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Title: Anxiety and depression after diagnosis of high-risk primary cutaneous melanoma: a four-year longitudinal study

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Abstract

Purpose: To quantify the prevalence of anxiety or depression (overall; melanoma-related) among people with high-risk primary melanoma, their related use of mental health services and medications, and factors associated with persistent new-onset symptoms across four years post-diagnosis.

Methods: A longitudinal study of 675 patients newly diagnosed with tumor-stage 1b-4b melanoma. Participants completed the Hospital Anxiety and Depression Scale, and answered questions about fear of cancer recurrence, use of medication and support, serially over four years. We identified anxiety and depression trajectories with group-based trajectories models, and factors associated with persistent symptoms with logistic regression.

Results: At diagnosis, 93 participants (14%) had melanoma-related anxiety or depression and 136 (20%) were affected by anxiety and/or depression unrelated to melanoma. After six months, no more than 27 (5%) reported melanoma-related anxiety or depression at any time, while the point-prevalence of anxiety and depression unrelated to melanoma was unchanged (16-21%) among the disease-free. Of 272 participants reporting clinical symptoms of any cause, 34% were taking medication and/or seeing a psychologist or psychiatrist. 11% (n=59) had new-onset symptoms that persisted; these participants were more likely aged <70.

Conclusions: Melanoma-related anxiety or depression quickly resolves in high-risk primary melanoma patients after melanoma excision, while prevalence of anxiety or depression from other sources remains constant among the disease-free. However, one-in-ten develop new anxiety or depression symptoms (one-in-twenty melanoma-related) that persist.

Implications for Cancer Survivors: Chronic stress has been linked to melanoma progression. Survivors with anxiety and depression should be treated early to improve patient- and potentially, disease-outcomes.

Key words: melanoma, anxiety, depression, distress, fear of recurrence

Introduction

Diagnosis of invasive melanoma is often perceived as life-threatening and can trigger psychological distress, even when the majority of patients today are diagnosed when the primary tumor is localized to the skin and <1mm thick [1] with a five-year survival rate of greater than 90% [2]. However, the subgroup of patients diagnosed with thicker or ulcerated primary melanomas (tumor stage 1b-4b) and defined as "high-risk", have a 13% risk of disease progression within two years [3] which in some is associated with ongoing anxiety and fear of cancer recurrence [4, 5]. These concerns differ over time and for patients with localized disease compared with regional or distant metastases [4, 6].

We have previously shown that immediately after diagnosis, 17% and 5% of patients with high-risk primary melanoma in Queensland, Australia, report clinical symptoms of anxiety and depression, respectively [7]. However, there is substantial variability between studies and a systematic review found that among patients with non-metastatic melanoma, the proportion of participants scoring within the clinical range for anxiety ranged from 18% to 44% [6]. Similarly, the frequency of clinically relevant depressive symptoms among patients with early-stage melanoma ranges widely: from 6% to 28% [6]. This variation may reflect methodological differences between studies in terms of time since diagnosis or treatment, involvement in clinical trials, and/or cultural attitudes or beliefs of patient groups studied. Limitations such as retrospective study design, reliance on a single cross-sectional assessment and small sample sizes also impede the generalization of previous findings. A prospective assessment of the burden of anxiety and depression over time in melanoma patients being followed-up in a non-clinical trial setting is not available, nor is it known how much anxiety and depression is caused by the melanoma and fear of its recurrence versus other causes, and what proportion of affected patients are receiving appropriate treatment.

Cross-sectional studies suggest fear of cancer recurrence warranting clinical intervention may affect upwards of 60% of people after treatment for localized melanoma [8]. Conceptual models suggest that if elevated, fear of cancer recurrence may lead to emotional distress [9]. In general, high fear of cancer recurrence does not appear to lessen over time for cancer survivors [10] although there is an absence of longitudinal studies to determine the prevalence of fear of cancer recurrence over time or its association with anxiety and depression in people with high-risk melanoma. Understanding the prevalence and the drivers (i.e. pre-existing conditions, fear of recurrence, other post-diagnosis stressful life events) of anxiety and depression may help us understand the

specific support service needs of this population. In addition to being aware of melanoma-related and other anxiety and depression among their patients during follow-up, care providers should be aware of levels of persistent anxiety, as there is experimental and clinical evidence that chronic stress, through the release of stress hormones and a consequent activation of the beta-adrenergic system, can affect melanoma progression [11].

