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Melanoma in women of childbearing age and in pregnancy in California, 1994–2015: a population-based cohort study

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Abstract

Background: Melanoma is one of the most common malignancies during pregnancy. There is debate regarding the impact of pregnancy on the prognosis of melanoma. Recent large population-based studies from the United States are lacking.

Objectives: To determine the characteristics and survival of women with pregnancy-associated melanoma.

Methods: This population-based, retrospective cohort study used California Cancer Registry data linked with statewide hospitalization and ambulatory surgery data to identify 15–44-year-old female patients diagnosed with melanoma in 1994–2015, including pregnant patients. Multivariable logistic regression compared demographic and clinical characteristics between pregnant and non-pregnant women with melanoma. Multivariable cox proportional hazards regression models assessed melanoma specific and overall survival.

Results: We identified 13108 patients, of which 1406 were pregnant. Pregnancy-associated melanoma was more frequent in Hispanic compared to non-Hispanic White women. Melanoma occurring postpartum was associated with greater tumor thickness (2.01–4.00 vs 0.01–1.00 mm, odds ratio 1.75, 95% confidence interval: 1.03–2.98). There were otherwise no significant differences between pregnant and non-pregnant women. Worse survival was associated

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with Asian, Black and Native American race/ethnicity (versus non-Hispanic White), lower neighborhood socioeconomic status, public insurance, tumor site, greater tumor thickness, and lymph node involvement, but not pregnancy.

Conclusions: Melanoma occurring postpartum was associated with greater tumor thickness, but pregnancy status did not affect survival after melanoma. Race/ethnicity, socioeconomic status and health insurance impacted survival, emphasizing the importance of reducing health disparities.

Keywords

skin cancer; melanoma; pregnancy; survival; melanoma in pregnancy; pregnancy-associated melanoma; epidemiology; management

INTRODUCTION

Melanoma is one of the most common cancers in pregnancy[1] and approximately one third of melanomas in women occur during child-bearing years,[2, 3] yet there is debate regarding the impact of pregnancy on melanoma prognosis. Initial reports suggested that pregnancy promotes malignant transformation, growth, and metastatic potential of melanoma.[3–5] Since then, various studies have shown mixed results on the characteristics and prognosis of pregnancy-associated melanoma (PAM) defined as melanoma diagnosed during antepartum and postpartum periods, with a limited number of large population-based studies showing no evidence of worsened prognosis of PAM.[3, 6–14]

The clinical management of women with PAM may also pose challenges.[15] As pregnancy may influence timing of surgery or lymph node procedures,[16] and delays in excision impact survival,[17] it is prudent to better understand the impact of pregnancy on management of melanoma.

Recent population-based studies on PAM are lacking from the United States and data on diverse patient populations are limited.[10] Additionally, investigations in the management of PAM such as timing of surgery are scarce. Therefore, we conducted a population-based, retrospective cohort study to investigate the clinical, tumor and management characteristics of PAM and the impact of pregnancy on the survival of women with PAM by studying a racially/ethnically diverse population in California using the population-based California Cancer Registry (CCR) data.

PATIENTS AND METHODS

Design, Setting and Population

IRB approval was obtained. Female patients 15–44 years of age diagnosed with first primary melanoma [International Classification of Diseases—Oncology, 3rd edition histology (8720–8790) and site (C44.0-C44.9) codes] during the period 1994–2015 were identified in the CCR and patient, tumor and management characteristics, and vital status were recorded. To eliminate the impact of a second cancer on survival, women who were subsequently diagnosed with a non-melanoma second cancer were excluded. Additionally, women who lacked data on diagnosis date or were lost to follow up were excluded. The CCR and

California Department of Health Care Access and Information (HCAI) hospitalization and ambulatory surgery center data were linked using a deterministic strategy based on social security number and gender to identify patients who were diagnosed with melanoma and pregnant (pregnancy or delivery related diagnosis codes from OSPHD are listed in Table S1). Similar to the study by O'Meara et al. [10], women were considered to have PAM if they had an obstetric delivery-related ICD9 or ICD10 code that occurred up to 9 months after (antepartum) or 12 months prior to the diagnosis of melanoma (postpartum).

Statistical Analysis

Descriptive statistics and chi-squared tests were utilized to compare patient, tumor, and management characteristics among women with PAM and women with non-PAM. Because women with PAM were younger, age-matched, non-pregnant women with melanoma were used in these descriptive analyses. The GREEDY algorithm was used to match 3 women with non-PAM to each woman with PAM with the closest age (age +/−1 year). In multivariable analyses, women with PAM and non-PAM were not matched on age; instead, age was adjusted as continuous variable in the models. Multivariable logistic regression was used to compare demographic and clinical characteristics between women with PAM and all women with non-PAM. Results are presented as adjusted odds ratio (OR) and 95% confidence intervals (CI). Multivariable cox proportional hazards regression models were used to assess the impact of pregnancy status, age, race/ethnicity, neighborhood SES, health insurance, tumor anatomic site, thickness, ulceration (available beginning in 2004), histologic type, stage, lymph node involvement, lymph nodes examined, and timing of surgical treatment on overall survival (OS) and melanoma specific survival (MSS). Regression models were stratified by primary tumor invasion status at diagnosis (in situ and invasive, invasive only) and timing of diagnosis (overall, antepartum, postpartum). For deceased patients, survival time was measured in days from the date of diagnosis to the date of death from any cause for OS, and to the date of death from melanoma for MSS. Patients who died from other causes were censored at the time of death in analyses of MSS. Patients alive at the study end date (12/31/2015) were censored at this time or at the date of last known follow-up. In all survival models, the proportional hazards assumption was assessed numerically based on cumulative sums of Martingale residuals and visually based on inspection of the survival curves [log (−log) of the survival distribution function by log (months)]; no variable violated this assumption. Results are presented as adjusted hazard ratios (HRs) and corresponding CIs. Statistical analyses were performed using SAS statistical software (version 9.4), and a 2-sided P value < 0.05 was considered statistically significant.

