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A cancer registry-based analysis on the non-white populations reveals a critical role of the female sex in early-onset melanoma

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Abstract

Purpose—Most melanoma studies have been performed in the white population who exhibits the highest incidence rate due to their skin sensitivity to UV radiation. Previous publications have shown that young women (approximately under the menopausal age) exhibit higher incidence rates than men of the same age, and the causes are mostly attributed to their sun behavior or indoor tanning. In our recent publications, we suggested that higher risk in younger women was due to pathophysiological factors, such as hormonal impact, and thus this higher risk in young women should be shared across ethnicities regardless of their skin color or UV behavior.

Methods—A total of 13,208 non-white melanoma patients from SEER and 15,226 from WHO CI5-Plus were extracted for analysis. Age-specific incidence rates, female to male incidence rate ratios, and p-values were calculated.

Results—As observed in the white population, younger women and older men showed higher melanoma incidence rates than their peers of the other gender in all ethnic groups. The highest female to male incidence rate ratios were observed in the pubescent and reproductive ages. Previously this gender discrepancy in the white population was attributed to the preference of skin tanning in young females. There is no evidence to show that darker skinned young females adopt a similar tanning preference. Thus the age-dependent gender difference in the risk of melanoma is shared across ethnic groups and is perhaps independent of UV behavior.

Conclusions—Our results highlight the importance of gender as one of the melanoma risk factors beyond traditional UV radiation, which warrants further investigation and may provide a base for an improved prevention strategy.

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Conflict of Interests

None of the authors has conflicts of interest.

Keywords

Melanoma; gender difference; sex; incidence rate; incidence rate ratio; multiple ethnicity; race; non-white population

Introduction

Cutaneous melanoma has been considered as a UV radiation-driven malignancy [1–5]. Therefore, deciphering the mechanisms involved in UV-mediated melanoma formation and development has been the top priority in the field of melanoma prevention [6]. Because the white population exhibits the highest incidence rate compared with other ethnic groups [7], related etiological mechanisms have been extensively studied in this population. For example, the rich pheomelanin in the whites is found not only less effective in protecting skin stem cells [8], but also more prone to produce reactive oxygen species (ROS) upon UV stimulation [9]. The UV-broken melanin fragments are also found to diffuse along with ROS into the nucleus to induce DNA mutations, immunosuppression, and photoaging [5, 10]. All these factors had led to the importance of melanin-related oxidative stress in the photobiological cause of melanoma in the whites. Fewer studies were based on other ethnic groups.

Recently, new epidemiology study on melanoma gender differences discovered that sex might play an independent role in early onset melanoma, which may add expanded levels of understanding to our current UV-based melanomagenesis mechanism [11]. Overall incidence rates of men in all races in the US were higher than that of women [12]. However when stratified by age, women under age 50 showed higher incidence rates as compared to men of the same age; and the incidence rates switched after age 50 [13]. The highest female to male incidence rate ratio (RR) was found to be between age 20 and 24 years in the whites [14]. Our previous study suggested that other ethnic groups should have shown a similar age-dependent gender differences pattern [14]. Therefore, in this study, we focused on the gender difference in the non-white ethnic populations based on a hypothesis that young women are at higher risk of melanoma than young men in the same age range regardless of their race or skin color. This hypothesis argued for the importance of gender-related factors in early onset melanoma based on two reasons: 1) skin from the non-whites usually contains higher eumelanin levels, which are more protective against UV radiation; 2) while tanning bed use is popular in the whites, there is no such popularity in the non-whites, thus it is presumed that the often-blamed tanning device use should be excluded from the risks of the observed gender difference for early onset melanoma. In order to address these questions and provide evidence for our hypothesis, data from the US Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute were used to analyze the incidence rate and rate ratio by age in the non-Hispanic blacks, Hispanics, Asians/Pacific Islanders, and American Indians/Alaska Natives. Furthermore, data from the Cancer Incidence in Five Continents, International Agency for Research on Cancer (IARC)/World Health Organization were used to validate the SEER findings.

