HHS Public Access

Author manuscript

Curr Epidemiol Rep. Author manuscript; available in PMC 2020 August 26.

Published in final edited form as:

Curr Epidemiol Rep. 2019 June ; 6(2): 112–118. doi:10.1007/s40471-019-00192-7.

Sex Differences in Melanoma

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Abstract

Purpose of Review: The goal of this review has been to elucidate the sex differences in cancer incidence and mortality in cutaneous melanoma. We have evaluated biological and behavioral research to determine where the critical questions exist.

Recent Findings: The most recent findings, through 2015, are exploratory in nature but seem to indicate that the differences are more likely due to biological variations rather than behavioral. While behavioral studies do show that women are more likely than men to seek health care and practice healthy behaviors, these differences are not sufficiently strong to explain the variation in incidence and mortality in cutaneous melanoma. Evolved differences in the immune systems of females and the role of sex steroid hormones in immunomodulation are two promising avenues for research. Studies in mice demonstrate that the newer immunotherapies are more effective in females and sex steroid hormones, such as estrogen receptor beta are inversely associated with tumor aggressiveness while testosterone increases it.

Summary: Our analysis indicates that biological factors need to be investigated more thoroughly to understand the variation in incidence and mortality in cutaneous melanoma. Such understanding could lead to reducing incidence and mortality for both males and females (male incidence is 27.4 per 100,000; female 16.8 per 100,000; male mortality is 3.9 per 100,000; female mortality 1.6 per 100,000). It is most likely that behavioral differences between the sexes cannot account for the

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Compliance with Ethical Standards

Conflict of Interest

Li Luo and Marianne Berwick each declare no potential conflicts of interest.

Human and Animal Rights

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutions/national research committee standards, and international/national/institutional guidelines).

preponderance of male mortality. In addition to the important role of genetic factors, it is critical to evaluate further additional biological factors and their interactions with genetics and behavior.

Keywords

Melanoma; sex; biology; genetics; behavior; sun exposure

Introduction

Sex differences in melanoma incidence and mortality are robust, consistent, and well-documented; overall, males have a higher risk of developing cancer and one-and-a-half times the risk of mortality than females[1]. This increased risk cuts across racial and ethnic groups and all cancer types [2–6]. To the age of 50, females actually have approximately twice the incidence of melanoma as males, but thereafter this difference changes, and by the age of 60 males have twice the incidence of females and by age 70 this difference rises to three times as great for males.[1] Although melanoma incidence over the last five years has increased for both sexes (1.2% for females and 2.3% for males), the good news is that mortality from melanoma has decreased by 2.8% for females and 3.0% for males[4]. Mortality from melanoma is relatively constant among males and somewhat greater than that for females until the age of 50 when male mortality consistently increases to almost three times that of females.[1]

In terms of sex differences in survival from cancer, cutaneous melanoma is one of the most striking [3]. Using follow up data from four Phase III European Organisation for Research and treatment of Cancer (EORTC), Melanoma Group, females retain a 38% survival advantage compared to males after adjusting for stage at diagnosis [7–9]. When compared to males, females have thinner tumors, less tumor ulceration, less progression to lymph node or organ metastases, a longer delay before relapse, and a higher cure rate [7,8,10].

Here we summarize the sex differences in melanoma, covering the spectrum from biologically-based pathways with immunological, hormonal, and genetic underpinnings, to behavioral-related pathways such as differences in UV exposure, primary care access, and skin awareness.

Immunity

Sex-specific differences in overall immune function are robust and well-documented. Women mount more effective cellular and humoral immune responses and are less likely to succumb to bacterial and viral infections than men [5,11–16].

Life history theory attributes these differences to sex-specific evolutionary trade-offs in energetic allocation to competing somatic demands such as reproduction [17–20]. One notable example of sex-specific reproductive asymmetry is the nine-month period of pregnancy. The mother’s immune system must be sufficiently suppressed through a complex interplay between energetics, immune cells, and hormones to allow the antigenically distinct fetus to grow without triggering an immune response, but not so suppressed that the mother cannot

fend off infections [21]. Over evolutionary time, such asymmetries have led to sexually dimorphic systems such as immunity, and are seen across all females regardless of gravidity.

As an immunogenic disease, the immune system is especially critical to detecting and destroying melanoma tumors. For this reason, alterations to the immune system such as systemic immunosuppression after a major organ transplant, are major risk factors for the development of melanoma [22]. In order to evade detection by the immune system, melanoma tumors down-regulate surface antigens, and secrete immunosuppressive cytokines in the tumor microenvironment, effectively suppressing the site-specific immune response [23,24]. If successful, malignant melanomas evade detection and spread throughout the body and into the lymphatic system, further compromising host immunity[25].