RESULTS

There were 13995 women aged 15 to 44 years, who were diagnosed with first primary melanoma in 1994–2015 in California. Our final study population that met inclusion criteria included 13108 women with 1406 diagnosed with PAM (463 women were diagnosed with PAM during antepartum period and 943 within the first year postpartum).

Characteristics of Women with PAM and Women with Non-PAM

Most PAMs occurred in 25–35-year-old women (66.0%; median age 33 in PAM vs 37 in non-PAM; Table S2). Among PAMs, 441 were in situ, 890 were invasive, and 75 had unknown stage at diagnosis; for non-PAMs, 3493 were in situ, 7456 were invasive, and 753 were unknown. Because women with PAM were younger, age-matched, non-pregnant women with melanoma were used in these descriptive analyses. Demographic, clinical and management characteristics of women with PAM and non-PAM are presented in Table 1. Most women in both groups were non-Hispanic white (78.2% [N=1100] in PAM vs 78.9% [N=3326] in non-PAM), followed by Hispanic (10.8% [N=152] in PAM vs 9.5% [N=399] in non-PAM), and Asian, Black and Native American (1.4% [N=19] in PAM vs 2.2% [N=91] in non-PAM) (Table 1). Over 60% of women had a high neighborhood SES level (66.3% in PAM vs 60.3% in non-PAM). More than 70% of women had a private health insurance (78.0% in PAM vs 75.0% in non-PAM).

The lower limb/hip (33.8% in PAM vs 31.9% in non-PAM) and trunk (31.9% in PAM vs 33.0% in non-PAM) were the predominant sites of melanoma in both groups, followed by the upper limb (22.8% in PAM vs. 23.7% in non-PAM). For melanomas that included information on the histologic subtype, the most common subtype in both groups was superficial spreading melanoma (30.0% in PAM vs 30.6% in non-PAM), followed by nodular melanoma (2.8% in PAM vs 3.4% in non-PAM). Most invasive melanomas were ≤1.0 mm thick (49.6% in both groups out of all cases) and non-ulcerated (87.9% in PAM vs 88.6% in non-PAM). The majority of melanomas were localized to skin in both groups (92.9% in PAM vs 92.3% in non-PAM). Regional lymph node involvement was present in 3.6% of women with PAM vs 4.7% in non-PAM.

Most women were treated with surgery in both groups (95.7% in PAM vs 94.7% in non-PAM) within 30 days from the diagnosis (70.3% in PAM vs 67.4% in non-PAM). Lymph nodes were examined histologically in 21.0% in PAM and in 23.0% in non-PAM. 51 (3.6%) deaths occurred in PAM and 228 (5.4%) in non-PAM. The overall mean follow-up time was 10.2 and 10.3 years in patients with PAM and non-PAM, respectively.

In multivariable analysis, PAM was associated with Hispanic race/ethnicity (OR 1.29, 95% CI 1.07–1.56) and higher SES level (lower vs. higher SES level OR 0.77, 95% CI 0.68–0.86) (Tables 2 and 3). Additionally, PAM occurring postpartum was associated with greater tumor thickness (2.01–4.00 mm vs. 0.01–1.00 mm, OR 1.75, 95% CI 1.03–2.98). Although no differences were detected in localized or regional (versus remote) disease between the groups, PAM was associated with unknown stage (OR 1.87, 95% CI 1.24–2.81). There were no differences in other demographic, clinical, or histological characteristics between women with PAM compared with non-PAM. Furthermore, PAM occurring postpartum was negatively associated with lymph node exam (lymph nodes not examined vs. examined, OR 1.62, 95% CI 1.17–2.23), but no differences between management or time to surgery were noted. Lastly, the results were similar when excluding women diagnosed with melanoma in situ.

