 'gender differences in melanoma' and 'sex differences in melanoma.' Additional articles were identified from cited references.
*Results:* Herein, we address the gender-linked physiologic differences in skin and melanoma. We discuss the influence of estrogen on a woman's risk for melanoma and melanoma outcomes with regard to pregnancy, oral contraceptives, hormone replacement therapy, and UV tanning.
*Conclusions:* The published findings on gender disparities in melanoma have yielded many advances in our understanding of this disease. Biological, environmental, and behavioral factors may explain the observed gender difference in melanoma incidence and outcome. Further research will enable us to learn more about melanoma pathogenesis, with the goal of offering better treatments and preventative advice to our patients.


## Introduction

The incidence of cutaneous melanoma (CM) continues to increase in the Caucasian population in the United States. In 2014, women only accounted for 42% of the 76,100 new melanoma cases and only 33% of the 9,710 deaths associated with CM in the United States [1]. These trends are consistently observed in populations around the world. Indeed, gender disparity in melanoma outcome is so consistently observed that gender has been suggested as an important prognostic factor, despite not being formerly incorporated in staging algorithms [2]. The source of this gender disparity in melanoma remains unclear, but likely represents both biological and behavioral etiologies. Here, we review the current knowledge of how the disease of melanoma differs between men and women.

## Gender-linked physiologic differences in skin

Skin is a dynamic, complex, integrated arrangement of cells, tissues, and matrix elements that mediates a diverse array of functions, including physical permeability barrier, protection from infectious agents, thermoregulation, sensation, ultraviolet (UV) protection, wound repair and regeneration, and outward physical appearance. These various functions of skin are mediated by its major layers: the epidermis, dermis, and subcutaneous fat. The dermis contains water, ground substance, and elastic fibers that, in combination with the layer of subcutaneous fat, account for the majority of the skin's thickness. The thickness of the skin is greater in men than in women at all ages [3,4]. Skin thickness decreases in men and women starting at the age of 45, and women's skin gets 10% thinner after menopause [5,6]. Skin color is modulated by melanin, hemoglobin, and other chromophores. Melanin is synthesized in melanocytes, dendritic cells located in the basal layer of the epidermis. Melanocytes are known to be differently distributed according to anatomic sites. No gender-related difference has been reported; however, within individual ethnic groups, men have been reported to have darker skin color [7], which may be related to a more vascularized upper dermis [8] and more melanin synthesis [9]. These differences are likely modulated, in part, by hormones, given that they manifest during puberty and increase with age [10].

Men and women differ in the metabolism of and response to androgens and estrogens [11]. Estrogens are known to accelerate wound healing, improve inflammatory disorders, increase epidermal thickness, and protect against photoaging of the skin [12]. The cellular effects of estrogens are mediated by estrogen receptors (ERs), ERα and ERβ, which

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belong to the nuclear steroid hormone receptor superfamily. ERα and ERβ are widely expressed in human tissue, but have differential distributions in various tissues, including the skin. ERα is primarily expressed in the uterus, liver, kidneys, breasts, and heart, whereas ERβ is primarily detected in what are known as nonclassical estrogen-responsive tissues: the ovaries, colon, lungs, adipose tissue, prostate, bladder, and skin [13]. Notably, melanomas do express ERβ, but its expression does not differ between male and female tumors [14]. Cutaneous ER levels are generally known to be higher in women as compared with men. However, relative levels of ERα and ERβ in men and women are not well understood. In women, the amount of ERs declines after menopause with declining levels of estradiol, which, through positive feedback, has a pro-synthetic effect on ERs [13]. Expression declines more rapidly in ERβ than in ERα, resulting in an increased ERα:ERβ ratio in the skin. In contrast to estrogens, androgens—such as testosterone and 5α-dihydroxytestosterone—may be able to promote melanoma tumorigenesis. Androgen receptors, which have a similar mechanism of action as estrogen receptors, have been described in human melanoma cells [15,16].

There are also several baseline differences in the immune systems of men and women. On average, women have higher measured IgG and IgM levels, as well as a greater percentage of CD3 + T lymphocytes, as compared with men, suggesting that men have a relative attenuation of the adaptive immune response compared with women [17]. This is further evidenced by observations that men are more susceptible to bacterial and viral infections [18], while women are more prone to autoimmune and inflammatory diseases [19]. Men are also more prone to skin cancer; this increased risk may be partly explained by their heightened susceptibility to ultraviolet-induced immunosuppression compared with women [20]. Ultraviolet (UV) irradiation is known to inhibit contact hypersensitivity or delayed-type hypersensitivity. Also, the sex hormones may have an additional differential effect on immune cells, as both estrogen and androgen receptors are expressed in immune cells [21].