We therefore aimed to prospectively quantify over a four-year period from time of diagnosis, the point prevalence and total burden of melanoma-related and other anxiety or depression; related use of mental health services and medication; and the proportions with new-onset anxiety or depression over time, and symptom trajectories including persistent new-onset anxiety and depression, among people with high-risk primary melanoma.

Methods

Participants

The Primary Melanoma Project is a prospective study of people newly diagnosed with high-risk primary cutaneous melanoma in Queensland, in 2010 to 2014. Two Human Research Ethics Committees approved the study. Participants were ascertained from urban and regional hospitals, through associated melanoma surgeons and private pathology companies. Altogether 1,254 patients with tumor stage 1b-4b were invited to participate by their treating doctors or study personnel with doctors' permission, and 825 consented to participate. We excluded 36 consented participants who, upon later definitive treatment were not tumor stage 1b-4b (mainly because loco-regional metastases were revealed), and thus they did not meet the eligibility criteria. Participants were mailed questionnaires every six months for the first two years then annually or until they died or withdrew. For this analysis a further 114 participants were excluded, 89 because their tumor stage was no longer classified as 1b-4b under the updated 2018 American Joint Committee on Cancer (AJCC) 8th edition of melanoma staging [12], one because of melanoma recurrence before completing the baseline questionnaire and 24 because they completed the baseline questionnaire more than ten weeks after diagnosis. Thus, 675 participants contributed data to this study.

Measures

Personal information (age, sex, relationship status, education level, history of melanoma, history of specific comorbidities including anxiety and depression and date of diagnosis) was gathered at baseline using a standard

questionnaire. Use of anxiolytic or antidepressant medication in the last five years was self-reported at baseline, and at each follow-up survey using a question that asked about any medication use for depression or anxiety/panic attacks and if yes, specification of drug name, dose, medical condition used for and dates of use. Drugs classification were verified against the World Health Organisation groupings [13]. Having a history of anxiety or depression was then classified as anyone who reported either a history of being diagnosed or having used anxiolytics or antidepressants within the 5 years prior to index melanoma diagnosis. Postcodes were used to classify remoteness of place of residence [14].

We assessed symptoms of anxiety and depression at each follow-up time-point using the 14-item Hospital Anxiety and Depression Scale (HADS). The scale has excellent psychometric properties with two sub-scales distinguishing between anxiety and depression (alphas coefficients 0.93 and 0.90, respectively) [15]. Scores on both sub-scales range 0-21. Within each sub-scale, scoring cut-offs distinguish between "normal" (0-7), "subclinical" (8-10), and "clinical" (11-21) symptom levels.

Participants were asked at baseline to indicate if they had consulted a psychologist or psychiatrist since diagnosis, and this was repeated at each follow-up. Fear about the cancer spreading was also measured at each follow-up using an item from the Supportive Care Needs Survey-Short Form 34 [16]; participants who reported a moderate-or-high unmet need on this item were classified as having fear of melanoma recurrence.

Details of the index primary melanoma (site, histological classification, thickness, mitoses, ulceration) were extracted from histopathology reports, and previous melanomas were confirmed histologically. Information about performance of sentinel lymph node biopsies (SLNB) and melanoma recurrences (defined as any spread of disease after definitive surgery of the primary melanoma) were obtained from medical records.

Statistical analysis

Data collected after a participant had a recurrence were excluded from these analyses because of our aim to assess anxiety and depression related to fear of recurrence among patients being routinely followed up after initial treatment, in the absence of disease. We used descriptive statistics to quantify point prevalence and total burden of anxiety or depression symptoms including use of anxiolytic or antidepressant medications. Participants were classified into four groups at each point of follow-up over four years, according to the level of

distress (anxiety or depression) they reported: (i) no distress & no medication; (ii) subclinical symptoms & no medication; (iii) medication use and no/sub-clinical symptoms; (iv) clinical distress symptoms ± medication. When participants reported clinical symptoms of anxiety or depression, we quantified their use of the services of a psychologist or psychiatrist, and/or of anxiolytic or antidepressant medications.

To determine the proportion with anxiety or depression related to fear of recurrence, we calculated the proportions with, and without, fear of recurrence at each follow-up point among participants with subclinical or clinical distress symptoms ± medication. To determine the proportion with new-onset distress we excluded the subgroup of participants with a history of diagnosed anxiety or depression or anxiolytic or antidepressant use in the five years prior to the index melanoma.