Factors Affecting Survival of Melanoma in Women

Risk of death did not differ between women with PAM and women with non-PAM, even when considering invasive melanoma only (Tables 4 and 5) or when stratifying by antepartum and postpartum PAM (Table S3). However, worse OS was observed in women of Asian, Black and Native American (vs non-Hispanic White) race/ethnicity (HR 1.51, 95% CI 1.05–2.17) and with women with lower (vs higher) neighborhood SES (HR 1.17, 95% CI 1.01–1.36). Both lower OS and MSS were observed in those with public or no (vs. private) health insurance (OS: HR 2.19, 95% CI 1.84–2.61; MSS: HR 2.15, 95% CI 1.76–2.64). As expected, women with invasive melanoma were 3.7 to 50.2 times more likely to die of melanoma than women with melanoma *in situ* (e.g., tumor thickness of 0.01–1.00 mm, 1.01–2.00 mm, 2.01–4.00 mm and >4.0 mm corresponding to primary tumor stages pT1, pT2, pT3 and pT4, respectively). Women with melanoma located on the trunk, face, scalp or neck (vs lower limb) were at least 55% more likely to die of melanoma. As expected, those with lymph node involvement were 2.81 times more likely to die of melanoma than those without. Finally, the risk of death appeared higher when surgery occurred more than 90 days from diagnosis compared with less than 30 days but was not statistically significant.

DISCUSSION

Melanoma is one of the most common malignancies in women during reproductive years and in pregnancy [18], yet the impact of melanoma diagnosed during pregnancy continues to be a controversial topic. Prior case-control studies have shown variable results and population-based studies are limited, especially from the United States [6, 8, 12]. The results of our population-based study show that melanomas diagnosed during the postpartum period were thicker. However, pregnancy status did not otherwise affect clinical, histological or management characteristics of melanoma or impact survival, suggesting that the evaluation of women with suspected or confirmed PAM should be similar to women with non-PAM. In addition, our study identified survival disparities by race/ethnicity, neighborhood SES and health insurance, highlighting the need for strategies to reduce health disparities in melanoma.

Our results showed that the survival of women with PAM is similar to that of non-PAM. Most population-based studies have reported similar findings [3]. While one meta-analysis demonstrated an increased risk of death in PAM [6], the methods were criticized by others, who found no differences between PAM and non-PAM.[19] Lens et al.[9] compared 185 women with PAM to 5348 women with non-PAM in 1958–1999 in Sweden and found no association with survival and pregnancy status. Similarly, Johansson et al. [11] detected no difference in survival in 1019 women with PAM and 5838 women with non-PAM in 1963–2009 in Sweden. In a study of all cancer types, including 160 women with PAM and 4460 women with non-PAM, Stensheim et al. [8] showed a slightly increased risk of death in PAM, but once tumor thickness was accounted for, no difference was found. Lastly, also utilizing the California Cancer Registry, O'Meara et al. [10] reported no differences in survival of 412 women with PAM and 2451 age-matched women with non-PAM diagnosed in 1991–1999. Combined with our data, these studies strengthen the conclusion that the risk of death is not increased in PAM compared with non-PAM.

We also investigated the time to surgery, and the frequency of lymph node examination, addressing some of the conundrums related to management of PAM. Determining if definitive surgery is delayed is particularly important because OS decreases for stage I melanoma when time to surgery exceeds 30 days [17]. As time to definitive surgery of melanoma was less than 30 days in most women and we did not observe significant differences between PAM and non-PAM, our findings suggest that surgical management of primary tumors in women with PAM follows standard procedures for melanoma. We did not detect significant differences in the frequency of lymph node examination in pregnant women with PAM, despite challenges related to these procedures, including low-dose radiation or tracers used for sentinel lymph node mapping [20, 21].

While the majority of studies report no differences between the characteristics of PAM vs non-PAM (reviewed in [3]), two studies from Northern Europe report a higher proportion of tumors of the trunk [8, 11] and thicker tumors in PAM [12, 22]. In our study, the most common tumor location was the lower extremity, followed by the trunk, upper extremity, and head and neck, comparable to prior data [10, 23]. Notably, anatomic location impacts survival, whereby melanoma of the head/neck and trunk is associated with worsened survival compared with the lower extremity [24], a result also detected in our study. Similar to most previously published studies (reviewed in [3]), we did not observe a difference in tumor thickness between women with PAM and non-PAM. However, we did find an association with increased thickness of PAM diagnosed postpartum, suggesting that biopsy of melanocytic tumors in the antepartum period may be delayed to the postpartum period. Additionally, unknown stage was more common in PAM. Prior studies have noted that unknown stage often represents patients not connected with health care, including diagnosed near time of death or diagnosed without further work up or treatment and have similar survival rates to regional stage melanoma [25, 26].

In this study, race/ethnicity, neighborhood SES, and health insurance were associated with an increased risk of death. Lower overall survival was associated with Asian, Black and Native American race/ethnicity, corresponding to the results from prior studies on melanoma [27–29]. While PAM was more frequent in Hispanic women, Hispanic women had similar survival to non-Hispanic white women in this study. Differences in birth rates among racial/ethnic groups[30] may contribute to the higher frequency of PAM in Hispanic women, so future studies are warranted to assess the incidence of melanoma in pregnant women stratified by race/ethnicity. The observed association of increased risk of death from melanoma and lower SES has been demonstrated in numerous studies from various countries [26, 29, 31–37]. Our findings of worse survival and public or lack of health insurance has also been previously reported [38] and may relate to reduced access to care. Disruptions in health insurance coverage are particularly common in low-income populations and result in lower receipt of prevention, screening and treatment [39]. Lack of public education and skin cancer screenings likely also play a role. Furthermore, race/ethnicity and insurance status also effect management of melanoma, with patients of Black race/ethnicity and with public insurance receiving immunotherapy less frequently and with longer time to treatment [40, 41]. In sum, it is imperative to address the disparities seen in melanoma survival, including implementing policies and programs for education of the public and addressing disparities related to race/ethnicity, SES and other factors [42, 43].