Melanoma, like many tumors, is chemoresistant, making previous treatments difficult and often ineffective. Fortunately, the recent development of successful alternatives to chemotherapy such as immune checkpoint inhibitors and targeted therapies are dramatically changing the treatment landscape for melanoma patients [26]. Interestingly, in mice, immune checkpoint inhibitors are significantly more effective in female mice than male mice[16]. Whether this is true for humans will await the results of further trials.

Endocrine Factors

Other sex-specific immune-modulating factors such as steroid hormones like estrogen and testosterone have been heavily implicated in host immune activation and response [27,27–37], largely through sex-steroid receptors located on immune cells [38–40]. Estrogen acts as a powerful immune-enhancer, potentiating antibody[12] and likely inflammatory responses [41–43]. Testosterone on the other hand, attenuates non-specific immune response [12].

The role of sex steroid hormones in melanoma is far from clear [44]. The expression of the estrogen receptor beta (ER-ß) is negatively associated with melanoma invasiveness and tumor thickness [45]. The exogenous addition of estrogen inhibits tumor growth in vitro [46] and in metastatic tumors [47], while testosterone increases tumor aggressiveness [44,48].

Reproductive status such as pregnancy and menopause have large within-sex differences in fluctuating sex-steroid hormones, conveniently presenting researchers with natural experimental conditions. Reproductive-age women have a more reactive inflammatory profile [5] and higher levels of T-lymphocytes when compared to post-menopausal women [12,49,50]. There appears to be no association between pregnancy and melanoma [44]. The relation between menopausal status and melanoma survival is conflicted, multiple studies have found no evidence of differences in post-menopausal groups [51–53], while others have documented significant differences in post-menopausal groups [39,54–58].

Genetic Factors

Phenotypic differences in both immunocompetence and steroid hormones are largely driven by differences in underlying genetic architecture. Until recently, the cost of genetic sequencing has been a major barrier to genomic research. However, decreasing sequencing costs has greatly increased the capacity to study the genotypic features of melanoma.

Several genetic factors are suggested as underlying a male survival disadvantage in melanoma outcome. The X chromosome alone has 1500 genes containing oncogenes and tumor suppressor genes whose regulation are critical to cancer progression and suppression compared to the 344 genes on the Y chromosome [44]. Additionally, men carry the potential deleterious effects of X chromosome monosomy and oncogenes on the Y chromosome (TSPY) [44].

Differences in autosomal genetic variations are important in understanding the mechanisms of sex disparity in melanoma. Previous studies have reported significant differential genetic effects for melanoma by sex. A non-synonymous single nucleotide polymorphism (SNP), rs16891982, in the SLC45A2 gene is shown to be associated with much higher risk for melanoma in males (OR=5.5 in males vs OR=2.37 in females)[59]. A study of melanoma in a Spanish population discovered that SNPs relating to pigmentation constitutes one potential genetic cause underlying a higher rate for melanoma in males [60]. SNPs in genes (TYR, GPR143, and F2RL1) were shown to increase melanoma predisposition in males as opposed to females, and these SNPs were also found to be associated with dark pigmentation and sun tolerance in females but not in males [60]. A recent study reported that sex differences in outcomes of cutaneous melanoma patients were associated with inherited abnormalities on TP53, MDM2 and BCL2 genes in the apoptosis pathway [61]. The MC1R red hair variants were demonstrated to contribute differentially to melanoma risks in males and females [62].

Melanoma has a high rate of missense mutations [63]. These antigenic mutations increase the likelihood of detection by the immune system [63]. Patients with these high tumor mutational burdens (TMB) have lower mortality rates [64,65] and greater prognosis with immunotherapy. Counterintuitively, Gupta et al. reported a higher burden of somatic missense mutations among men (median of 298) compared to women (median of 211.5) using data from 266 metastatic melanomas from The Cancer Genome Atlas (TCGA) project [63], despite a higher overall male mortality.

While driver mutations in BRAF [66–68], NRAS [68], and KIT [69] are essential in the development and progression of melanoma, very few studies have observed evidence of differential mutations between males and females for these important genes [68,70,71] warranting future larger studies performing comprehensive assessments of sex differences in driver mutations.