We used descriptive statistics to report attrition rates. We determine if there was a difference in distress (any or melanoma-related) between participants with complete follow-up data versus those who withdrew before 48 months versus who died or had data removed data after recurrence, with chi-squared tests.

Group-based trajectory models [17, 18] were used to identify groups with distinct patterns over time. Among the subgroup with new-onset distress, we used group-based trajectory models to identify clusters of participants with at least one follow-up observation who followed similar symptom trajectories of anxiety and depression. We specified the models to used continuous HADS scores and censored normal models first with uniform orders fitted (all linear, all quadratic, all cubic then all quartic). Trajectory groups were selected based on the Bayesian Information Criterion. We then used combinations of linear, quadratic, cubic and quartic orders to find the best fit.

We used logistic regression models to explore which baseline demographic, clinical and health factors were associated with persistent anxiety or depression versus decreasing symptoms (as identified in these trajectory models) in order to assess, among cases, the risk factor profile of those with persistent symptoms who represent the most severe cases and who may be at higher risk of melanoma progression.

Results

Of 675 participants (mean age (SD) 62 years (14), 58% men), 19% had a confirmed previous melanoma and 14% a history of anxiety or depression in the five years prior to index melanoma diagnosis (Table 1).

Total burden of anxiety and depression

At diagnosis, 112 participants (17%) reported clinical symptoms of anxiety (15%) and/or depression (5%), with an additional 38 (6%) reporting use of anxiolytic or antidepressant medications and a further 80 (12%) reported subclinical (HADS 8-10) symptoms (Figure 1a). The proportion of participants with melanoma-related anxiety or depression dropped from 14% at diagnosis to 2-5% after six months in those who remained recurrence-free, while the proportion of patients with other sources of anxiety and depression remained fairly constant (16-21%) over time (Figure 1b). The proportion of clinical cases, that is participants with symptoms at clinical levels or using anxiolytics or antidepressants, reduced substantially from 23% to 12% at six months and remained at similar prevalence (11-14%) thereafter (Figure 1a), reflecting the initial reduction in melanoma-related anxiety or depression. Among those without anxiety or depression, the proportion with fear of cancer recurrence was negligible (0-5%) (Figure 1b).

Overall, 48% of recurrence-free participants had anxiety or depression at some point during the four-year follow-up, 31% at clinical levels and/or requiring medication (Figure 1a), and with 17% reporting fear of recurrence (Figure 1b). Among those with no history of anxiety or depression within five years prior to the index melanoma, the proportions with new-onset anxiety or depression were 41% at some point after diagnosis, 21% at clinical levels and/or requiring medication and 14% with fear of recurrence.

Of the 675 participants, 636 (94%) completed at least one follow-up questionnaire. Of the 675, 447 (66%) remained active and disease-free in the study to 48 months after diagnosis, while 148 (22%) died or had a recurrence and had their data after recurrence excluded, and 80 (12%) withdrew. The prevalence of (a) any or (b) clinical anxiety or depression within the first 4 years, did not differ significantly (any $p=0.417$; clinical $p=0.260$) among participants with complete data (any 48%; clinical 30%) versus those who had data prior to a recurrence or death (any 45%; clinical 27%) versus those who withdrew (any 54%; clinical 38%).

Use of mental health services and medication

When participants reported clinical symptoms of anxiety or depression (counts over the 4 years of follow-up=272), at the time only 34% (count=92) reported taking related medication (27%; count=74) and/or seeing a psychologist or psychiatrist (15%; count=41).

Trajectories of new-onset anxiety and depression symptoms

The trajectory models revealed six groups that follow similar trajectories for new-onset anxiety and depression symptoms. In both models, three groups were always in the HADS normal range and thus we collapsed these into one group which we defined as 'normal stable' (Fig 2). Based on the trajectories and established HADS thresholds, we defined the other groups as 'persistent symptoms' (at clinical or sub-clinical levels), 'symptoms decreasing to normal' and 'normal increasing to borderline symptoms'. We found that in the absence of recurrence, there were small groups with persistent symptoms of anxiety (11%) and depression (3%) and small groups who were symptomatic for anxiety (6%) and depression (5%) after their cancer diagnosis and returned to normal within six months. The majority of participants had no symptoms of anxiety (84%) or depression (92%) in the four years after diagnosis; although 8% approached borderline depression symptoms at 24 months.