The intrinsic sex impact on melanoma development has been understudied because in the past, most of the sex disparity of melanoma incidence rates at younger age was attributed to differential artificial and solar UV exposure [15–18]. Therefore the emphasis for prevention and molecular studies has been focused on UV effect. This is partially due to the early incorrect conclusion that estrogen receptors were absent in melanoma[19]. All three estrogen receptors (ERα, ERβ and GPER1) were recently reported in melanoma tissues and cell lines [20–23]. These results provide molecular and cellular supports for our epidemiological observations, in which the female sex is independent of UV radiation and serves as a risk factor at younger age [24]. Naturally the high estrogen levels in pre-menopausal women become potential driving forces for melanoma. Our previous studies showed that the female to male rate ratios approach 1 around 45–54 years of age [14], which is approximate age for menopause in women in the US [25]. Therefore young or old ages in this study refer to ages younger or older than this menopause approximated-age. This study aims to show that the melanoma incidence rates are also higher in young women as compared to young men in non-white ethnic groups, thus potentially excluding the indoor tanning bed use as a major attributor for the observed sex difference at young ages.

Our results may open discussions in melanoma research field on non-UV risk factors, thus novel prevention strategies can be initiated. As large effort of public education on sunscreen use has been in place for many years, the incidence rate of melanoma continues to increase. The understudied non-UV risk factors may therefore be an explanation for the observed ineffectiveness of sun protection behaviors.

Materials and methods

Study population

SEER13 database (Incidence - SEER13 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (1992–2014) <Katrina/Rita Population Adjustment>) was downloaded through SEER*Stat software (version 8.3.4). Melanoma cases were collected from 13 SEER registries, including San Francisco-Oakland SMSA, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, and Rural Georgia. Melanoma cases from 5 new registries collected between the year 2000 and 2014 in the SEER18 database, including California (excluding SF/SJM/LA), Kentucky, Louisiana, New Jersey, and Greater Georgia were combined with SEER13 data. Non-Hispanic black (B, n=1,533), Hispanic (Spanish-Hispanic-Latino, n=9,122), non-Hispanic Asian or Pacific Islander (API, n=1,968), and non-Hispanic American Indian or Alaska Native (AI, n=585) melanoma cases were included in this study.

The Cancer Incidence in Five Continents database (CI5) is the result of a long collaboration between the International Agency for Research on Cancer (IARC)/World Health Organization and the International Association of Cancer Registries. The CI5-Plus (1978–2007) database, which contains updated annual incidence rates for 118 selected populations from 102 cancer registries published in CI5 volumes I to X, was downloaded for analysis to validate the findings from SEER. Cancer cases from registries of the US SEER were excluded (registry codes 84001-84099). Black (registry code 80002 “Uganda”, n=90),

Hispanic (registry codes 7602 “Brazil”, 17001 ”Colombia”, 18800 “Costa Rica”, 21801 “Ecuador”, 72410, 72404, 72406, 72407, 72408, 72410, 72413 “Spain”, n=10,645), and Asian (registry codes 35064, 35606, 35607 “India”, 39203, 39204, 39206 “Japan”, 60801 “Philippines”, 70200 “Singapore”, 76401, 76404, 76405 “Thailand”, n=4,491, no melanoma cases documented in China registries up to 2007) melanoma cases were included for validation analysis.

Definition of melanoma

Melanoma was defined in the SEER database based on the Site Recode ICD-O-3/WHO 2008 as “Melanoma of the skin”, and having AYA site recode/WHO 2008 category “7.1 Melanoma”. The Primary Sites “C00.0-C80.9” were all included. ICD-O-3 Hist/behave, malignant categories of invasive melanoma “8720/3-8723/3, 8726/3, 8727/3, 8730/3, 8740/3-8746/3, 8761/3, 8770/3-8774/3, and 8780/3” were included, with exclusion of those in situ and non-cutaneous morphologies. Malignant melanoma was defined as “C43 Melanoma of the skin” using the ICD-10 site code in the CI5 database with exclusion of in situ melanomas, as well as having the cancer code of “65 Melanoma of the skin”. Therefore, melanoma in this study refers to invasive malignant melanoma and does not include in situ melanoma.

Statistics

Age-adjusted incidence per 100,000 person-years was derived using US 2000 Census Standard Population in 19 five-year age groups (0, 0–4, 5–9,…, 80–84, and 85+) in SEER [26], and using World (WHO 2000–2025) Standard Million in 19 age groups in CI5. All further analysis and data management were carried out in RStudio (version 3.2.2), Stata or Microsoft Excel 2010, if not specified. Incidence rate ratio was calculated using female age-specific incidence rate divided by male age-specific incidence rate. The 95% confidence intervals of rate ratios were calculated by Stata software using standard errors calculated from natural log rate ratios [27]. The p-value of trend for rate ratio change over different time period was calculated by chi-square test for trend according to the Cochran-Armitage method [28].