The main limitation of our population-based study was that it lacked tumor details, such as presence or absence of ulceration (prior to 2004), number of mitoses, and presence of immune infiltrates. It is also notable that discordance in interpreting melanocytic tumors, particularly thin melanomas, by pathologists is common. As this study was based on cancer registry data, the accuracy of histopathologic diagnoses could not be confirmed via secondary review. Additionally, it is possible that our measure of PAM was subject to some misclassification if patients diagnosed during antepartum died of melanoma prior to delivery or if patients had a spontaneous pregnancy loss or an abortion. In addition, data on placental and fetal metastases, which can be associated with high-risk PAM, were unavailable. The alterations of the immune system during pregnancy mirror those seen in malignancies, where regulatory T cells proliferate and Th1 immune response changes to Th2 immune response [44–46]. In a prior retrospective case-control study of 34 PAM, no differences were found in tumor thickness or other histological parameters, but interestingly, PAM showed more marked inflammation around the tumor compared with non-PAM [47]. As it is becoming standard of care to initiate immunotherapy for resected early stage melanoma [48, 49], the impact of pregnancy on the immune microenvironment of melanoma warrants further study. Despite these limitations, our study addresses the current knowledge gaps by including a large, racially/ethnically diverse population and by including data from the most recent decades when melanoma incidence has been increasing [50, 51]. Furthermore, with a median follow up of 10 years, our study was able to make meaningful comparisons between PAM and non-PAM and prior published studies.

Conclusion

We report a population-based analysis of melanoma in pregnancy in California. Melanoma occurring postpartum was associated with greater tumor thickness, but pregnancy status did not otherwise affect survival or characteristics of melanoma. This suggests that the evaluation and surgical management of women with PAM should be similar to non-PAM, including during the antepartum period, to avoid delays in diagnosis. Race/ethnicity, neighborhood SES and health insurance impacted survival, underscoring the importance of reducing health care disparities in the US. Future goals include addressing these disparities by promoting skin cancer prevention and early detection strategies in racial and ethnic minorities and by improving access to care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

The data that support the findings of this study are available from the California Cancer Registry and California Department of Health Care Access and Information. Access is granted through an application process by the management or data custodians for each data resource.

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Table 1.

Demographic, clinical, histopathological and management characteristics of women with pregnancy-associated melanoma (PAM) and non-PAM, California, 1994–2015.

Characteristics	PAM N (%)	Age-matched* non-PAM N (%)	P value
Total	1406	4218	
Pregnant	1406		
Antepartum	406		
Postpartum (within 12 months)	903		
Age group (years)			
<25	90 (6.4%)	270 (6.4%)	
25–35	928 (66%)	2762 (65.5%)	
>35	388 (27.6%)	1186 (28.1%)	0.9295
Race/ethnicity			
Non-Hispanic white	1100 (78.2%)	3326 (78.9%)	
Asian, Black and Native American	19 (1.4%)	91 (2.2%)	
Hispanic	152 (10.8%)	399 (9.5%)	
Other/unknown	135 (9.6%)	402 (9.5%)	0.1371
Neighborhood SES			
Low	474 (33.7%)	1675 (39.7%)	
High	932 (66.3%)	2543 (60.3%)	<.0001
Insurance			
Private	1096 (78%)	3162 (75%)	
Public/none	95 (6.8%)	324 (7.7%)	
Unknown	215 (15.3%)	732 (17.4%)	0.0774
Tumor site			
Face	99 (7%)	228 (5.4%)	
Lower limb and hip	475 (33.8%)	1344 (31.9%)	
Scalp and neck	49 (3.5%)	178 (4.2%)	
Trunk	448 (31.9%)	1394 (33%)	
Upper limb and shoulder	321 (22.8%)	1001 (23.7%)	
Other	14 (1%)	73 (1.7%)	0.0353
Histologic type			
Superficial spreading melanoma	422 (30%)	1291 (30.6%)	
Nodular melanoma	39 (2.8%)	143 (3.4%)	
Rare subtypes	37 (2.6%)	113 (2.7%)	
Malignant melanoma, NOS	908 (64.6%)	2671 (63.3%)	0.6526
Tumor thickness (Breslow depth)			
In situ	441 (31.4%)	1226 (29.1%)	
0.01–1.00 mm	697 (49.6%)	2091 (49.6%)	
<0.80 mm	591 (42.0%)	1794 (42.5%)	
0.80–1.00 mm	106 (7.5%)	297 (7.0%)	