In total (Table 2), 59 participants (11%) were classified as having experienced new-onset persistent symptoms of anxiety or depression. Of note, 28 (47%) of whom reported fear of recurrence at baseline, and 23 (39%) reported fear of recurrence after baseline. A further 39 (7%) were classified as having experienced high then decreasing anxiety or depression symptoms after their melanoma diagnosis. In exploring baseline factors associated with persistent new-onset anxiety or depression versus decreasing symptoms, we found that participants aged <50 years and especially those aged 50-69 years were more likely to be affected compared to those aged ≥70 (Supplementary Table). Lack of power prevented confirmation in a multivariable model.

Discussion

Tailored psychosocial care is integral to quality care of patients with cancer. In this prospective study of psychological distress after diagnosis of high-risk primary melanoma, we have shown that melanoma-related anxiety and depression peaks at diagnosis (14%) then quickly resolves for most patients, suggesting that fear of recurrence is short-lived in this patient group after excision of the melanoma. However, the proportion of

patients with anxiety and depression for other reasons remained unchanged (16-21%) in the absence of disease recurrence over the four years of follow-up.

We also found the total burden of clinical symptoms of anxiety and depression in this population to be lower than the 30% previously indicated [6], but the former estimate included patients who had experienced recurrence and metastases. In this recurrence-free high-risk melanoma study population, less than a quarter reported clinical symptoms at any point in the four years after diagnosis. Indeed the peak clinical symptoms of anxiety (15%) and depression (5%) at diagnosis in this study were comparable to general population norms for anxiety (13%) and depression (4%) [19]. After this, the proportion with clinical symptoms of anxiety or depression was less than 7% at any time-point. This is much lower than the prevalence generally seen among cancer survivors (21-22% for anxiety and 13% for depression at 6 to 12 months after diagnosis) [20].

On the other hand, nearly two-thirds of participants who reported clinical symptoms of anxiety or depression were not receiving appropriate care, namely taking anxiolytic or antidepressant medication and/or seeing a psychologist or psychiatrist [21]. Our findings are in line with national data that indicate 54% of Australians with a 12-month mental disorder do not consult a general practitioner, psychologist or psychiatrist [22]. Appropriate treatment is important, not only to reduce the effect of anxiety and depression on family and social functioning, and work performance for example [23], but also because of evidence that chronic anxiety and depression may be linked to melanoma progression [11, 24]. Guidelines recommend that clinicians should screen for distress on diagnosis of cancer, at start and end of treatment, and periodically during follow-up [21, 25, 26] and provide appropriate referral as needed [21]. In cancer cohorts, the sub-clinical threshold (HADS≥8) has been identified as clinically relevant for treatment [27]. Excluding the 14% of participants in the present study who had pre-existing anxiety or depression, we found a small but substantial proportion of participants (11%) had new clinical or sub-clinical symptoms of anxiety or depression that persisted over the four years of study follow-up and half of these individuals also experienced melanoma-related fear of recurrence. Since psychological intervention for melanoma survivors is associated with decreases in anxiety, melanoma-related distress and melanoma recurrence rates [28], clinicians ideally should normalize fear of recurrence, provide adequate information about prognosis, signs and symptoms of recurrence and reinforce behavioral strategies for risk reduction [29]. To optimize patient outcomes it may be useful for clinicians to collect personalized risk information about which patients are likely to have ongoing anxiety and depression. Persistent anxiety and

depression for all types of cancer are unclear and relatively under-researched [30], and larger longitudinal studies than ours would be required to assess this for melanoma.

The strengths of this study were its multicenter longitudinal design with low rate of loss to follow-up, with a study sample that reflected the corresponding age and sex distributions of all melanomas registered in the Queensland Cancer Registry [31]. Missing data analysis showed no major differences in the proportions of participants with any or melanoma-related anxiety and depression according to completeness of follow-up data. Thus, we believe our estimates to be largely unbiased by dropout and generalizable to most patients with high-risk primary melanoma. However, the HADS is a screening tool, not a diagnostic tool, for anxiety and depression. While the diagnostic accuracy of the HADS in the cancer setting is considered adequate for anxiety (sensitivity 0.73; specificity 0.65) and depression (sensitivity 0.73 and specificity of 0.66) [27], it is possible that we have identified some false positives and false negatives cases. Furthermore while this is one of the first studies to additionally measure anxiolytic or antidepressant medication use, our measure was self-reported and may underestimate the proportion of people using medication. An innovation was the use of trajectory modelling that enabled us to distinguish group-based patterns of anxiety and depression symptoms rather than traditional modelling techniques that simply average trajectories of outcomes over time.