Results

Patient characteristics

Cancer cases of all causes documented in the SEER13 database (1992–2014), as well as the 5 new registries in the SEER18 database (2000–2014), encompassed approximately 27.8% of the entire US population [29]. Melanoma cases extracted from SEER13 and 18 databases included 1,533 (12%) non-Hispanic blacks, 9,122 (69%) Hispanics, 1,968 (15%) non-Hispanic Asians or Pacific Islanders, and 585 (4%) non-Hispanic American Indians or Alaska Natives (Table 1).

The Cancer Incidence in Five Continents database (CI5-Plus, 1978–2007), downloaded from the International Agency for Research on Cancer (IARC), World Health Organization, included 90 (0.6%) black melanoma cases extracted from the Uganda registry, 10,645 (70%) Hispanic cases extracted from the Brazil, Colombia, Costa Rica, Ecuador, and the Spain

registries, and 4,491 (29%) Asian cases extracted from the India, Japan, Philippines, Singapore, and the Thailand registries. In both the SEER and CI5 databases, the female case numbers are higher than the case numbers of the male.

Age-specific incidence rate patterns

In both the SEER and CI5 databases, the age-adjusted incidence per 100,000 person-years of all ages shows that men have a higher overall incidence rate as compared to women in the Asian or Pacific Islander and the American Indian or Alaska Native populations. However, in the non-Hispanic black (black for short) and Hispanic groups, women have overall higher incidence rates than men (Table 2).

As reported before, melanoma incidence rates increase with age, with age > 50 years showing higher incidence rates than younger age in almost all ethnic groups (Fig. 1A–1F). One exception is that the highest age-specific rate is found in the group of 80–84 years in the Hispanic males and the American Indians or Alaska Natives (both male and females) (Fig. 1B, 1D). The oldest group (85+ group) in fact shows a slightly decreased rate (Fig. 1B, 1D). Among the ethnic groups in the CI5 database, the highest age-specific incidence rate is observed in the oldest men (85+ group).

In the SEER database, black women show higher incidence rates at the age of 15–49 years. No incidence was reported before age 15. Men, on the other hand, exhibit higher risk after age 50. In the Hispanics, women exhibit higher incidence rates when younger than 59 years, and men present higher risks after age 60 (Fig. 1B). A similar trend is also observed in the Asian or Pacific Islander (Fig. 1C) and the American Indian or Alaska Native groups (Fig. 1D). Higher incidence rates are found between the age of 20 to 54 years in the females, and the trend reverses after age 55, with males showing higher incidence rates in the Asian or Pacific Islander group. However, among American Indians or Alaska Natives, women show higher rates at the age of 20–44 years, while men show higher incidences after age 45.

Age-specific incidence rate ratio pattern

Age- and gender-specific incidence RRs were calculated and listed in Table 3. A higher risk of melanoma is evident in younger women in the non-Hispanic blacks, Hispanics, Asians or Pacific Islanders, and the American Indians or Alaska Natives in the SEER database (Table 3). The highest female to male RRs are 3.85 (95% CI 1.04–21.2), 2.51 (95% CI 1.11–6.19), and 4.36 (95% CI 0.87–42.2, not significant) at the 20–24 age group in the non-Hispanic blacks, Asians or Pacific Islanders, and the American Indians or Alaska Natives, respectively, similar to what was observed in the white population [14]. Overall the pooled population showed RR of 2.67 (2.17–3.30) at 20–24 years of age category (Table 3). Men present higher incidence rates of melanoma after age 60 in all four ethnic groups.

In the CI5 database, the case numbers for blacks are too small when stratified by age and sex (each age group has less than 10 cases and many groups have 0 cases), and thus blacks are excluded for further age-specific rate ratio analysis.

In accordance with what we have found in the US SEER database, the Hispanics (Fig. 1E) and the Asians (Fig. 1F) in the CI5 database show similar trend to the SEER results, in

which younger Hispanic women (< 55 years) and younger Asian women (< 40 years) exhibit higher incidence rates than men, whereas men have higher risks of melanoma at older ages.