	PAM	Age-matched* non-PAM	P value
1.01–2.00 mm	124 (8.8%)	416 (9.9%)	
2.01–4.00 mm	47 (3.3%)	153 (3.6%)	
> 4.00 mm	22 (1.6%)	68 (1.6%)	
Unknown	75 (5.3%)	264 (6.3%)	0.4374
Tumor ulceration (2004+)			
No	673 (87.9%)	1918 (88.6%)	
Yes	33 (4.3%)	109 (5%)	
Unknown	60 (7.8%)	139 (6.4%)	0.3315
Summary stage			
Localized	1306 (92.9%)	3893 (92.3%)	
Regional	51 (3.6%)	191 (4.5%)	
Remote	10 (0.7%)	58 (1.4%)	
Unknown	39 (2.8%)	76 (1.8%)	0.0132
Remote disease			
No/unknown	1396 (99.3%)	4160 (98.6%)	
Yes	10 (0.7%)	58 (1.4%)	0.0486
Primary surgery			
No	60 (4.3%)	217 (5.1%)	
Yes	1345 (95.7%)	3996 (94.7%)	0.3745
Time to surgery			
<30 days	988 (70.3%)	2841 (67.4%)	
30–59 days	268 (19.1%)	869 (20.6%)	
60–89 days	58 (4.1%)	171 (4.1%)	
≥90 days	28 (2%)	103 (2.4%)	
No	60 (4.3%)	217 (5.1%)	0.4746
Lymph nodes examined			
No	1111 (79%)	3248 (77%)	
Yes	295 (21%)	970 (23%)	0.1171
Lymph nodes involvement			
Regional lymph nodes	51 (3.6%)	197 (4.7%)	
No lymph node involvement	1259 (89.5%)	3703 (87.8%)	
Unknown	96 (6.8%)	318 (7.5%)	0.1577
Subsequent melanoma			
No	1330 (94.6%)	3932 (93.2%)	
Yes	76 (5.4%)	286 (6.8%)	0.0688
Vital status			
Alive	1355 (96.4%)	3990 (94.6%)	
Dead	51 (3.6%)	228 (5.4%)	0.0078

Abbreviations: mm: millimeter; SES: socioeconomic status; NOS: not otherwise specified

*Women with PAM and non-PAM are matched by age (+/− 1 year) with 1:3 ratio.

Table 2.

Adjusted* logistic regression model of factors associated with pregnancy-associated melanoma (PAM) compared to non-PAM by primary tumor invasion status at diagnosis.

	All Invasive and in situ melanomas**	**Invasive melanoma**
Characteristics	OR (95% CI)	OR (95% CI)
Age (each year)	0.94 (0.93, 0.95)	0.94 (0.93, 0.95)
Race/ethnicity		
Non-Hispanic white	Reference	Reference
Asian, Black and Native American	0.81 (0.50, 1.30)	0.54 (0.28, 1.05)
Hispanic	1.29 (1.07, 1.56)	1.39 (1.12, 1.73)
Other/unknown	1.02 (0.83, 1.24)	1.02 (0.78, 1.33)
Summary stage		
Localized	Reference	Reference
Regional	0.82 (0.43, 1.56)	0.85 (0.44, 1.63)
Remote	0.82 (0.37, 1.80)	0.74 (0.33, 1.67)
Unknown	1.87 (1.24, 2.81)	1.75 (1.15, 2.65)
Tumor site		
Lower limb and hip	Reference	Reference
Face	1.07 (0.84, 1.36)	1.09 (0.81, 1.46)
Scalp and neck	0.83 (0.60, 1.13)	0.79 (0.55, 1.13)
Skin of trunk	0.95 (0.82, 1.09)	0.94 (0.79, 1.11)
Upper limb and shoulder	0.88 (0.76, 1.02)	0.85 (0.71, 1.03)
Other	0.58 (0.30, 1.11)	0.58 (0.29, 1.18)
Histologic type		
Superficial spreading melanoma	Reference	Reference
Nodular melanoma	1 (0.68, 1.45)	0.99 (0.68, 1.45)
Rare subtypes	0.95 (0.65, 1.38)	1.51 (0.87, 2.62)
Malignant melanoma, NOS	1.04 (0.91, 1.18)	1 (0.86, 1.16)
Tumor thickness (Breslow depth)		
In situ	Reference	
0.01–1.00 mm	0.95 (0.82, 1.09)	Reference
1.01–2.00 mm	0.9 (0.70, 1.17)	0.97 (0.77, 1.22)
2.01–4.00 mm	0.93 (0.65, 1.35)	1 (0.70, 1.42)
> 4.00 mm	1.03 (0.62, 1.72)	1.11 (0.67, 1.83)
Unknown	0.77 (0.57, 1.05)	0.81 (0.60, 1.10)
Neighborhood SES		
High	Reference	Reference
Low	0.77 (0.68, 0.87)	0.7 (0.61, 0.82)
Time to surgery		
<30 days	Reference	Reference
30–59 days	0.88 (0.76, 1.03)	0.85 (0.72, 1.02)

