The Incidence of Second Primary Invasive Melanoma in Queensland, 1982 to 2003

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Abstract

Objective To describe the incidence of second primary invasive melanoma.

Methods Data describing 52,997 subjects with melanoma notified to The Queensland Cancer Registry between 1982 and 2003. We calculated incidence rates of second primary invasive melanoma (per 1,000 person-years) by sex, age, and characteristics of the first primary.

Results The rate of second primary invasive melanoma was relatively constant over twenty years of follow-up at 6.01 per 1,000 person-years indicating a high, constant lifetime risk of second primary invasive melanoma. Rates were 62% higher in males than in females and increased with age at first diagnosis with the rate in older patients (80+years) more than double the rate observed in younger patients (40 to 49 years). Rates in patients with melanomas thicker than 2mm were over 50% higher than in patients with thinner melanomas.

Conclusions Melanoma patients are at high risk of a second primary invasive melanoma. This risk does not diminish with time and does not differ significantly between patients first diagnosed with lentigo maligna, in situ melanoma or invasive melanoma. These results indicate that all melanoma patients require lifetime surveillance. Current treatment guidelines should be modified to reflect this.

Keywords:

Melanoma;

Neoplasms, Second Primary/epidemiology;

Incidence;

Cohort Studies

Introduction

Queensland has the highest incidence of melanoma in the world (1) and the incidence is increasing (2). Several studies have found that people who have had one melanoma are at increased risk of a second melanoma, but most of these have been comparatively small hospital-based studies (3-8).

There have been few large population-based cohort studies of the risk of second primary melanoma (9-11), but none have been performed in Queensland.

Guidelines for the on-going surveillance of melanoma patients have been developed in a number of countries, but there is little consensus as to who should be followed up, how frequently, or for how long (12). While surveillance is obviously motivated by the risk of recurrence, this risk diminishes within a few years of diagnosis (13). Two studies, however, have found that the risk of a second primary melanoma does not decline with time (11, 14).

For this study we used data describing melanomas notified to the Queensland Cancer Registry between 1982 and 2003. We defined four cohorts of patients based on the histological classification of their first melanoma diagnosis: invasive lentigo maligna, in situ lentigo maligna, other invasive melanoma, and other in situ melanoma. The aim of the study was to describe in detail the incidence of second primary invasive melanoma in these four cohorts.

Materials and methods

The records of all Queensland residents diagnosed with melanoma between January 1982 and December 2003 (n=53,743) were obtained from the population-based Queensland Cancer Registry. We then excluded all subjects with zero survival time (n=59), all subjects first diagnosed with more than one melanoma at the same time (synchronous melanomas, n=652), and all subjects with incompatible coding of level and behaviour (n=35). After these exclusions, our study cohort contained 52,997 subjects.

This cohort accumulated person-time from the date of diagnosis of the first lesion until date of death, date of diagnosis of a second lesion, or the censoring date (31 December 2003), whichever came first. We counted second primary invasive melanomas as incident cases and treated second primary in situ melanomas as censored observations.

We classified patients into four cohorts according to the histology of their first melanoma: lentigo maligna (invasive or in situ) and other melanoma (invasive or in situ). In each of these, we obtained crude estimates of cumulative risk of second primary invasive melanoma using Kaplan-Meier survival analysis. We also calculated crude incidence rates (per 1,000 person-years) by sex, by age at first diagnosis in 10-year age groups and anatomic site of the first lesion (head and neck, upper limb, trunk and lower limb) and, for patients first diagnosed with invasive melanomas, by level and thickness ($\leq 1\text{mm}$, 1.01 – 2mm, 2.01-4mm, and $>4\text{mm}$).

In addition to overall crude rates, we also stratified the person-time by year of follow-up to calculate annual incidence rates and by age to calculate age-specific incidence rates.