In conclusion, this study has comprehensively characterized anxiety and depression after diagnosis of a high-risk localized melanoma. It provides evidence that fear of cancer recurrence is highest at diagnosis at which time it may contribute to the emotional distress of people diagnosed with melanoma, suggesting the benefit of screening for fear of cancer recurrence after primary treatment. Those identified with symptoms of anxiety and depression as well as fear of recurrence should be referred for appropriate psychosocial support as part of follow-up clinical care.

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Table 1. Characteristics of 675 participants with high-risk primary melanoma

	n (%)
DEMOGRAPHICS	
Age (years)	
<50	129 (19)
50-69	329 (49)
≥70	217 (32)
Sex	
Male	392 (58)
Female	283 (42)
Relationship status	
No partner	171 (25)
Partner	502 (75)
Level of education	
Grade 10 (15-16 years) or less	279 (41)
Grade 12 (age 17-18 years) or diploma	263 (39)
University	132 (20)
Remoteness of residence	
Major city	378 (56)
Inner regional	199 (29)
Outer regional/remote/very remote	98 (15)
CLINICAL CHARACTERISTICS	
AJCC-8th edition tumor stage (tumor width)	
T1b (≤1.0 mm)	118 (17)
T2a (>1.0 to 2.0 mm)	232 (34)
T2b (>1.0 to 2.0 mm)	67 (10)
T3a (>2.0 to 4.0 mm)	117 (17)
T3b (>2.0 to 4.0 mm)	56 (8)
T4a (>4.0 mm)	37 (5)
T4b (>4.0 mm)	48 (7)
Primary site	
Head/Neck	149 (22)
Trunk	236 (35)
Upper Limb	140 (21)
Lower Limb	150 (22)
Histological type	
SSM	269 (40)
Nodular	164 (24)
Other[a]	242 (36)
PREMORBID HEALTH	
Previous history of melanoma	
No	546 (81)
Yes	129 (19)
Diagnosis of anxiety or depression within 5 years prior to index melanoma diagnosis	
No	580 (86)
Yes	95 (14)
Comorbidities[b]	
No	347 (51)
Yes	328 (49)

[a] including lentigo maligna, desmoplastic, neutrotropic, naevoid, spitzoid, lentiginous, acral lentiginous, mixed, unable to classify, not stated or other

[b] heart disease, diabetes, hypertension/stroke or cancers other than skin cancer

Table 2. New-onset anxiety and depression trajectory groups in participants who remain recurrence-free

Anxiety	Depression			Total
	Normal stable	Decreasing symptoms	Persistent symptoms	
	n (%)	n (%)	n (%)	n (%)
Normal stable	428 (81)	10 (2)	4 (1)	442 (84)
Decreasing symptoms	15 (3)	14 (3)	0 (0)	29 (6)
Persistent symptoms	40 (8)	4 (1)	11 (2)	55 (11)
Total	483 (92)	28 (5)	15 (3)	526 (100)

Note: Of the 675 participants, 149 participants were ineligible for this analysis: 95 who had a diagnosis of anxiety or depression within 5 years prior to index melanoma diagnosis and 54 who did not have any follow-up data or follow-up data prior to recurrence.

Supplementary Table. Predictors of new-onset persistent (n=59) versus decreasing (n=39) symptoms of anxiety or depression.