	All Invasive and in situ melanomas**	Invasive melanoma
60–89 days	1 (0.75, 1.33)	1.05 (0.76, 1.45)
≥90 days	0.77 (0.51, 1.14)	0.96 (0.62, 1.49)
No surgery/unknown	0.95 (0.71, 1.27)	1.26 (0.87, 1.81)
Lymph nodes involvement		
No lymph node involvement	Reference	Reference
Regional lymph nodes	0.97 (0.51, 1.83)	0.91 (0.48, 1.74)
Unknown	0.99 (0.77, 1.26)	1.01 (0.79, 1.29)
Lymph nodes examined		
Yes	1.12 (0.94, 1.34)	1.14 (0.95, 1.37)
No	Reference	Reference
Insurance		
Private	Reference	Reference
Public/none	0.95 (0.76, 1.20)	1.01 (0.78, 1.30)
Unknown	0.83 (0.70, 0.97)	0.71 (0.57, 0.89)

Abbreviations: OR: Odds ratio; CI: confidence interval; mm: millimeter; SES: socioeconomic status; NOS: not otherwise specified

*Adjusted for all the variables in the table

**Total number of patients 13108

Table 3.

Adjusted* logistic regression model of factors associated with pregnancy-associated melanoma (PAM) compared to non-PAM, by primary tumor invasion status at and timing of diagnosis.

	Invasive and in situ melanomas**		**Invasive melanomas**	
Characteristics	PAM, antepartum OR (95% CI)	PAM, postpartum OR (95% CI)	PAM, antepartum OR (95% CI)	PAM, postpartum OR (95% CI)
Age	0.95 (0.94, 0.95)	0.94 (0.92, 0.95)	0.95 (0.94, 0.96)	0.94 (0.92, 0.95)
Race/ethnicity				
Non-Hispanic white	Reference	Reference	Reference	Reference
Asian, Black and Native American	1.02 (0.61, 1.72)	0.38 (0.12, 1.21)	0.76 (0.38, 1.50)	0.15 (0.02, 1.11)
Hispanic	1.45 (1.17, 1.80)	0.99 (0.70, 1.39)	1.59 (1.24, 2.04)	1.01 (0.68, 1.50)
Other/unknown	1.09 (0.86, 1.38)	0.87 (0.62, 1.24)	1.10 (0.81, 1.50)	0.85 (0.53, 1.36)
Neighbourhood SES				
High	Reference	Reference	Reference	Reference
Low	0.82 (0.71, 0.95)	0.68 (0.56, 0.84)	0.74 (0.62, 0.88)	0.66 (0.51, 0.84)
Insurance				
Private	Reference	Reference	Reference	Reference
Public/none	0.97 (0.74, 1.28)	0.92 (0.63, 1.36)	1.03 (0.76, 1.39)	0.97 (0.64, 1.48)
Unknown	0.84 (0.69, 1.02)	0.79 (0.60, 1.05)	0.76 (0.59, 0.98)	0.62 (0.43, 0.91)
Tumor site				
Lower limb and hip	Reference	Reference	Reference	Reference
Face	1.03 (0.77, 1.37)	1.16 (0.78, 1.72)	0.96 (0.67, 1.39)	1.35 (0.86, 2.13)
Scalp and neck	0.62 (0.40, 0.94)	1.27 (0.81, 1.99)	0.64 (0.39, 1.02)	1.09 (0.63, 1.85)
Skin of trunk	0.89 (0.75, 1.05)	1.08 (0.86, 1.36)	0.9 (0.74, 1.10)	1.02 (0.77, 1.35)
Upper limb and shoulder	0.89 (0.75, 1.06)	0.85 (0.65, 1.11)	0.88 (0.71, 1.10)	0.79 (0.57, 1.09)
Other	0.76 (0.37, 1.54)	0.24 (0.05, 1.16)	0.78 (0.36, 1.69)	0.25 (0.05, 1.22)
Histologic type				
Superficial spreading melanoma	Reference	Reference	Reference	Reference
Nodular melanoma	1.14 (0.73, 1.80)	0.77 (0.41, 1.44)	1.16 (0.74, 1.83)	0.73 (0.39, 1.37)
Rare subtypes	1.01 (0.65, 1.56)	0.81 (0.42, 1.57)	1.43 (0.73, 2.83)	1.63 (0.69, 3.89)