The mechanisms and mechanics of oxidative stress also differ between sexes. By-products of oxygen metabolism lead to the production of reactive oxygen species (ROS), which can damage a wide range of molecules, leading to oxidative stress [22]. Male cells of various tissue types have an elevated ROS cellular environment, due to the expression of lower levels of antioxidant enzymes as compared with females [23]. Additionally, estrogens appear to have direct antioxidant and protective effects, while testosterone may potentiate oxidative stress. This difference between testosterone and estrogen may contribute to disparities in melanoma outcome [24].

## Gender-specific differences in melanoma

Gender-specific differences in melanoma epidemiology are well established. The probability of developing melanoma during one's lifetime is 1.72% in males and 1.22% in females [25]. In the Netherlands, a large population-based cohort study including 10,538 melanoma patients from 1993 to 2004 analyzed the gender difference in melanoma survival after adjusting for tumor-related variables (Breslow thickness, histology, tumor site, and metastatic and nodal status). They found that the relative excess risk of mortality was 2.70 (95% CI [2.38, 3.06]) in males versus females. The female survival advantage remained after adjusting for multiple confounding variables, including tumor thickness [26]. Gamba et al. [27] analyzed data from 26,107 individuals, aged 15–39 years, from the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results registry. They reported that young men had a 55% lower rate of melanoma survival compared with age-matched young women, and concluded that male sex, within all specific age groups and across all tumor thickness categories, histologic subtypes, and anatomic sites, is associated with a disproportionate burden of melanoma deaths. A population-based cohort study including 11,774 melanoma patients from the Munich Cancer Registry (Germany) analyzed gender differences in survival and disease progression across all stages of CM. Localized melanomas in women showed a lower risk of metastasis, resulting in better survival when compared with men, even after first disease progression [28]. In localized melanoma, men generally had worse characteristics at diagnosis, such as older age; increased likelihood of having an ulcerated or thicker primary tumor; and melanomas more commonly located on the head, neck, and trunk instead of the extremities. However, even after diagnosis, men continue to have disadvantages compared with women [28]. In various studies, women showed a longer delay before relapse and a higher cure rate compared to men [26,28]. Table 1 summarizes the sex risk estimates of melanoma survival in various studies.

The natural history of melanoma in women parallels the physiologic hormonal changes they experience. The incidence of melanoma is rare before puberty, rises abruptly through the reproductive ages until approximately 50 years of age, and then diminishes after menopause [33]. In agreement with the aforementioned survival advantages of young women and women with localized melanoma, women who present with stage IV disease also show higher survival rates compared to men, who have a two-fold greater death rate from melanoma [34]. Kemeny et al. [35] also reported that premenopausal women show a higher survival rate compared to postmenopausal women, which was more pronounced in women with advanced disease. Although the survival advantage decreases with age, postmenopausal women still have better rates of survival compared with men.

Gender disparity in melanoma may have genetic underpinnings. Kocarnik et al. [36] confirmed eight single nucleotide polymorphisms that modulate melanoma risk. Interestingly, one single nucleotide polymorphism, rs16891982, in the *SLC45A2* gene influenced melanoma risk differently by sex, with higher risk association observed in males (*OR* 5.5 in males vs. 2.37 in females). The *SLC45A2* gene codes for an ion transporter protein in the melanosome and likely shapes melanoma risk by modulating melanosome activity by changing the internal pH [37]. Notably, estrogen increases expression of tyrosinase [38], the rate-limiting enzyme in melanin production located in the melanosome, and rs16891982 has been associated in this enzyme's activity and expression [39]. Synthesizing these observations, Kocarnik et al. [36] hypothesize that the gender-modified risk associated with rs16891982 may be mediated through hormonal influence on a critical enzyme in melanogenesis. While this study explored inherited germline polymorphisms, inherent differences in genetic burden or immunogenicity of the tumors themselves are an intriguing, yet poorly explored, area of research.