X-linked genes have been implicated in sex differences in melanoma outcome. The PPP2R3B gene, located on the X chromosome in females and the Y chromosome in males, was reported to have lower expression in males than in females and was independently associated with poor melanoma outcome [72]. Autosomal gene expression levels differ between males and females and may also play an important role in exploring the mechanisms for the sex disparity in melanoma [44,73]. The miR-221&222 and miR-506–514 clusters, which could be related to sex differences, were demonstrated to have oncogenic roles in melanoma progression and melanocyte transform [74,75]. In addition, long non-coding RNAs are emerging as important modulators of melanoma proliferation, survival and metastatic behavior, which have the potential to be used as novel prognostic and diagnostic markers and contribute to understanding the sex differences in melanoma [13,76].

Behavioral Factors

The continued increase in melanoma-specific cancer incidence is often thought to be the result of a combination of increased detection (possibly over-diagnosis) and exposures such as tanning bed use and harmful recreational UV exposure [77]. However, while women are more likely to use tanning beds [78–81], the relative risk for melanoma from using tanning beds is similar for each sex [82].

Health Behavior

One of the hypothesized causes of later tumor stages at the time of diagnosis among males is the fact that they are less likely to go to the doctor [83–85] or find a tumor until it has grown deeper, while females tend to utilize more primary care than men [83,86].

Skin awareness, skin self-examination and physician examination are all associated with the discovery of thinner lesions by both males and females [87]. However, females are more likely to be aware of their skin and to conduct skin self-screening as well as visit physicians for health reasons.

Paddock et al found that in females the practice of routine skin self-examination increased the likelihood that the lesion would be self-discovered; females were significantly more likely to conduct skin self-examination than males (58.1 percent vs 41.9 percent, $p = 0.03$) [88].

“Skin awareness” (that is, being aware of one’s skin for medical or cosmetic reasons) was associated with a 50% decrease in melanoma mortality [89]. Females reported being approximately twice as likely to be aware of their skin and any problems. However, once a lesion was noticed, there was no difference by sex in the delay to seeing a clinician [90].

Brady et al, showed that females were more likely to self-detect melanoma lesions than men[91]; others have shown that females are also more aware of their skin [88] and more likely to utilize sunscreen[92,93].

Sun Exposure

Ultraviolet radiation, including both sun exposure and tanning bed use has been clearly and definitively associated with the development of melanoma by the International Agency for Cancer Research [94]. There are different types of sun exposure with “intermittent” sun exposure, the type of exposure one gets on weekends after being inside all week, often leading to sunburns, considered the major type of sun exposure associated with the development of melanoma [95]. This type of sun exposure is in contrast to chronic exposure, the type of sun exposure received on an almost daily basis, such as in occupation or gardening. Chronic exposure, in meta-analyses, does not increase the risk of melanoma [96].

The incidence pattern for melanoma differs dramatically by age and sex (Figure 1), such that females have a slightly higher rate of melanoma until around the age of 50 and then the incidence increases slowly while male incidence increases dramatically at that point[97]. Further, the anatomic site of melanoma differs by sex. These differences are consistent

across latitudes. Males tend to have the highest incidence of melanoma on the trunk and a higher incidence of melanoma on the head and neck than females. Females have a high incidence of melanoma on the leg. It is not clear whether these differences are a function of sun exposure patterns, a genetically controlled sex-linked characteristic, or a combination of both.

Gordon et al, analysed sun exposure data from Stockholm-Gotland healthcare region (average population 1.7 million), representing 20% of the Swedish population during the time period 1977 to 2001[98]. Their data demonstrates clearly that males received more UV radiation (intermittent overall and intermittent on the core) than females. This is in contrast to the lack of a difference between the sexes for ultraviolet radiation on the extremities (peripheral) and chronic. Such information underlines the differences between intermittent sun exposure and chronic exposure and their respective risks for developing melanoma.

Sun Protection

It is important to evaluate the association between sunscreen and other sun protection methods in reducing melanoma risk. The most persuasive evidence for the use of sunscreens comes from a randomized clinical trial conducted in Queensland, Australia, where there appeared to be a large reduction in the rate of invasive melanoma incidence in the group who used sunscreen (HR 0.29, 95% CI 0.08,0.97), three melanomas in the intervention group and 11 in the control group. [99]

A National Health Interview Survey interviewed a representative sample of 31,162 US adults in 2015. It appears that females generally use more sun protection than males (shade, sunscreen and sun avoidance). However, males appeared to use more clothing in the sun.