	Invasive and in situ melanomas**		Invasive melanomas	
Malignant melanoma, NOS	1.08 (0.92, 1.26)	0.96 (0.77, 1.19)	1.08 (0.91, 1.29)	0.85 (0.67, 1.09)
Tumor thickness (Breslow depth)				
In situ	Reference	Reference	n/a	n/a
0.01–1.00 mm	0.96 (0.81, 1.13)	0.93 (0.74, 1.18)	Reference	Reference
1.01–2.00 mm	0.76 (0.55, 1.04)	1.29 (0.85, 1.95)	0.80 (0.61, 1.07)	1.4 (0.96, 2.04)
2.01–4.00 mm	0.70 (0.44, 1.12)	1.61 (0.93, 2.81)	0.74 (0.47, 1.17)	1.75 (1.03, 2.98)
> 4.00 mm	0.75 (0.38, 1.46)	1.78 (0.84, 3.79)	0.78 (0.41, 1.51)	2.00 (0.95, 4.19)
Unknown	0.80 (0.56, 1.14)	0.71 (0.41, 1.23)	0.83 (0.59, 1.18)	0.76 (0.44, 1.30)
Summary stage				
Localized	Reference	Reference	Reference	Reference
Regional	0.84 (0.39, 1.84)	0.82 (0.28, 2.35)	0.91 (0.41, 2.00)	0.8 (0.28, 2.30)
Remote	0.67 (0.25, 1.78)	1.19 (0.34, 4.19)	0.62 (0.23, 1.70)	1.05 (0.29, 3.76)
Unknown	2.12 (1.34, 3.36)	1.31 (0.59, 2.90)	1.94 (1.21, 3.11)	1.32 (0.59, 2.94)
Time to surgery				
<30 days	Reference	Reference	Reference	Reference
30–59 days	0.87 (0.73, 1.03)	0.93 (0.73, 1.19)	0.84 (0.68, 1.04)	0.89 (0.66, 1.20)
60–89 days	0.96 (0.68, 1.35)	1.1 (0.69, 1.77)	1.04 (0.71, 1.53)	1.08 (0.63, 1.87)
≥90 days	0.52 (0.30, 0.92)	1.29 (0.75, 2.22)	0.70 (0.39, 1.28)	1.52 (0.82, 2.81)
No surgery/unknown	0.87 (0.61, 1.23)	1.14 (0.71, 1.83)	1.11 (0.72, 1.73)	1.58 (0.88, 2.84)
Lymph node involvement				
No lymph node involvement	Reference	Reference	Reference	Reference
Regional lymph nodes	0.85 (0.40, 1.84)	1.16 (0.41, 3.32)	0.77 (0.35, 1.69)	1.16 (0.41, 3.33)
Unknown	0.99 (0.74, 1.32)	0.98 (0.64, 1.48)	1.01 (0.76, 1.36)	1.00 (0.66, 1.52)
Lymph nodes examined				
Yes	Reference	Reference	Reference	Reference
No	0.96 (0.78, 1.19)	1.58 (1.15, 2.17)	0.98 (0.79, 1.22)	1.62 (1.17, 2.23)

Abbreviations: OR: Odds ratio; CI: confidence interval; mm: millimeter; SES: socioeconomic status; NOS: not otherwise specified

*Adjusted for all the variables in the table

**Total number of patients 13108

Table 4.

Adjusted* Cox proportional hazards regression model of factors associated with overall and melanoma-specific survival among women with in situ and invasive melanoma**

Characteristics	Overall survival HR (95% CI)	Melanoma specific survival HR (95% CI)
Age (each year)	1.04 (1.03, 1.05)	1.03 (1.02, 1.04)
Race/ethnicity		
Non-Hispanic white	Reference	Reference
Asian, Black and Native American	1.51 (1.05, 2.17)	1.22 (0.78, 1.91)
Hispanic	0.98 (0.78, 1.22)	0.90 (0.69, 1.17)
Other/unknown	0.08 (0.02, 0.24)	0.04 (0.01, 0.30)
Neighborhood SES		
High	Reference	Reference
Low	1.17 (1.01, 1.36)	1.01 (0.85, 1.20)
Insurance		
Private	Reference	Reference
Public/none	2.19 (1.84, 2.61)	2.15 (1.76, 2.64)
Unknown	0.62 (0.48, 0.80)	0.47 (0.33, 0.66)
Year of diagnosis		
1994–2000	Reference	Reference
2001–2005	0.73 (0.61, 0.88)	0.66 (0.54, 0.82)
2006–2010	0.78 (0.63, 0.96)	0.75 (0.59, 0.95)
2011–2015	0.49 (0.35, 0.68)	0.42 (0.29, 0.62)
Tumor site		
Lower limb and hip	Reference	Reference
Face	1.66 (1.22, 2.27)	1.61 (1.10, 2.35)
Scalp and neck	2.77 (2.06, 3.73)	2.93 (2.10, 4.10)
Skin of trunk	1.46 (1.20, 1.78)	1.55 (1.23, 1.95)
Upper limb and shoulder	1.16 (0.93, 1.44)	1.00 (0.76, 1.31)
Other	4.27 (2.95, 6.17)	3.67 (2.40, 5.63)
Tumor thickness (Breslow depth)		
In situ	Reference	Reference
0.01–1.00 mm	1.97 (1.44, 2.71)	3.69 (2.15, 6.34)
1.01–2.00 mm	6.80 (4.79, 9.67)	17.70 (10.11, 30.99)
2.01–4.00 mm	11.38 (7.85, 16.50)	33.01 (18.64, 58.45)
> 4.00 mm	17.85 (12.05, 26.43)	50.20 (27.84, 90.52)
Unknown	5.45 (3.83, 7.75)	14.66 (8.38, 25.65)
Histologic type		
Superficial spreading melanoma	Reference	Reference
Nodular melanoma	1.25 (0.96, 1.63)	1.21 (0.90, 1.65)
Rare subtypes	1.06 (0.62, 1.79)	1.14 (0.59, 2.21)
Malignant melanoma, NOS	1.08 (0.90, 1.30)	1.06 (0.85, 1.32)