Poisson regression was used to obtain adjusted incidence rate ratios of second primary invasive melanoma. We fitted Poisson models separately for each of the four cohorts and used Chow's test(15) to determine if differences in relative rate estimates between these models could simply be due to chance.

All Poisson regressions were examined for evidence of over-dispersion by re-fitting them using negative binomial regression. Little evidence of over-dispersion was found. The scale parameter

estimated in each of the negative binomial models was very small and the coefficients and standard errors were virtually identical to those obtained from the corresponding Poisson regression.

In those models where we estimated the independent effects of both level and thickness, we tested each regression for multi-collinearity(16). In all regressions fitted, condition numbers were less than three and we concluded that there was little evidence that the results were affected by multi-collinearity.

When modelling the morphology of first primary invasive melanoma we included as a separate category those reported simply as melanoma, NOS. Since this is a category where the morphology is missing, this approach can potentially bias regression models(17). We repeated the regression analyses excluding the melanoma, NOS, and obtained similar results to those that included melanoma NOS. We also used multiple imputation to impute values for these missing morphology cases(18, 19) and the results from these analyses differed little from those obtained in the original models.

All analyses were conducted using Stata Release 10 (StataCorp, College Station, Texas).

Results

In this cohort of 52,997 patients, 54.9% were male and the average age at diagnosis was 57.1 years (SD 17.6) for males and 53.0 years (SD 17.9) for females. The cohort was observed for a total of 361,588 person-years during which 2,505 second primary invasive melanomas were diagnosed giving an overall crude incidence of 6.93 per 1,000 person-years (95% C.I.: 6.66 – 7.20). The cumulative risk at 5 years was 3.8% and, at 10 years, 6.4%.

We defined four cohorts based on the histology of the first melanoma diagnosed. These comprised invasive lentigo maligna (3.6% of all patients), in situ lentigo maligna (11.8%), all other invasive melanomas (61.5%), and all other in situ melanomas (23.1%). Within these four cohorts the five-year and ten-year cumulative risks of subsequent invasive melanoma were 5.0% and 8.5%, 3.7% and 7.0%, 3.8% and 6.2%, and 3.6% and 6.1%, respectively.

In each of the four cohorts, the annual incidence of second primary invasive melanoma was high and comparatively constant over time apart from the rate observed in the first year of follow-up, which was much higher than in subsequent years (Figure 1). The effect of this first year was to inflate estimates of overall incidence. For example, while the overall incidence was 6.93 per 1,000 person-years, the incidence in the first year was 12.7 per 1,000 person-years and 6.01 per 1,000 person-years thereafter.

The overall incidence rate in the years after the first year of follow-up therefore provides a more accurate estimate of long-term risk of second primary invasive melanoma since annual rates are comparatively constant over time. We therefore excluded all person-time and incident cases accumulated in the first year of follow-up to estimate the long-term incidence for various characteristics of the first melanoma (Table 1). Regardless of the first diagnosis, the incidence of second primary invasive melanoma was higher in males than in females and increased with age at first diagnosis. Those first diagnosed with lentigo maligna on the trunk or upper limb had the highest rates whereas, for other melanomas, the highest rates were observed in those first diagnosed with other invasive or in situ melanomas on the head and neck.

The crude rates in Table 1 are confounded by age however. Few patients were diagnosed with lentigo maligna, either invasive or in situ, before age 40 years, so the higher rates observed in these patients may simply be a reflection of this. For example, when we calculated the overall crude incidence of subsequent invasive melanoma in patients aged 40 years or more at first diagnosis we found comparatively little difference between the rates in patients with invasive or in situ lentigo maligna (8.16; 95%CI: 6.63 – 10.03 and 7.09; 95%CI: 6.26 – 8.03) and the rates in those patients with other invasive or in situ melanomas (7.16; 95%CI: 6.72 – 7.63 and 7.36; 95%CI: 6.61 – 8.20).