## Estrogen and melanoma

The most widely studied mechanism regarding gender disparity in melanoma is the influence of sex hormone levels and estrogen receptor expression. Various laboratory studies with cultured cells and animal models support a role for estrogens in contributing to the better survival rates among women. Kanda and Watanabe [40] showed that incubation of 17-β-estradiol inhibited the growth of human metastatic melanoma cells in vitro, and concomitantly reduced constitutive interleukin-8 (IL-8) mRNA and secretion. The melanoma cell growth inhibited by 17-β-estradiol was counteracted by exogenously added IL-8, which suggests that estrogen mediates growth suppression in melanoma cells by inhibiting IL-8 expression. Of note, this effect was only observed in ER-positive cells, indicating that estrogen may mediate an inhibitory effect on melanomas via ER and IL-8 in vitro. Richardson et al. [41] and Roy et al. [42] reported that 17-β-estradiol inhibited the invasive activity of melanoma cells, but did not have antitumor activity in C57BL/6 mice inoculated with syngeneic B16 tumors. Cho et al. [43] reported that implanted B16 murine melanoma cells grew more rapidly in ERβ knockout mice compared to congenic C56BL/6 mice with intact ERβ, therefore suggesting that the presence of ERβ was protective against tumor growth. It has been demonstrated that melanocytic lesions express detectable levels of ERα and ERβ mRNA and protein [44,45]. However, ERβ was the predominant ER type in melanocytic lesions, indicating that estrogen might play a role in melanocyte physiology via ERβ [44]. ERβ immunoreactivity of melanoma cells was dependent on the microenvironment: melanoma cells in close contact with keratinocytes were more reactive than invasive melanoma, and the

**Table 1**
Summary of Selected Studies Demonstrating Female Survival Advantage.

| Reference | Year | End Point | Country | No. of Patients | Adjusted Risk Estimates[1] | 95% CI |
|---|---|---|---|---|---|---|
| Balch et al. [29] | 2001 | DSS | United States | 13,581 | 0.84 | 0.76 to 0.92 |
| de Vries et al. [26] | 2008 | RS | The Netherlands | 10,538 | 0.53[2,3] | 0.48 to 0.61 |
| Xing et al. [30] | 2010 | DSS | United States (SEER) | 37,519 | 0.67[3] | 0.60 to 0.75 |
| Joosse et al. [28] | 2011 | DSS | Germany | 11,774 | 0.62 | 0.56 to 0.70 |
| Collins et al. [31] | 2011 | DSS[4] | United States (SEER) | 142,653 | 0.65[3] | 0.62 to 0.68 |
| Thompson et al. [32] | 2011 | DSS | International AJCC Consortium | 10,233 | 0.69 | 0.61 to 0.79 |

Abbreviations: AJCC, American Joint Committee on Cancer; DSS, disease-specific survival; RS, relative survival (estimate of DSS).
[1] Relative risk of women compared with men; presented as hazard ratio unless otherwise specified.
[2] Presented as relative excess risk.
[3] Value reported here is the inverse of the original risk estimate, because men were compared with women in the cited publication.
[4] For patients who underwent surgery.

ERβ protein expression decreased progressively with increased Breslow thickness and resulted in more invasive melanoma [46]. Another study demonstrated that ERβ expression in CMs without and with lymph node metastases were higher and lower, respectively, than in the healthy skin surrounding them, suggesting a role for ERβ in the metastatic process of melanoma [44]. Together, these studies suggest that the loss of ERβ expression may be an important step in melanoma progression and/or the stimulation of melanoma proliferation.

## Pregnancy, oral contraceptives, and hormone replacement therapy

Approximately one third of all women diagnosed with CM are of childbearing age [47]. The observation of physiological hyperpigmentation on multiple cutaneous sites during pregnancy yielded the hypothesis that pregnancy-related hormones might influence the course of CM in women. Pregnancy is also considered to be a state of immunosuppression, one that helps prevent the rejection of the fetus expressing paternal alloantigens [48]. However, recent studies found no significant dermatoscopic or abnormal histologic changes in nevi during pregnancy [49]. Also, clinical, epidemiologic, and laboratory studies have found that pregnancy does not significantly change the characteristics or prognosis of CM [50]. Multiple controlled studies in the 1980s consistently showed no significant impact on the survival of women diagnosed with localized melanoma (AJCC stage I or II) during pregnancy [51–56]. Since pregnancy does not seem to influence the prognosis or evolution of localized malignant melanoma, the recommendations set forth by the European Society of Medical Oncology for evaluating a patient diagnosed with melanoma remain the same regardless of pregnancy status [57]. Counseling patients diagnosed with melanoma regarding future pregnancies and hormone replacement therapy should be based on established prognostic factors. If poor prognostic factors exist, clinicians will often advise patients to wait 2 to 3 years to become pregnant, thereby avoiding pregnancy during the window of time with the highest likelihood of recurrence [50]. However, there are no standardized guidelines for the postponement of the further pregnancies after the diagnosis of melanoma; counseling must be individualized for each patient, taking into consideration her age, fertility status, availability of oocyte cryopreservation, disease prognosis, and family support.