	Overall survival	Melanoma specific survival
Time to surgery		
<30 days	Reference	Reference
30–59 days	0.93 (0.76, 1.13)	0.90 (0.71, 1.13)
60–89 days	0.79 (0.54, 1.16)	0.90 (0.60, 1.37)
≥90 days	1.35 (0.96, 1.88)	1.35 (0.92, 2.00)
No surgery/unknown	2.92 (2.14, 3.98)	3.41 (2.37, 4.91)
Lymph nodes examined		
Yes	Reference	Reference
No	0.96 (0.78, 1.18)	0.97 (0.76, 1.24)
Lymph nodes involvement		
No lymph node involvement	Reference	Reference
Regional lymph nodes	2.61 (2.14, 3.19)	2.81 (2.25, 3.51)
Unknown	1.76 (1.40, 2.21)	2.02 (1.55, 2.62)
Pregnancy		
Yes	0.75 (0.56, 1.01)	0.75 (0.54, 1.05)
Non pregnant	Reference	Reference

Abbreviations: HR: hazards ratio; CI: confidence interval; mm: millimeter; SES: socioeconomic status; NOS: not otherwise specified

*Adjusted for all the variables in the table

**Total number of patients 13108

Table 5.

Adjusted* Cox proportional hazards regression model of factors associated with overall and melanoma-specific survival among women with invasive melanoma**

	Overall survival	Melanoma specific survival
Characteristics	HR (95% CI)	HR (95% CI)
Age (each year)	1.04 (1.03, 1.05)	1.03 (1.02, 1.04)
Race/ethnicity		
Non-Hispanic White	Reference	Reference
Asian, Black and Native American	1.49 (1.03, 2.17)	1.24 (0.79, 1.95)
Hispanic	0.99 (0.79, 1.25)	0.91 (0.70, 1.20)
Other/unknown	0.06 (0.02, 0.24)	0.05 (0.01, 0.32)
Neighbourhood SES		
High	Reference	Reference
Low	1.14 (0.98, 1.33)	0.98 (0.82, 1.17)
Insurance		
Private	Reference	Reference
Public/none	2.12 (1.77, 2.54)	2.12 (1.73, 2.61)
Unknown	0.56 (0.42, 0.74)	0.45 (0.31, 0.64)
Year of diagnosis		
1994–2000	Reference	Reference
2001–2005	0.72 (0.60, 0.87)	0.66 (0.54, 0.82)
2006–2010	0.81 (0.65, 1.00)	0.78 (0.62, 0.99)
2011–2015	0.52 (0.37, 0.74)	0.44 (0.30, 0.65)
Tumor site		
Lower limb and hip	Reference	Reference
Face	1.57 (1.12, 2.19)	1.61 (1.10, 2.37)
Scalp and neck	2.70 (1.99, 3.66)	2.82 (2.00, 3.96)
Skin of trunk	1.49 (1.22, 1.83)	1.56 (1.24, 1.97)
Upper limb and shoulder	1.16 (0.92, 1.45)	1.02 (0.77, 1.34)
Other	3.43 (2.33, 5.05)	3.18 (2.06, 4.91)
Histologic type		
Superficial spreading melanoma	Reference	Reference
Nodular melanoma	1.28 (0.98, 1.67)	1.21 (0.89, 1.64)
Rare subtypes	1.15 (0.62, 2.14)	1.22 (0.61, 2.44)
Malignant melanoma, NOS	1.12 (0.93, 1.35)	1.06 (0.85, 1.32)
Tumor thickness (Breslow depth)		
0.01–1.00 mm	Reference	Reference
1.01–2.00 mm	3.52 (2.76, 4.47)	4.89 (3.65, 6.57)
2.01–4.00 mm	5.92 (4.51, 7.76)	9.21 (6.70, 12.66)
> 4.00 mm	9.14 (6.77, 12.35)	13.93 (9.81, 19.80)
Unknown	3.14 (2.40, 4.10)	4.60 (3.34, 6.33)

	Overall survival	Melanoma specific survival
Time to surgery		
<30 days	Reference	Reference
30–59 days	0.89 (0.73, 1.09)	0.91 (0.72, 1.14)
60–89 days	0.78 (0.53, 1.15)	0.91 (0.60, 1.37)
≥90 days	1.35 (0.96, 1.90)	1.32 (0.89, 1.96)
No surg/unknown	2.90 (2.08, 4.05)	3.20 (2.20, 4.67)
Lymph node involvement		
No lymph node involvement	Reference	Reference
Regional lymph nodes	2.66 (2.18, 3.25)	2.81 (2.25, 3.51)
Unknown	1.62 (1.29, 2.04)	1.85 (1.42, 2.41)
Lymph nodes examined		
Yes	Reference	Reference
No	1.03 (0.84, 1.26)	1.03 (0.81, 1.31)
Pregnancy		
No	Reference	Reference
Yes	0.75 (0.56, 1.02)	0.73 (0.52, 1.04)

Abbreviations: HR: hazards ratio; CI: confidence interval; mm: millimeter; SES: socioeconomic status; NOS: not otherwise specified

*Adjusted for all the variables in the table

**Total number of patients 9174