To investigate whether there was confounding by age, we used Poisson regression to model rates of second invasive melanoma in the cohorts of patients with invasive and in situ lentigo maligna. When we compared the coefficients from these models we found no significant difference. Similarly, when the coefficients obtained in models for other invasive melanomas and other in situ melanomas were compared, no significant differences were found. Finally, we restricted comparison to all those aged 40 years or more at first diagnosis and tested the coefficients across all four Poisson regression models and found no significant difference. Combining all four cohorts (Table 2), we found that the incidence was strongly associated with age at first diagnosis and sex. Rates in males were more than 60% higher than in females and in older patients aged over 70 years when first diagnosed more than double the rates observed in patients aged 40 to 49 years at first diagnosis. In contrast, rates of subsequent invasive melanoma were only weakly associated with histology, anatomic site, or year of first diagnosis of the first lesion.

We should note that in this final model we have modelled rates classified by age at first diagnosis, rather than age-specific rates. This is because when we examined age-specific rates by age at first diagnosis (Figure 2) we found that they were essentially constant over time.

To gauge the influence of level and thickness of invasive melanomas on the incidence of subsequent invasive melanoma we compared patients first diagnosed with invasive lentigo maligna melanoma to those with other invasive melanomas (Table 3) and restricted comparison to those aged 40 years or more at first diagnosis. We found that rates tended to increase with both level and thickness. We used Poisson regression to model these rates separately for patients with lentigo maligna melanoma and with other invasive melanomas adjusting for age, sex, anatomic site and year of first diagnosis.

Testing the coefficients across these models, we found no significant difference and combined both cohorts in one analysis (Table 4). We found that a significant association with thickness of the first melanoma remained and that the risk of a second primary invasive melanoma in patients first diagnosed with melanomas thicker than 2 mm was over 50% higher than in patients first diagnosed with melanomas less than 1mm thick. In contrast, there was little association with histology or level of the first lesion.

Discussion

In this study we followed 52,997 patients who had been diagnosed with either invasive melanoma or in situ melanoma. In this cohort we observed the incidence of subsequent invasive melanoma over 20 years of follow-up. We ignored the incidence in the first year of follow-up and found that in the years after this, the overall incidence of second invasive melanoma was 6 per 1,000 person-years. By ignoring the incidence in the first year, we do not wish to imply that it was unimportant. On the contrary, the incidence in the first year of follow-up was double the incidence in subsequent years, but this was most likely an effect of surveillance. We believe that the incidence in the years after the first year gives a better indication of the true risk of second invasive melanoma.

We found that the factors most strongly associated with the risk of second invasive melanoma were age at first diagnosis and sex. After adjusting for other factors, the risk in males was over 60% higher than in females and the risk in patients aged 70 years or more when they were first diagnosed was more than double the risk in those aged in their 40s. We also found that the risk in patients first diagnosed with invasive melanomas greater than 2mm thickness was over 50% higher than in those diagnosed with melanomas less than 1mm thick.

In contrast, we could find little evidence that the incidence of second invasive melanoma varied to any great extent by histology of the first lesion. While the crude rates in patients with lentigo maligna appeared higher than in those with other melanomas, this was largely due to confounding by age.

In previous studies various measures of the incidence of second primary melanoma have been reported. It is common, for example, to find studies that have simply reported the overall percentage of patients who developed a second melanoma (6, 20, 21), but these results are not interpretable either as measure of risk or incidence since they ignore the time over which the incident cases of second primary melanoma were accrued.

Other studies have reported the 5-year cumulative incidence (5, 8, 10, 11, 22), but risk estimates from these studies have varied from 2.1% to 11.4%. This variation seems to be largely due to differences in the definition of incident cases. Some studies included synchronous melanomas in their estimate (10, 11) and others included both synchronous and second in situ melanomas (5, 22).

Few previous studies have examined the incidence of second primary melanoma over time since the first diagnosis, but those that have found it to be relatively constant (11, 14).

