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Incidence and outcomes of pregnancy-associated melanoma in New South Wales 1994-2008

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Abstract

Background: There is controversy about the interaction between melanoma and pregnancy. There is a lack of Australian data on pregnancy outcomes associated with melanoma in pregnancy, despite Australia having the highest incidence of melanoma in the world.

Aims: Describe trends, maternal characteristics and pregnancy outcomes associated with pregnancy-associated melanoma in New South Wales

Materials and Methods: Population-based cohort study of all births (n=1,309,501) of at least 20 weeks gestation or 400g birthweight in New South Wales, 1994-2008. Logistic regression was used to analyse the association between melanoma in pregnancy and adverse birth outcomes.

Results: 577 pregnancy-associated melanomas were identified, including 195 diagnosed during pregnancy and 382 diagnosed within 12 months postpartum. The crude incidence of pregnancy-associated melanoma increased from 37.1 per 100,000 maternities in 1994 to 51.84 per 100,000 maternities in 2008. Adjusting for maternal age accounted for the trend in pregnancy-associated melanoma. Melanomas diagnosed in pregnancy were thicker (median=0.75mm) than melanomas diagnosed postpartum (median=0.60mm) (p=0.002). Pregnancy-associated melanoma was associated with increased risk of large for gestational age infant but not preterm birth, planned birth, caesarean section or stillbirth. Parity was inversely associated with pregnancy-associated melanoma, as women with 3 or

more previous pregnancies had 0.59 times the odds of pregnancy-associated melanoma compared to nulliparous women (95% CI 0.42-0.84, p=0.003).

Conclusions: The incidence of pregnancy-associated melanoma has increased with increasing maternal age. The observation of thicker melanomas in pregnancy and increased risk of large for gestational age infants may suggest a role for growth-related pregnancy factors in pregnancy-associated melanoma.

Introduction

One-third of all melanoma cases in women are diagnosed during their reproductive years [1]. There is controversy about whether the progression and prognosis of melanoma diagnosed during pregnancy or lactation is poorer than in non-pregnant women [1]. Early case reports reported the rapid development of metastases and a poorer prognosis for women diagnosed during pregnancy [2-5] and some laboratory evidence suggests that melanomas undergo more rapid growth and more frequently metastasize during gestation [6, 7]. In contrast, population studies have found no difference in either survival or disease-free survival between pregnant and non-pregnant women with melanoma [8-10], with the exception of one study that found a slightly increased risk of cause-specific death for melanoma diagnosed during pregnancy, but not when lactating, compared to non-pregnant women [11]. Although there are several population studies on cancer in pregnancy that examine pregnancy outcomes [12-14], there is only one study, conducted in California using data for 1991-1999, that specifically examined pregnancy outcomes of women with melanoma-affected pregnancies [9].

There are limited data on melanoma in pregnancy in Australia, which has the highest rates of melanoma in the world [15]. A previous study reported that melanoma is the most common cancer diagnosed in pregnancy in New South Wales (NSW) and the incidence of pregnancy-associated melanoma in NSW is more than double the rate for the general female population of reproductive age (SMR 2.22, 95% CI 2.05–2.41) [13]. The aim of this

study is to describe trends, maternal characteristics and pregnancy outcomes associated with pregnancy-associated melanoma in NSW.

Materials and Methods

The study population was defined as a cohort of all women who gave birth in NSW in 1994-2008. Births in NSW comprise approximately one-third of all Australian births.

The data sources for this study were three linked population health datasets; the NSW Central Cancer Registry ('cancer data'), a statutory case-based registry of all incident cancers diagnosed in NSW; the NSW Perinatal Data Collection ('birth data'), a legislated surveillance system of all births of live or stillborn infants of at least 20 weeks gestation or 400g birthweight in NSW; and the NSW Admitted Patients Data Collection ('hospital data'), a census of discharges from NSW hospitals that includes demographic, diagnostic and procedural data. The data were linked by the NSW Centre for Health Record Linkage. Anonymised data were provided to the researchers. The study was approved by the NSW Population & Health Services Research Ethics Committee.