Again, the age-specific female to male incidence rate ratios were calculated and listed in Table 4. The Hispanic females start to show a higher rate ratio of 1.81 (95% CI 1.18–2.81) at the age of 15–19 years up until the age of 45–49 years (RR=1.23, 95% CI 1.07–1.41), similar to the trend observed in the Hispanic population documented in the US SEER database (Table 3). The highest rate ratio of 1.81 (95% CI 1.18–2.81) is found in the 15–19 age group (Table 4), somewhat deviating from 25–29 age group in the US SEER Hispanic population where the rate ratio is the highest at 3.31 (95% CI 2.59–4.25) (Table 3). Incidence rates in the Hispanic men exceed that in women after age 55, comparable to age 60 in the US SEER data. In the Southeast Asia, females under age 39 exhibit higher risk of melanoma than males and males tend to have a higher risk of melanoma after age 40 (Table 4). The significance levels are compromised in most of the young age group as the RR intervals containing 1, except for age group 30–34 (RR=1.44, 95% CI 1.04–2.00). The highest rate ratio was observed at the youngest age categories with non-significant 95% confidence intervals (0–4 and 5–9, Table 4).

As shown in Fig. 2, age-specific incidence rate ratios were plotted for both the US SEER (Fig. 2A) and WHO CI5 (Fig. 2B) databases. Younger women across all races show higher incidence than men in the same age range, with a female to male rate ratio greater than 1. In contrast, older men (> 60 years) of all races show higher incidence rates than women in the same age range, with a rate ratio less than 1. Data from the US SEER and WHO CI5 show similar trends, but the difference is manifested at slightly different levels, with CI5 data showing lower rate ratios (i.e. showing less gender differences) than the US SEER data. Overall, the same gender difference pattern is observed across all races between the two databases.

UV is the most important environmental risk factor for melanoma. In order to examine whether geographical UV radiation impacts the female to male rate ratios, we separated the US SEER registries by latitude of 40°N, resulting in two strata: South (California, Utah, New Mexico, Louisiana, Georgia, and Kentucky and Hawaii) and North (Alaska, Washington, Iowa, Illinois, Connecticut, and New Jersey). The North and South Age-specific melanoma rate ratios were calculated and plotted in Fig. 2C. Overall the rate ratio patterns are similar in North and South; incidence rates are higher in young women than in young men. The peak difference shows a slight age shift: peak at 20–24 in the North group and 25–29 in the South group.

In order to examine whether this gender ratio changes over time, we combined all non-white populations for every 8-year period in the US SEER data, namely years 1992–1999, 2000–2007, and 2008–2014 (the last period only contains 7 years of data) (Fig. 2D). Over these different periods of time, there are the same patterns of the female to male rate ratio, in which females show higher incidence rates at younger age and lower rates at older age as compared to males. The peak difference is at age 20–24 for all three periods, exactly as we reported before in the Caucasian population [14]. When we selectively examined the 20–24 years age group, it is quite interesting that the female/male rate ratios increased over the

time, from 1.99 (95% 1.71–2.31) in 1992–1999, to 2.17 (95% CI 1.90–2.50) in 2000–2007, and 2.74 (95% CI 2.34–3.23) in 2008 to 2014 (Fig. 2E). The trend of ratio increase is significant (p_{Trend} =0.0058).

Discussion

In this cancer registry-based study, we show that there is a coherent age-dependent gender difference in the risk of melanoma across all ethnic groups. Specifically, in the SEER database, black women under the age of 50 exhibit higher incidence rates of cutaneous melanoma; above that age women showed lower incidence rates. The switching age is 60 in the Hispanics, 55 in the Asians, and 45 in the American Indians. In the WHO CI5 database, Hispanics women under age 55 and Asian women under age 40 have higher incidence rates of cutaneous melanoma. Men over the age of 60 years, in general, unanimously exhibit higher risk for melanoma than the same age range women in the above mentioned ethnic groups. The switching age shows a slight shift among these populations. The female to male rate ratios also vary from slightly over 1 to nearly 4 (with significant 95% confidence intervals, Tables 3, Table 4, and Fig. 2). The highest age-specific female to male incidence rate ratios in the SEER database are found in the 20–24 years age group in the blacks, Asians, and American Indians, and 25–29 years in the Hispanics. In the WHO CI5 database, Asians also show general higher female to male rate ratios at the reproductive age but the trend is less consistent. The highest rate ratio is observed at 0–4 (RR = 2.92, 95% CI 0.87–12.59) and 5–9 (RR=1.70, 95% CI 0.49–6.59); neither reached significance level of 0.05. In the WHO CI5 Hispanics population, the highest age-specific female to male incidence rate ratios (RR=1.81, 95% CI 1.18–2.81) are observed in the 15–19 years pubescent age group, similar to that in the SEER dataset. Previously this gender difference pattern was reported in the Caucasian population [11, 14]. Now we demonstrate that the age-dependent gender differences in melanoma risk are shared across ethnic groups, which may suggest gender as one of the melanoma risk factors in addition to the traditional UV radiation.