There are distinct advantages to be gained from reporting annual rates of second invasive melanoma as we have done in Figure 1. First, these estimate the ongoing risk of a second invasive melanoma at any time up to 20 years after diagnosis of the first lesion, whereas 5-year cumulative incidence only estimates risk from the date of diagnosis of the first lesion and consequently provides no information about the risk in patients who have survived some period of time since their first diagnosis.

Second, they allow us to rule out bias from misclassification of metastatic disease. In studies of second primaries generally, there is always a concern that rates of second primaries may be biased if metastatic disease arising from the first lesion is being misclassified as a new primary cancer. While this may occur, it would seem unlikely to be occurring to an extent to be causing significant bias in our study. In melanoma patients, the risk of recurrence is high in the first few years following diagnosis and rare thereafter(13). It follows then that if misclassification of recurrence were occurring to any significant extent, we would see evidence of this in the annual rates of second melanoma.

While rates in the first year of follow-up were elevated, the rates in the years after this were remarkably uniform over time, suggesting little effect of misclassification of recurrence.

While we found higher rates of second melanoma in males than in females, consistent with previous studies (10, 11), we also found that the risk increased with age at first diagnosis. This is in marked contrast to results from previous studies that have concluded that the risk was higher in younger age groups than in older age groups(8, 22-24). These studies, however, used indirect standardization to investigate differences in risk of a second primary melanoma. Within several cohorts defined by age at first diagnosis, they calculated the ratio of the number of second primaries observed to the number expected: the standardized incidence ratio (SIR). They found that the SIRs declined with age at first diagnosis and interpreted this as indicating a decline in the risk of a second primary. This conclusion, however, is based on a comparison of SIRs and in these studies such a comparison is not valid. The SIR is not simply the ratio of observed to expected cases in a cohort, it is the ratio of the observed to expected rate where the expected rate is calculated by standardizing population age-specific rates to the age-specific person-years of the cohort. For SIRs calculated in different cohorts to be comparable,

the age-specific distribution of person-years must be similar in each of the cohorts (25, 26). This will ensure that the expected rates in each of the cohorts are similar and therefore any differences between SIRs will be due to differences in the observed rate: differences in risk. In studies of second primary melanoma, however, the SIRs were calculated in cohorts that were defined by age at first diagnosis of melanoma. Clearly, the age-specific distribution of person-years in each of these cohorts will be distinctly different and as a consequence the SIRs cannot be compared nor can they be used to draw any inferences concerning age differences in the risk of second primary melanoma.

Our results have major implications for the follow-up of melanoma patients. At present, Australian clinical practice guidelines for the treatment of cutaneous melanoma are under review, but current guidelines (27) recommend a protocol for the follow-up of melanoma patients that is based primarily on tumour thickness. This specifies that all patients be reviewed every three or four months in the first two years of follow-up. After this, it is recommended that patients with tumours thicker than 1mm continue to be reviewed every six months for the first five years, and then annually thereafter. Patients with tumours less than 1mm thick are not considered to require review after two years of follow-up, unless they are at high risk for a second primary melanoma due to multiple dysplastic naevi or a history of melanoma in close relatives. There are no recommendations for the follow-up of patients initially diagnosed with in situ melanoma.

While these guidelines reflect a concern for the risk of recurrence, we believe that they are underestimating the risk of a subsequent invasive melanoma. We estimated the overall rate of subsequent invasive melanomas to be 6.01 per 1,000 person-years or, equivalently, 601 per 100,000 person years and in older patients (Table 1), rates approached or exceeded 1,000 per 100,000 person-years. As a comparison, in the Queensland population the highest age-specific rate of invasive melanoma in 2004 was 340 per 100,000, observed among males aged 80-84 years (28). The rates of subsequent invasive melanoma we have found therefore indicate a very high risk of invasive melanoma, much higher than the risk of invasive melanoma in the general population. More importantly, apart from patients who were very old when first diagnosed, these rates of subsequent invasive melanomas did not diminish over time (Figure 2).