Pregnancy-associated melanoma was defined as the diagnosis of incident melanoma during pregnancy or up to 12 months postpartum. The 12 month postpartum period is included as a pregnancy-associated period [9, 13] because melanomas that develop during pregnancy may be incorrectly attributed to physiological changes of pregnancy (especially hyperpigmentation and stretching of nevi with gestational weight gain), diagnostic tests and treatments may be delayed until after delivery, and post-partum hormone changes

related to lactation may also represent a risk period [11]. Maternal demographic characteristics including age, parity, plurality, country of birth, socioeconomic status (Socioeconomic Indexes for Areas [SEIFA]), remoteness (Accessibility and Remoteness Index of Australia [ARIA+]) and smoking in pregnancy are recorded in the birth data. Induction of labour, maternal hypertension and maternal diabetes were identified in either the birth data or the hospital data. Pregnancy outcomes derived from the birth data include gestational age at birth, size for gestational age (small; $<10^{th}$ percentile, large; $>90^{th}$ percentile), mode of delivery and stillbirth. Month of melanoma diagnosis, melanoma staging, Breslow thickness and cause of death were identified in the cancer data. Frequency and interval to subsequent pregnancy were derived from the birth data.

The crude incidence of pregnancy-associated melanoma per 100,000 women giving birth, referred to as 'maternities', was calculated by dividing the number of incident pregnancy-associated melanomas by the total number of women who delivered in NSW for the years 1994-2007. Maternities in 2008 were excluded from incidence calculations as the full 12 months of postpartum data were unavailable and therefore pregnancy-associated melanoma would be underestimated. Age-adjusted incidence per 100,000 maternities was calculated by directly standardizing to the 1994 NSW maternity population.

The melanoma stage and Breslow thickness at diagnosis were compared for women diagnosed during pregnancy, women diagnosed within 6-10 weeks postpartum, and for women diagnosed up to 12 months postpartum. The Wilcoxon test was used to test for differences in median thickness.

Maternal characteristics were described for women who were diagnosed with melanoma during pregnancy or during the 12 months postpartum, and compared to women who did not have pregnancy-associated melanoma. Pregnancy outcomes were only presented for women who were diagnosed with melanoma during pregnancy and compared to women who did not have pregnancy-associated melanoma. Logistic regression was used to calculate adjusted odds ratios for the association between pregnancy-associated melanoma and maternal characteristics, and for the association between melanoma diagnosed during pregnancy only and pregnancy outcomes, compared to women with no pregnancy-associated melanoma. Odds ratios were adjusted for age, parity, plurality, country of birth, remoteness, socioeconomic status, maternal smoking in pregnancy, maternal diabetes, maternal hypertension and hospital level. To explore whether melanoma diagnoses during the 12 month postpartum period may represent delayed diagnoses of melanomas that were suspected in pregnancy, the odds ratio for planned birth for women diagnosed up to 12 months postpartum compared to women without pregnancy-associated melanoma was also calculated. Missing data were rare (<1% for each variable except Breslow thickness, 29% missing) and addressed by restricting to complete-case analysis.

The number of women who had subsequent pregnancies and median inter-pregnancy interval were calculated and compared to women without pregnancy-associated melanoma using the Wilcoxin test for difference in medians.

Results

The study population comprised 781,907 women who had 1,309,501 maternities and gave birth to 1,329,306 infants. There were 577 cases of pregnancy- associated melanoma recorded in NSW between 1994 and 2008, including 195 diagnosed during pregnancy and 382 diagnosed within 12 months post-partum. Of the 195 cases diagnosed during pregnancy, there were 9 women whose diagnosis during pregnancy was also within 12 months of a previous delivery. Of the 382 women diagnosed within 12 months postpartum, 42 were diagnosed within 6-10 weeks postpartum. The crude incidence of pregnancy-associated melanoma, calculated for 1994-2007, was 45.14 per 100,000 maternities and the age-adjusted incidence was 41.77 per 100,000 maternities. The crude incidence increased from 37.1 per 100,000 maternities in 1994 to 51.84 per 100,000 maternities in 2007 (p=0.01). There was no evidence of an increasing trend in pregnancy-associated melanoma over time in the age-adjusted incidence (p=0.64) (Figure 1). The increasing disparity between the crude and age-adjusted incidence rates over time reflects the increasing average maternal age in the general maternity population from 28.9 years in 1994 to 30.6 years in 2007.