The higher incidence rates in younger females in the Caucasians have been speculated to be associated with their life style and tanning bed use [30, 31]. In other words, women of the younger age are less covered in the sun and use tanning devices more frequently [31, 32]; hence they are more exposed to solar and/or artificial UV radiation. Ultimately, UV radiation is assumed responsibility for the gender difference at younger age. However, it was reported that indoor tanning only accounted for 2.6–9.4% of melanoma incidence [17] and the overall UV radiation contribution was approximately 50% to melanoma etiology [33]. Also, females are reported to use more sun protection strategies than males [34, 35]. Therefore, the life style and UV device use do not seem to completely explain the over 2 fold of incidence rate ratio (female/male) in the peak age (20–24 years) in the Caucasians [14]. Our previous results have demonstrated that the female sex is independent of ambient UV radiation as a risk factor for early-onset melanoma [24]. However, the tanning device use may still be a confounder for the female sex. We could not rule out the alternative explanation from tanning device use for the higher incidence of early-onset melanoma in women. Tanning device use is a habit for the white population as tan skin color is considered fashionable and desired. On the other hand, despite the possibility of tanning among some non-white populations, such behavior might be unpopular in these ethnicity groups. Findings from the

present study reveal that darker skinned females under the age of 40–55 still have higher risk of melanoma than their male peers, indicates that tanning device use may not be a common determinant for the observed higher risk of early-onset melanoma in women.

A better health consciousness in younger women may be a partial reason for the observed gender differences due to early detection that explains the higher incidence in this age range. In a retrospective case-control study in the non-Hispanic whites, it was found that women were more likely to notice melanomas on their partners, as well as to their own bodies compared with men [36]. This resulted in women having statistically significant smaller and thinner melanomas and better outcomes than men. Women at all ages also showed fewer melanoma metastases and fewer melanoma-related deaths than men. In addition, a survey conducted in Texas found that women were more likely to limit outdoor activity, and seek shade when being outdoors as compared to men [37]. Socioeconomic factors such as income, educational level, and access to healthcare might be the background determinants in shaping the health consciousness [38]. How socioeconomic factors contribute to the observed sex difference in incidence rates requires further exploration.

A pathophysiological factor may provide an alternative explanation for the observed gender differences. Melanoma is the most frequently diagnosed cancer during pregnancy and also in the 25–29 age group [39]. It is well documented that pregnancy impacts cutaneous melanocyte homeostasis [40]. In our recent study, cutaneous melanoma cases from 31 European cancer registries and SEER18 database were extracted and correlated to geographical UV radiation [11]. Results showed that local ambient UV differentially affected cutaneous melanoma incidence rates between genders. No correlation between female cutaneous melanoma incidence rates and UV index was found, but men showed a significant correlation to ambient UV index [11]. Assuming the female sex exhibits a significant impact on early-onset melanoma risk, the lack of significant association between female rates and ambient UV index can be explained. The current study provides further evidence that it may be the female sex itself that promotes melanoma risk under the age of 50, although indirect.

On the other hand, old men show higher incidence rates than old women in almost all ethnicity groups. In the US, men not only show overall higher melanoma incidence than women, they also show worse outcome [41]. The precise reason is not fully understood, but it is known that men use less sun protection and thus are likely to accumulative more UV damage at older age [42]. If our hypothesis of hormonal regulation is correct, the sharp decrease of testosterone levels and/or increase of estrogen levels at older age in men may also contribute to melanoma risk.

Recent publications suggested possible roles of estrogen and its receptors in melanoma etiology [20, 43, 44]. Estrogen can potentially induce melanocyte growth during pregnancy [45]. Although expression of estrogen receptors was found in melanoma cells, different subtypes (namely, ERα, ERβ and GPER1) may exhibit different function [20]. Genetic variations in ESR1 (ERα) were found to impact melanoma risk [46]. However, overall the role of estrogen in melanoma risk remains to be further elucidated. Through our current

study we hope to confirm an independent role of sex in melanoma development, which will help to build a base for further investigations on sex hormones and melanoma.