In conclusion, we have shown that patients diagnosed with melanoma in Queensland have an extremely high and continuing risk of developing a subsequent invasive melanoma and we recommend that current guidelines for the on-going surveillance of melanoma patients be amended. All patients with melanoma should receive regular and on-going surveillance for the rest of their lives regardless of the histology, thickness, or site of the first lesion.

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Table 1: Incidence of second primary invasive melanoma following diagnosis of lentigo maligna (invasive or in situ) or other melanoma (invasive or in situ); excluding first year of follow-up.

		Lentigo Maligna		Other Melanoma	
		Invasive	In situ	Invasive	In situ
Overall		7.99 6.50 – 9.83	6.80 6.01 – 7.69	5.79 5.46 – 6.13	5.90 5.34 – 6.52
Sex	Male	10.4 8.13 – 13.4	8.57 7.36 – 9.99	7.12 6.61 – 7.66	7.32 6.43 – 8.33
		5.35 3.72 – 7.70	4.86 3.94 – 6.01	4.44 4.05 – 4.88	4.59 3.93 – 5.38
	Female				
Age	<20	0	0	2.40 1.45 – 3.98	1.15 0.29 – 4.59
	20-29	0	0	2.81 2.20 – 3.59	1.70 0.94 – 3.08
	30-39	0	1.89 0.61 – 5.85	3.20 2.67 – 3.84	3.28 2.38 – 4.50
	40-49	3.06 0.99 – 9.50	4.41 2.85 – 6.84	4.41 3.81 – 5.11	4.77 3.74 – 6.09
	50-59	8.00 4.97 – 12.9	4.90 3.57 – 6.74	6.43 5.64 – 7.32	7.38 6.01 – 9.05
	60-69	8.37 5.82 – 12.1	7.70 6.25 – 9.49	8.62 7.68 – 9.68	8.79 7.21 – 10.7
	70-79	7.35 4.88 – 11.1	9.38 7.56 – 11.7	10.3 8.97 – 11.8	9.41 7.31 – 12.1
	80+	13.5 8.49 – 21.4	7.86 5.07 – 12.2	12.6 9.87 – 16.1	11.4 7.09 – 18.3

Site	Head and neck	7.93 5.88 – 10.7	6.81 5.83 – 7.96	6.83 5.82 – 8.01	8.47 6.68 – 10.7
	Arm/Shoulder	7.43 4.79 – 11.5	7.66 5.77 – 10.2	5.80 5.15 – 6.53	5.61 4.59 – 6.86
	Trunk	10.5 6.43 – 17.1	7.12 4.88 – 10.4	5.60 5.07 – 6.19	5.97 5.03 – 7.09
	Leg/Hip	8.72 4.69 – 16.2	4.39 2.28 – 8.43	5.73 5.10 – 6.44	5.09 4.06 – 6.38
	Other	2.13 0.30 – 15.1	5.55 2.89 – 10.7	5.10 3.96 – 6.57	4.29 2.54 – 7.24
Year	1982-85	5.48 3.31 – 9.10	5.69 4.25 – 7.63	4.70 4.10 – 5.38	6.31 4.79 – 8.30
	1986-89	6.21 4.00 – 9.62	5.32 4.08 – 6.95	5.23 4.65 – 5.90	5.52 4.40 – 6.93
	1990-94	10.7 7.63 – 15.2	7.65 6.17 – 9.48	6.28 5.64 – 6.99	6.35 5.32 – 7.57
	1995-99	10.9 7.02 – 16.9	9.42 7.30 – 12.2	6.65 5.91 – 7.49	5.90 4.91 – 7.08
	2000-03	5.16 1.29 – 20.6	5.66 3.04 – 10.5	7.67 6.00 – 9.80	4.36 2.78 – 6.84

Table 2: Relative rates of second invasive melanoma in patients aged 40 years or more at first diagnosis of lentigo maligna (invasive or in situ) or other melanoma (invasive or in situ)