Of the 577 melanomas diagnosed in pregnancy or within 12 months postpartum, 524 (90.8%) were *in situ* or localized melanomas at diagnosis (Table 1). The median thickness of pregnancy-associated melanomas was 0.69mm. Melanomas diagnosed during pregnancy were thicker (median=0.75mm) than melanomas diagnosed within 12 months

postpartum (median=0.60mm) (p=0.002). Women diagnosed within 6-10 weeks postpartum had melanomas with a median thickness of 0.88mm, which is higher than the median thickness of melanomas diagnosed in pregnancy or up to 12 months postpartum but there is limited statistical evidence for these differences(p=0.40 and p=0.06 respectively). The median gestational age at diagnosis for women diagnosed during pregnancy was 18-22 weeks and ranged from the time of conception to delivery.

Women with pregnancy-associated melanoma were older, of lower parity, more likely to be born in Australia and more likely to live in regional and remote areas than women with pregnancies unaffected by melanoma (Table 2). The risk of pregnancy-associated melanoma increased substantially with age; women aged 40-55 had 7.55 times the odds of pregnancy-associated melanoma compared to women aged 15-24. Women who had at least three previous pregnancies of at least 20 weeks gestation had 41% lower odds of pregnancy-associated melanoma compared to nulliparous women. Women born outside of Australia had 74% lower odds of pregnancy-associated melanoma than Australian-born women. Women in inner regional and outer regional or remote areas had about 30% higher odds of pregnancy-associated melanoma than women residing in major cities.

After adjusting for maternal characteristics, there was no evidence that women with melanoma during pregnancy were more likely to have a preterm birth (p=0.40), planned birth (p=0.97) or operative delivery (p=0.43) than women without pregnancy-associated melanoma (Table 3). There was also no evidence that women diagnosed with melanoma in the postpartum period were more likely to have had a planned birth than women

without pregnancy-associated melanoma (p=0.62).There were no stillbirths amongst the 195 women with melanoma during pregnancy or the 382 women diagnosed with melanoma within 12 months postpartum. Women with melanoma during pregnancy had 75% higher odds of having a large-for-gestational-age (LGA) infant but were no more likely to have a small for gestational age infant compared to women with no pregnancy-associated melanoma.

Of the 577 women with pregnancy-associated melanoma, 191 (33%) had a subsequent pregnancy within the years 1994-2008. All subsequent pregnancies occurred in women who had an *in situ,* localized or unknown stage of melanoma at time of diagnosis. The median time to a subsequent pregnancy after a pregnancy-associated melanoma diagnosis was 2.64 years (IQR 1.85 years, range 1.05 to 7.89 years), similar to the median inter-pregnancy interval of 2.43 years for women without pregnancy-associated melanoma (p=0.1). There were no cases of incident pregnancy-associated melanoma or other cancer subsequent to a pregnancy-associated melanoma. In the period 1994-2008, there were 13 deaths due to melanoma amongst the 577 women with pregnancy-associated melanoma, occurring between 50 days and 8.5 years after the earliest possible date of melanoma diagnosis.

Discussion

In this cohort of 577 women with pregnancy-associated melanoma, we found that melanoma in pregnancy is not associated with increased risk of preterm birth, planned

birth, caesarean section or stillbirth compared to women without pregnancy-associated melanoma, in contrast to the adverse pregnancy outcomes reported for women with non-melanoma cancers in pregnancy [13]. This difference may arise from the relative safety with which melanoma diagnosis and surgical excision procedures can be performed in pregnancy, compared to more invasive surgeries, radiotherapy or chemotherapy for other cancers which may necessitate planned preterm or caesarean birth.

We found that the crude incidence of pregnancy-associated melanoma increased with time, which reflects the substantially increased risk of pregnancy-associated melanoma with age and the increasing average maternal age of the NSW maternity population. Previous studies report an increased risk of developing melanoma with advancing age at first pregnancy [16, 17].

We have previously reported that incidence of pregnancy-associated melanoma was higher than expected when compared to the general female population aged 15-44 years [13]. The higher rates of pregnancy-associated melanoma compared to the general female population may be driven by endocrine and growth changes of pregnancy that contribute to tumorigenesis [6]. Some support for this hypothesis may be evident with the increased risk of large-for-gestational-age infants, as reported here and previously [13], and the finding that melanomas diagnosed during pregnancy were thicker than melanomas diagnosed up to 12 months postpartum. Alternatively, increased detection may result from more frequent interactions between women and the health care system in pregnancy. This may also explain the greater likelihood of women in rural/remote areas having a melanoma-

affected pregnancy, with perinatal care visits acting as a screening tool for women who otherwise may have limited health care utilization.