Multiple studies have investigated the relationship between the use of oral contraceptives (OCs) and the risk of CM, including two recently published meta-analyses. The first of these, an analysis of 18 studies, reported an overall *OR* of 0.95 (95% CI [0.82, 1.15]) [58]. The second, an analysis of 10 studies encompassing 3,796 cases and 9,442 controls, also reported a summation *OR* of 0.95 (95% CI [0.87, 1.04]) [59]. The authors of a pooled analysis of 10 case–control studies also failed to find an association between risk of CM and ever-use of OCs (pooled *OR*, 0.86; 95% CI [0.74, 1.01]) [60]. There were also no relationships between risk of melanoma and OC length of use, age at first use, or current use. These studies all make the consensus conclusion that there is no evidence of a relationship between risk of melanoma and use of OCs. Based on a limited number of studies, a similar conclusion has been made regarding the relationship, or lack thereof, between hormone replacement therapy (HRT) and risk of malignant melanoma. Gupta and Driscoll [61] analyzed 12 studies, 10 of which showed no association between use of HRT and melanoma. The two studies that showed increased risk of melanoma with HRT use did not control for potential confounding variables. Consequently, a history of localized melanoma is not considered a contraindication for the use of HRT.

## UVA tanning: a major melanoma risk factor for young women

Melanoma is the most prevalent cancer among 25- to 29-year-old females, and under the age of 40, women have a higher incidence of melanoma than men [62]. In several studies, risky tanning behavior was more common among women, younger people, and people of low socioeconomic status [63]. These emerging data on the incidence rates of skin cancers in young women younger than age 40 years compared with men of that age group suggest that the etiology is partly due to excessive, repeated exposures to unnaturally large amounts of ultraviolet A (UVA) light from UVA-rich lamps. Indoor tanning has been widely practiced in northern Europe and the United States since the 1980s [64]. Indoor tanning equipment mainly emits light in the UVA range, but a fraction (<5%) of this spectrum is in the ultraviolet B range [65]. In frequent users of UVA-rich lamps, the amount of annual UVA exposure is roughly doubled. It was also reported that high-pressure UVA tanning beds, with dose rates up to 13 times that of the summer sun, have the potential to quadruple the annual UVA exposure of frequent tanners [66]. Two recent meta-analyses [65,67] reported that the risk of CM is increased by 16% and 20%, respectively, for those who have ever used indoor tanning devices. Even more concerning, the risk of melanoma doubled when use started before the age of 35 years. These findings—that early exposure and more frequent use of indoor tanning beds significantly increases the risk of melanoma—represent a global trend [65]. Therefore, in 2009, the International Agency for Research on Cancer classified the entire ultraviolet spectrum and indoor tanning devices as carcinogenic to humans (group 1) [68]. This classification was based on evidence from basic and epidemiologic studies demonstrating that UVA has an important role in skin carcinogenesis [69] and that UVA-producing tanning lamps are capable of inducing the types of DNA damage associated with photocarcinogenesis [70].

As melanomas arising in young women are commonly associated with tanning bed use, these diseases can be minimized by educating patients to avoid artificial tanning habits and strongly regulating their use. The World Health Organization, the International Commission on Non-Ionizing Radiation Protection, and the European Society of Skin Cancer Prevention have all maintained that the highest regulatory priorities should be the restriction of sunbed use by people younger than 18 years of age and the banning of unsupervised indoor tanning facilities. Such restrictions have been implemented in Australia and several European countries, including Austria, France, Germany, Portugal, Belgium, Scotland, and Spain.

In May 2014, the U.S. Food and Drug Administration formally reclassified sunlamp products and UV lamps intended for use in sunlamp products from low-risk (class I) to moderate-risk (class II) devices. Along with this reclassification came the mandate that all sunlamp

products carry a visible black-box warning on the device that explicitly states that the sunlamp product should not be used on persons younger than 18 years of age. Furthermore, certain marketing information associated with these devices must provide additional and specific warning statements and contraindications (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm399222.htm). On legislative fronts, only nine states (CA, DE, IL, LA, MN, NV, OR, TX, and VT) have banned access to indoor tanning for adolescents younger than age 18 years.

## Conclusion

Mounting evidence suggests that both biological and environmental factors explain observed gender differences in melanoma incidence and outcome. Innate gender differences in hormones, immune homeostasis, and oxidative stress likely contribute to the sexual disparity in melanoma survival. Beyond these innately biological differences, behaviors, such as tanning bed use, also clearly shape melanoma risk. Understanding gender differences allows for targeted interventions. For instance, increased awareness of the modifiable risks of tanning behavior has yielded bans in nine states, with pending legislation in additional states that promises to explicitly ban under-18 indoor tanning. Similarly, better understanding of innate biological differences in melanoma between the genders may yield improved targeted therapies.

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