As shown in Table 2, the absolute age-adjusted incidence rates in the SEER database are much lower than the corresponding rates in CI5 for all races. In the CI5 database, the number of black cases is small because the only available source was the Uganda registry. The higher rate in this population may be associated with its high average annual UV index (UVI=11–12, higher than annual average UVI of 10 in Hawaii). Hispanic is a mixed heritage with much heterogeneity of skin color and genetic background. Their skin color can range from light (the “white Hispanics” [47]) to dark shades. It is unclear whether the Hispanics from CI5 datasets are “whiter” than their peers in the US; the dramatic difference of melanoma incidence in these two datasets for Hispanics may provide a good model for genetic epidemiological research and warrant further investigation [48]. As for the different rates in the two datasets for Asian population, we also do not understand the underlying reasons, but it is known that the cancer incidence patterns in immigrants change after the first generation, presumably due to the diet and environmental changes [49].

To conclude, age-dependent gender differences in the incidence rates of melanoma are observed in all ethnic groups and both datasets. Younger women at pubescent and reproductive ages show higher risks than men in the same age range, while older men exhibit a higher risk than their women peers. The switching age is close to women’s menopause period (i.e. 40–55 years), suggesting a hormonal effect. These new findings may provide a base for promoting additional prevention strategies. The role of gender in melanoma risk and the underlying mechanisms warrant further investigation.

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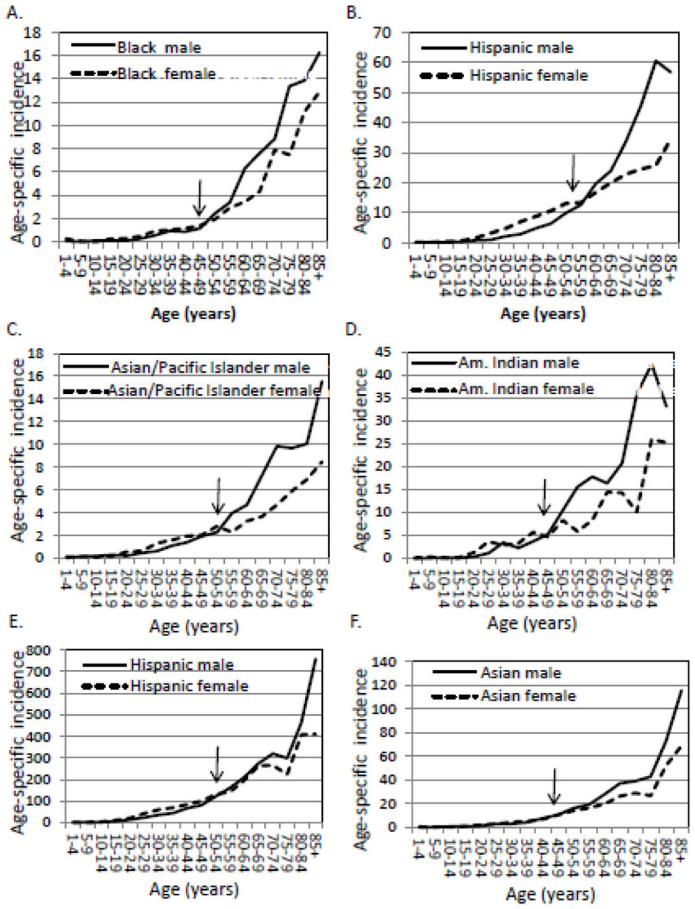

Fig. 1. Age-specific incidence rates of melanoma by gender

A. Non-Hispanic blacks (SEER data); B. Hispanics (SEER data); C. Asians or Pacific Islanders (SEER data); D. American Indians or Alaska Natives (SEER data); E. Hispanics (CI5 data); F. Asians (CI5 data).