Despite the increased frequency of health care interactions, the observation of thicker melanomas in pregnancy may reflect delayed diagnosis during pregnancy, either because hyperpigmentation in pregnancy is common and makes diagnosis more challenging, or because diagnosis and staging procedures may be delayed until the pregnancy advances [8]. Few prospective studies have examined changes in nevi during pregnancy but the available evidence suggests that nevi do not typically change size or darken during pregnancy [18]. Therefore, changing nevi should undergo biopsy regardless of pregnancy status.

We found parity to have a protective effect against developing melanoma in pregnancy, with an odds ratio of 0.59 for women who had at least three previous pregnancies of at least 20 weeks gestation as compared to nulliparous women. The influence of parity is controversial with few studies and conflicting results. A meta-analysis of 10 case-control studies found no association between previous pregnancies and melanoma risk [16] while two cohort studies reported a protective effect on survival associated with previous pregnancy [17, 19]. Interestingly, one of these studies [17] found similar trends for men, leading to the hypothesis that lifestyle factors associated with having children rather than pregnancy may explain the protective role of parity. In our study, approximately one-third of women with melanoma-affected pregnancies went on to have a subsequent pregnancy, with a similar inter-pregnancy interval to women without pregnancy-associated

melanoma. Women are often advised to defer subsequent pregnancies for 2 – 3 years [20] after a diagnosis of melanoma, however this reflects the period with highest risk of recurrence rather than a negative impact of subsequent pregnancy. Women should be offered advice about subsequent pregnancy based on established prognostic factors for melanoma.

The strengths of our study include reporting the largest cohort of pregnancies affected by melanoma to date, in an Australian setting which has the highest incidence of melanoma in the world [15], and the linkage of three large, validated population data collections to provide recent data on the pregnancy outcomes of women with melanoma in pregnancy. The limitations of our study include that Breslow thickness was missing for 29% of women, therefore differences in tumour thickness between women diagnosed in pregnancy compared to postpartum should be interpreted with caution. Other studies have reported similar levels of missing data for Breslow thickness [8, 9]. We did not have data on cause-specific deaths beyond 2008 so deaths from melanoma are under ascertained for women diagnosed in the later years of the study period. Though we observed no new incident pregnancy-associated cancers subsequent to a pregnancy-associated melanoma diagnosis in the study period, there were no reliable data available on the recurrence of a primary melanoma in subsequent pregnancies, as the cancer data collects information on incident cancers only and melanoma is poorly ascertained in hospital data [21]. The birth data are restricted to pregnancies of at least 20 weeks gestation, so earlier miscarriages and terminations affected by melanoma were not detected. There was some uncertainty

about the timing of melanoma diagnoses as the cancer data reports on the month of diagnosis, therefore the timing of diagnosis of some melanomas may be misclassified.

In summary, the incidence of pregnancy-associated melanoma has increased in NSW. As the incidence of pregnancy-associated melanoma is likely to further increase with the trend towards delayed childbearing, it is important that timely diagnosis of suspicious nevi in pregnancy occurs. Women diagnosed in pregnancy had thicker melanomas than women diagnosed within 12 months postpartum. Melanoma in pregnancy is not associated with adverse pregnancy outcomes except large-for-gestational-age infants. It is possible that tumour thickness and large-for-gestational-age are related through endocrine and growth changes of pregnancy and this should continue to be a topic of further research.