A large systematic review and meta-analysis involving 313,731 participants, 10,813 cases or non-melanoma skin cancer 857 cases found no association between the use of sunscreen and the development of melanoma[100]. A contradictory study by Rueegg et al, found protective associations for use of sunscreen in hospital-based studies, one ecological study and a randomized controlled trial[101] although there was large heterogeneity among study designs and among the case-control studies. When adjusted for confounding by sun exposure, sunburns and patient phenotype, all estimates moved to lower melanoma risk among sunscreen users.. However, population-based cases control and cohort studies found significant positive associations between the use of sunscreen and the development of melanoma. A case-control study of more than 1,000 participants in Minnesota also evaluated the use of sunscreens and other methods of sun protection and found that sunscreens were associated with a reduced risk of developing melanoma but that other sun protection methods, such as seeking shade and using clothing were far stronger in their association with a reduced risk of melanoma [93].

Conclusion

Despite major progress in melanoma treatment in the development of immunotherapy, understanding the relation between mutational loads and the immune system, and the rich

literature documenting marked sex differences in immunocompetence, hormones, and genetics in melanoma, sex disparities in survival persist.

Although there are multiple differences between men and women in terms of behavior in the sun and in utilization of primary care; differences in these behaviors would suggest higher incidence in women not lower. Thus, it seems much more likely that the biological differences are critical in terms of developing advanced melanoma and that more investigation of these is needed.

Biological sex is a fundamental factor in melanoma. It is critical that future studies be powered sufficiently to account for sex differences. These sex disparities in melanoma outcomes provide an excellent opportunity to test clear hypotheses and to develop new insights into the underlying mechanisms of melanoma, cancer, and the immune system.

Acknowledgements:

This work was supported by P01 CA 206980-01A1 to MB and 3P01CA206980-02SZ to MS.

Matthew Robert Schwartz reports grants from NCI 3P01CA206980-01 - Diversity Supplement to Schwartz - during the conduct of the study.

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•• Of major importance

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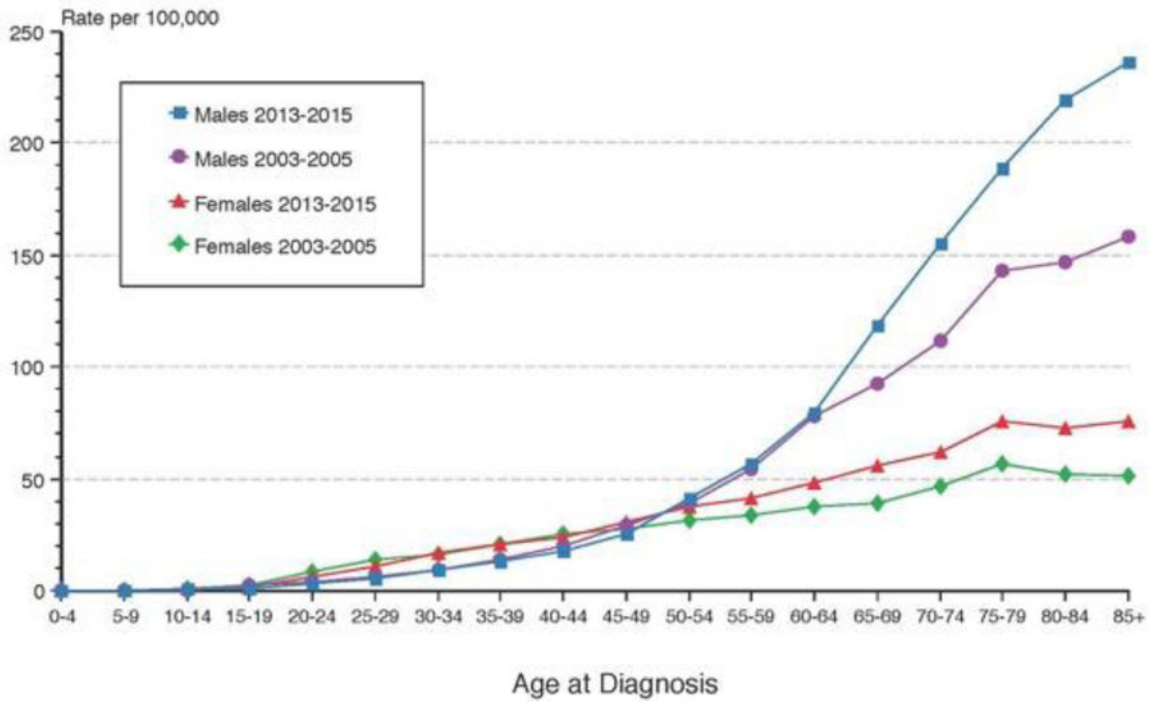

Figure 1.

Melanoma incidence comparing 2003–2005 to 2013–2015 among whites (including Hispanics) by age and sex. From SEER.