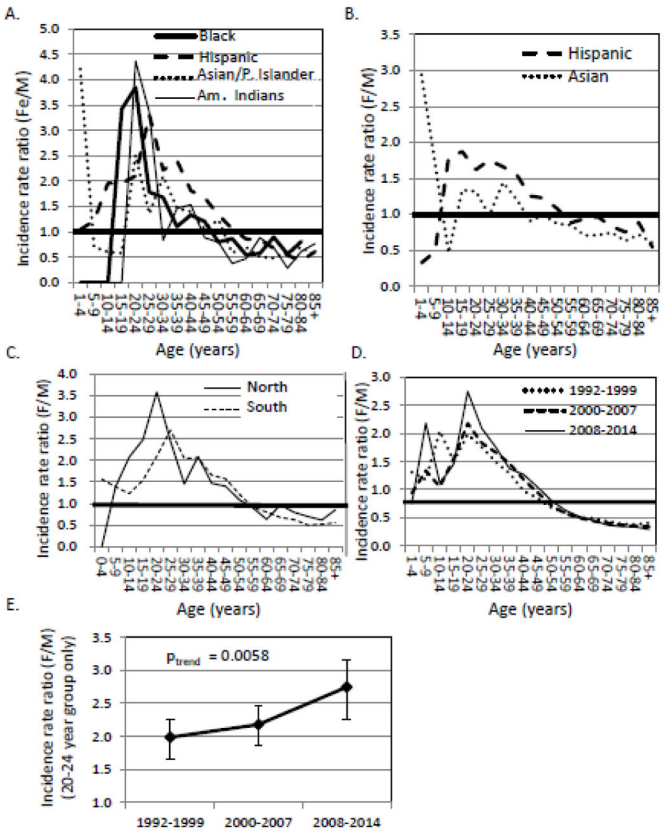

Fig. 2. Age-specific female to male incidence rate ratios by race, age and years of diagnosis

A. SEER data by race and age; B. CI5 data by race and age; C. SEER data with all races stratified by geographical location (South and North is divided by latitude of 40°N); D, SEER data with all races stratified by diagnosis years. E, the trend of female to male rate ratio at 20–24 years of age in different period of time. Thick black horizontal line: RR=1.

Table 1

Cutaneous melanoma patient characteristics of the SEER and CI5 databases.

Registry		SEER	IARC/WHO CI5-Plus[a]
Year		1992–2014	1978–2007
Melanoma (N, Total)		13,208	15,226
Sex	Male (%)	5,953 (45%)	7,271 (48%)
	Female (%)	7,255 (55%)	7,973 (52%)
Ethnicity	Black (%)	1,533 (12%)	90 (0.6%)[b]
	Hispanic (%)	9,122 (69%)	10,645 (70%)[c]
	Asian or Pacific Islander (%)	1,968 (15%)	4,491 (29%)[d]
	American Indian or Alaska Native (%)	585 (4%)	N/A
Age	Mean	56	58
	Standard deviation	59	60
	Median	57	57

[a] Excluding melanoma cases from the US SEER registries.

[b] Source available only from the Uganda registry.

[c] Including registries from Brazil, Colombia, Costa Rica, Ecuador, and Spain.

[d] Including registries from India, Japan, Philippines, Singapore, and Thailand.

Table 2

Summary of the SEER and CI5 data.

	SEER[a]		CI5[b]	
	Male	**Female**	**Male**	**Female**
No. of melanoma in study (%)	5,953 (45%)	7,255 (55%)	7,271 (48%)	7,973 (52%)
Age-adjusted incidence per 100,000 person-years of all ages				
Black	2.27	1.81	13.05	22.46
Hispanic	8.49	7.99	69.96	72.08
Asian or Pacific Islander	2.24	1.75	9.07	7.44
American Indian or Alaska Native	6.74	4.79	N/A	N/A

[a]Age-adjusted incidence per 100,000 person-years was done by using US 2000 Census Standard Population in 19 age groups in SEER.

[b]Age-adjusted incidence per 100,000 person-years was done by using World (WHO 2000–2025) Standard Million in 19 age groups in CI5.

Table 3

Age-specific incidence rate ratios by ethnicity (SEER 1992–2014).