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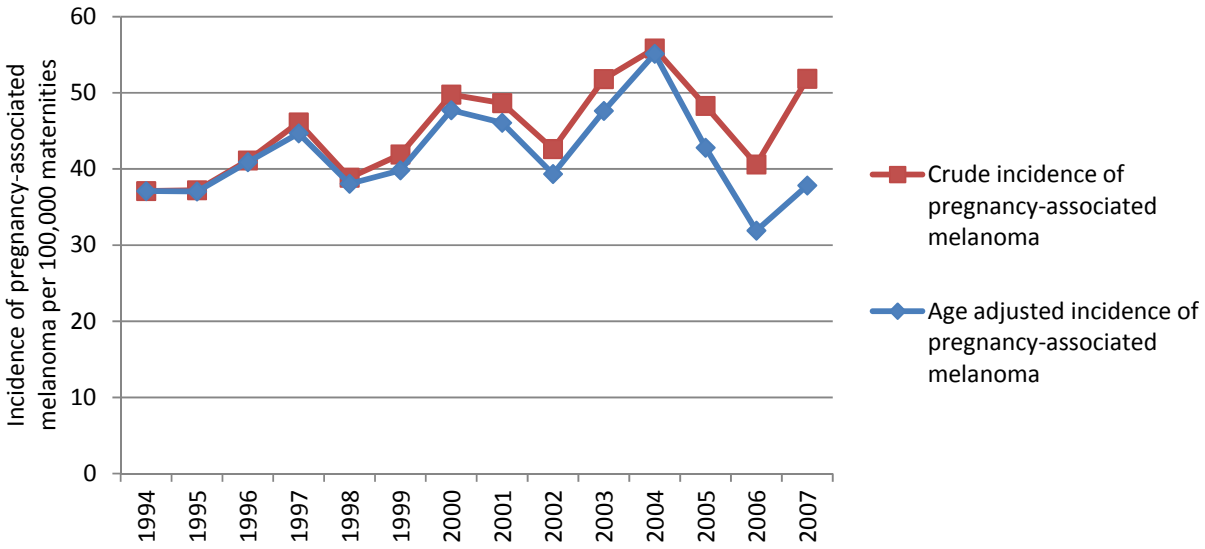
Figures

Figure 1: Crude and age-adjusted incidence of pregnancy-associated melanoma in New South Wales, 1994-2007



Tables

Table 1: Melanoma staging and thickness in 577 women with pregnancy-associated melanoma in New South Wales, 1994-2008

	Pregnancy (n=195)		6-10 weeks postpartum (n=42)		12 months postpartum[a] (n=382)	
	n	(%)	n	(%)	n	(%)
Melanoma staging						
In situ	48	(24.6)	11	(26.2)	98	(25.7)
Localised	133	(68.2)	24	(57.1)	245	(64.1)
Regionalised/distant	8	(4.1)	4	(9.6)	20	(5.3)
Unknown	6	(3.1)	3	(7.1)	19	(5.0)
Melanoma thickness[b]						
<1mm	82	(62.1)	17	(56.7)	179	(73.1)
>=1mm	50	(37.9)	13	(43.3)	66	(26.9)
Median (IQR)	0.75	(0.80)	0.88	(1.00)	0.60	(0.60)
Range	0.20 - 8.20		0.25 - 3.90		0.15 – 17.00	

[a] Includes diagnoses 6-10 weeks postpartum; [b] Data is missing for 170 women

Table 2: Characteristics of 577 women with pregnancy-associated melanoma compared to 1,328,720 unaffected pregnancies in New South Wales, 1994-2008

	Melanoma in pregnancy (n=195)		Melanoma 12 months postpartum (n=382)		No pregnancy-associated melanoma (n=1328720)		Adj. OR*(95% CI)		p
Maternal characteristics	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**			
Age									<0.001
15-24	17	(8.7)	28	(7.3)	266792	(20.1)	Ref.		
25-29	43	(22.1)	96	(25.1)	395811	(29.8)	2.21	(1.57 - 3.11)	
30-34	76	(39.0)	150	(39.3)	421280	(31.7)	3.54	(2.53 - 4.95)	
35-39	42	(21.5)	86	(22.5)	204710	(15.4)	4.45	(3.10 - 6.39)	
40-55	17	(8.7)	22	(5.8)	39498	(3.0)	7.55	(4.81 - 11.86)	
Parity									0.003
0	70	(36.1)	137	(35.9)	546717	(41.2)	Ref.		
1 - 2	112	(57.7)	216	(56.5)	655173	(49.4)	1.07	(0.89 - 1.28)	
3 +	12	(6.2)	29	(7.6)	124754	(9.4)	0.59	(0.42 - 0.84)	
Country of birth									<0.001
Australia	178	(91.3)	343	(90.0)	961153	(72.5)	Ref.		
Outside Australia	17	(8.7)	38	(10.0)	364859	(27.5)	0.26	(0.20 - 0.35)	
Remoteness (ARIA+)									0.05
Major cites	122	(62.6)	238	(74.5)	925090	(69.8)	Ref.		
Inner regional	47	(24.1)	91	(23.9)	247699	(18.7)	1.33	(1.06 - 1.68)	
Outer regional/remote	26	(13.3)	51	(13.4)	153016	(11.5)	1.28	(0.94 - 1.73)	
Socioeconomic status									0.12
Lowest 1st quintile	36	(18.5)	52	(13.7)	277998	(21.1)	0.77	(0.58 - 1.04)	
2nd quintile	28	(14.4)	93	(24.5)	272527	(20.7)	0.83	(0.63 - 1.09)	
3rd quintile	32	(16.4)	68	(17.9)	268304	(20.4)	0.69	(0.52 - 0.91)	
4th quintile	52	(26.7)	76	(20.0)	262396	(19.9)	0.84	(0.66 - 1.09)	
Highest 5th quintile	47	(24.1)	91	(23.9)	235171	(17.9)	Ref.		
Smoking in pregnancy									0.77
No	170	(87.2)	322	(84.3)	1097616	(82.9)	Ref.		
Yes	25	(12.8)	60	(15.7)	227046	(17.1)	0.96	(0.76 - 1.23)	
Plurality									0.52