		IRR	95% C.I.	p value
First lesion	Invasive lentigo maligna	0.96	0.76 – 1.19	0.28
	In situ lentigo maligna	0.86	0.74 – 1.01	
	Invasive Melanoma	1.00	(ref)	
	In situ melanoma	1.02	0.90 – 1.15	
Sex	Females	1.00	(ref)	<0.001
	Males	1.62	1.46 – 1.80	
Age	40-49	1.00	(ref)	<0.001
	50-59	1.42	1.22 – 1.67	
	60-69	1.84	1.58 – 2.14	
	70-79	2.12	1.80 – 2.49	
	80+	2.56	2.05 – 3.19	
Site	Head and neck	1.00	0.87 – 1.15	0.36
	Upper limb	1.05	0.91 – 1.22	
	Trunk	1.00	(ref)	
	Lower limb	1.09	0.94 – 1.27	
	Other	0.85	0.66 – 1.09	
Year	1982-85	1.00	(ref)	0.06
	1986-89	1.05	0.90 – 1.24	
	1990-94	1.17	1.01 – 1.37	
	1995-99	1.20	1.03 – 1.40	
	2000-03	0.97	0.75 – 1.24	

Table 3: Incidence of second primary invasive melanoma by morphology, thickness and level in patients aged 40 years or more when first diagnosed with invasive lentigo maligna or invasive other melanomas

		Lentigo maligna	Other melanoma
Overall		8.16 6.63 – 10.03	7.20 6.72 – 7.63
Morphology	Melanoma NOS		7.07 6.25 – 8.00
	Nodular Melanoma		8.83 7.37 – 10.6
	Superficial spreading melanoma		6.80 6.26 – 7.38
	Other melanoma		11.33 7.88 – 16.3
Thickness	< 1mm	8.41 6.70 – 10.6	6.24 5.73 – 6.80
	1 – 1.99mm	9.85 5.12 – 18.9	8.03 6.83 – 9.44
	2 – 4 mm	2.18 0.31 – 15.5	11.1 9.17 – 13.3
	> 4 mm	12.4 1.74 – 87.8	10.9 7.89 – 15.0
Level	2	8.07 6.33 – 10.3	6.50 5.91 – 7.15
	3	8.45 4.80 – 14.9	6.56 5.68 – 7.57
	4	8.67 4.34 – 17.3	9.29 8.04 – 10.7
	5	0	11.4 7.73 – 16.9

Table 4: Relative rates of second invasive melanoma in patients aged 40 years or more at first diagnosis of invasive melanoma; adjusted for age at first diagnosis, sex, anatomic site of first melanoma, and year of first diagnosis.

		IRR	95% CI	p value
Morphology	Melanoma NOS	0.99	0.83 – 1.18	0.79
	Nodular Melanoma	0.88	0.68 – 1.14	
	Lentigo maligna melanoma	1.08	0.84 – 1.37	
	Superficial spreading melanoma	1.00	(ref)	
	Other melanoma	1.10	0.69 – 1.75	
Level	2	1.00	(ref)	0.78
	3	0.91	0.76 – 1.11	
	4	0.99	0.77 – 1.29	
	5	1.03	0.61 – 1.75	
Thickness	< 1.00 mm	1.00	(ref)	0.04
	1.00 – 1.99 mm	1.27	1.01 – 1.60	
	2.00 – 4.00 mm	1.55	1.15 – 2.10	
	> 4.00 mm	1.50	0.95 – 2.38	

Figure 1: Overall annual incidence of second invasive melanoma in patients first diagnosed with invasive lentigo maligna, in situ lentigo maligna, other invasive melanomas, and other in situ melanomas; Queensland, 1982 to 2003

Figure 2: Age-specific incidence of second invasive melanoma by age at first diagnosis of melanoma (either invasive or in situ); Queensland, 1982 to 2003invasive melanoma