	Black			Hispanic			Asian			American Indians			All non-Whites		
		95% CI			95% CI			95% CI			95% CI			95% CI	
Age	RR (F/M)	lower	upper	RR (F/M)	lower	upper	RR (F/M)	lower	upper	RR (F/M)	lower	upper	RR (F/M)	lower	upper
0–4	0.91	0.07	12.52	1.04	0.37	2.97	3.69	0.70	36.40	N/A	N/A	N/A	1.44	0.67	3.21
5–9	N/A	N/A	N/A	1.21	0.52	2.88	0.70	0.14	2.94	N/A	N/A	N/A	1.26	0.74	2.16
10–14	0.00	0.00	1.57	**1.95**	1.03	3.84	0.60	0.13	2.36	N/A	N/A	N/A	**1.70**	1.13	2.59
15–19	3.42	0.88	19.35	**1.96**	1.19	3.29	0.58	0.18	1.70	N/A	N/A	N/A	**2.17**	1.66	2.85
20–24	**3.85**	1.04	21.24	**2.10**	1.56	2.85	**2.51**	1.11	6.19	4.36	0.87	42.19	**2.67**	2.17	3.30
25–29	1.78	0.80	4.27	**3.31**	2.59	4.25	1.35	0.75	2.49	**3.36**	1.39	9.31	**1.93**	1.65	2.25
30–34	1.68	0.97	2.99	**2.22**	1.86	2.65	**2.09**	1.32	3.39	0.83	0.41	1.65	**1.96**	1.71	2.25
35–39	1.10	0.69	1.77	**2.40**	2.04	2.82	**1.46**	1.00	2.16	1.46	0.68	3.21	**1.61**	1.43	1.82
40–44	1.33	0.83	2.17	**1.81**	1.57	2.09	1.39	0.99	1.99	1.53	0.85	2.84	**1.42**	1.26	1.60
45–49	1.20	0.77	1.89	**1.67**	1.45	1.92	1.05	0.76	1.47	0.88	0.48	1.62	1.27	0.65	2.51
50–54	0.80	0.55	1.15	**1.33**	1.17	1.52	1.23	0.90	1.69	0.79	0.49	1.28	1.18	1.05	1.32
55–59	0.86	0.61	1.21	1.06	0.92	1.22	0.58	0.42	0.80	0.37	0.21	0.65	0.88	0.78	0.98
60–64	0.54	0.39	0.75	0.86	0.74	0.98	0.69	0.51	0.94	0.47	0.26	0.83	0.75	0.67	0.84
65–69	0.57	0.41	0.79	0.83	0.72	0.96	0.50	0.37	0.68	0.88	0.48	1.61	0.72	0.64	0.81
70–74	0.89	0.65	1.22	0.68	0.58	0.79	0.48	0.35	0.64	0.69	0.35	1.36	0.66	0.59	0.75
75–79	0.56	0.40	0.78	0.54	0.46	0.63	0.61	0.44	0.84	0.28	0.11	0.63	0.55	0.48	0.62
80–84	0.81	0.55	1.19	0.42	0.35	0.51	0.69	0.47	1.00	0.61	0.28	1.32	0.53	0.45	0.61
85+	0.79	0.53	1.19	0.61	0.50	0.75	0.54	0.38	0.77	0.76	0.30	2.02	0.63	0.54	0.74
All age	1.02	0.92	1.13	1.36	1.31	1.42	0.92	0.84	1.00	0.90	0.76	1.06	1.19	1.15	1.23

N/A: not applicable. Bolded: significant numbers for higher F/M ratio.

Table 4

Age-specific incidence rate ratios by ethnicity (CI5 1978–2007).

	Hispanic			Asian			All CI5		
		95% CI			95% CI			95% CI	
Age	RR(F/M)	lower	upper	RR (F/M)	lower	upper	RR (F/M)	lower	upper
0–4	0.32	0.08	1.04	2.92	0.87	12.59	0.94	0.44	1.99
5–9	0.47	0.13	1.48	1.70	0.49	6.59	0.92	0.42	2.02
10–14	1.77	0.88	3.70	0.45	0.17	1.07	1.06	0.63	1.77
15–19	**1.81**	1.18	2.81	1.27	0.64	2.52	**1.71**	1.20	2.46
20–24	**1.58**	1.19	2.11	1.25	0.79	2.00	**1.61**	1.27	2.05
25–29	**1.71**	1.39	2.10	0.97	0.69	1.37	**1.53**	1.29	1.82
30–34	**1.61**	1.35	1.92	**1.44**	1.04	2.00	**1.67**	1.43	1.95
35–39	**1.52**	1.29	1.79	1.26	0.94	1.70	**1.53**	1.33	1.76
40–44	**1.25**	1.09	1.45	0.94	0.73	1.20	**1.24**	1.09	1.40
45–49	**1.23**	1.07	1.41	1.03	0.83	1.28	**1.23**	1.10	1.38
50–54	1.08	0.95	1.23	0.87	0.72	1.06	1.07	0.96	1.19
55–59	0.89	0.78	1.01	0.85	0.70	1.03	0.91	0.82	1.02
60–64	0.94	0.83	1.07	0.70	0.58	0.84	0.88	0.79	0.98
65–69	0.97	0.86	1.10	0.70	0.59	0.83	0.88	0.80	0.97
70–74	0.83	0.73	0.94	0.71	0.58	0.86	0.79	0.72	0.88
75–79	0.75	0.66	0.85	0.59	0.48	0.73	0.69	0.62	0.77
80–84	0.84	0.72	0.98	0.68	0.53	0.87	0.74	0.65	0.84
85+	0.54	0.46	0.64	0.66	0.50	0.87	0.52	0.45	0.60
All age	1.14	1.10	1.19	0.96	0.91	1.02	1.13	1.09	1.17

All CI5: including Hispanic, Asian and Black ethnicities. Bold: significant F/M ratios.

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