Singleton	191	(97.9)	369	(96.6)	1289560	(97.1)	Ref.		
Multiple	4	(2.1)	13	(3.4)	39160	(3.0)	0.85	(0.52 - 1.38)	
Delivery hospital level									0.96
Tertiary hospital	68	(34.9)	123	(32.2)	527177	(39.7)	Ref.		
Private hospital	57	(29.2)	105	(27.5)	277370	(20.9)	1.01	(0.81 - 1.26)	
Public hospital	70	(35.9)	154	(40.3)	524171	(39.5)	1.03	(0.82 - 1.30)	
Any diabetes									0.51
No	188	(96.4)	364	(95.3)	1263402	(95.1)	Ref.		
Yes	7	(3.6)	18	(4.7)	65318	(4.9)	0.87	(0.58 - 1.31)	
Any hypertension									0.15
No	172	(88.2)	341	(89.3)	1213088	(91.3)	Ref.		
Yes	23	(11.8)	41	(10.7)	115632	(8.7)	1.21	(0.93 - 1.58)	

*OR; Odds ratios for association between pregnancy-associated melanoma (including diagnosed in pregnancy and up to 12 months postpartum) and maternal characteristics were adjusted for age, parity, plurality, country of birth, remoteness, socioeconomic status, maternal smoking in pregnancy, maternal diabetes, maternal hypertension and hospital level.

Table 3: Pregnancy outcomes for 195 women with melanoma diagnosed in pregnancy compared to women without pregnancy-associated melanoma in New South Wales, 1994-2008

	Melanoma in pregnancy (n=195)		No pregnancy-associated melanoma (n=1328720)		Adj OR* (95% CI)		p
Pregnancy outcomes	**n**	**(%)**	**n**	**(%)**			
Gestational age at birth							0.55
<37 weeks	11	(5.6)	93253	(7.0)	0.83	(0.44 – 1.56)	
37+ weeks	184	(94.4)	1235467	(93.0)	Ref.		
Planned birth							0.60
Spontaneous labour	119	(61)	834784	(62.9)	Ref.		
Induced labour	46	(23.6)	315941	(23.8)	0.87	(0.61 - 1.23)	
Pre-labour caesarean section	30	(15.4)	177607	(13.4)	1.84	(0.55 - 1.28)	
Mode of delivery							0.98
Spontaneous vaginal birth	121	(62.1)	872530	(65.7)	Ref.		
Instrumental birth	20	(10.3)	139227	(10.5)	0.95	(0.58 - 1.56)	
Caesarean section	54	(27.7)	316160	(23.8)	0.98	(0.70 - 1.38)	
Birth weight for gestational age							0.004
SGA	12	(6.2)	133803	(10.2)	0.74	(0.41 - 1.34)	
LGA	37	(19)	136565	(10.4)	1.75	(1.22 – 2.53)	
Appropriately grown	146	(74.9)	1044495	(79.4)	Ref.		
Stillbirth							N/A
No	195	(100.0)	1319500	(99.4)	Not estimable		
Yes	0	(0.0)	8300	(0.6)			

*OR; Odds ratios for association between melanoma diagnosed during pregnancy and pregnancy outcomes were adjusted for age, parity, plurality, country of birth, remoteness, socioeconomic status, maternal smoking in pregnancy, maternal diabetes, maternal hypertension and hospital level. SGA, small for gestational age (<10^{th} percentile); LGA, large for gestational age (>90^{th} percentile)