	n	Unadjusted Odds Ratio (95% CI)	p-value
DEMOGRAPHICS			
Age (years)			
<50	27	2.0 (0.7-6.2)	0.07
50-69	47	3.3 (1.2-9.2)	
≥70	24	Referent	
Sex			
Male	43	1.2 (0.5-2.7)	0.6
Female	55	Referent	
Relationship status			
No partner	29	1.4 (0.6-3.4)	0.5
Partner	69	Referent	
Level of education			
Grade 10 (15-16 years) or less	38	Referent	0.7
Grade 12 (age 17-18 years) or diploma	41	0.8 (0.3-2.0)	
University	19	1.4 (0.4-4.5)	
Remoteness of residence			
Major city	56	Referent	0.4
Inner regional	28	0.6 (0.2-1.4)	
Outer regional/remote/very remote	14	1.0 (0.3-3.4)	
CLINICAL CHARACTERISTICS			
Tumor stage (AJCC-8th edition)			
T1b-T2b	63	Referent	0.7
T3a-T4b	35	1.2 (0.5-2.8)	
Primary site			
Head/Neck	18	Referent	0.9
Trunk	35	1.4 (0.4-4.3)	
Upper Limb	22	1.0 (0.3-3.4)	
Lower Limb	23	1.5 (0.4-5.3)	
Histological type			
SSM	43	Referent	0.2
Nodular	16	0.6 (0.2-1.8)	
Other[a]	39	1.6 (0.7-4.0)	
Sentinel lymph node biopsy			
Not done	60	1.4 (0.6-3.2)	0.4
Done	38	Referent	
BASELINE HEALTH			
Previous history of melanoma			
No	86	Referent	0.6
Yes	12	1.4 (0.4-4.9)	
Other comorbidities[b]			
No	56	Referent	0.6
Yes	42	0.8 (0.4-1.8)	
Moderate-severe other stressful life event at baseline			
No	71	Referent	0.4
Yes	27	1.5 (0.6-3.7)	
Moderate-high fear of cancer spreading at baseline			
No	54	Referent	0.2
Yes	43	1.7 (0.7-3.8)	

[a] including lentigo maligna, desmoplastic, neutrotropic, naevoid, spitzoid, lentiginous, acral lentiginous, mixed, unable to classify, not stated or other

[b] heart disease, diabetes, hypertension/stroke or cancers other than skin cancer

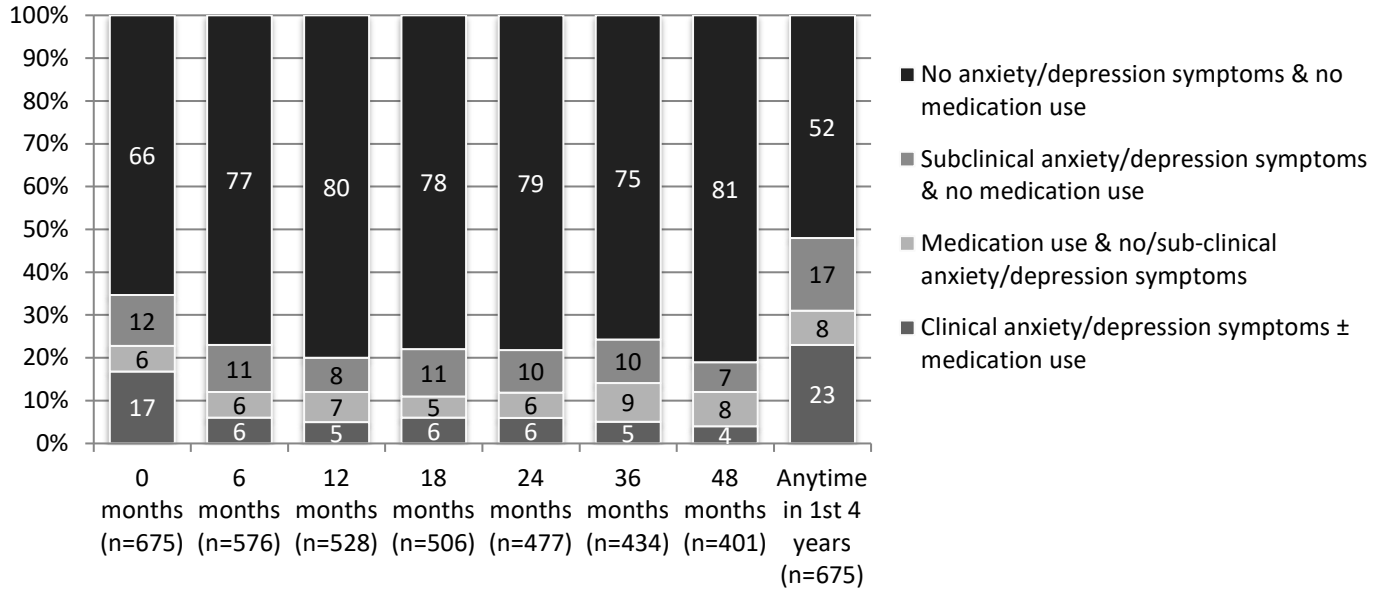


Figure 1a: Overall proportion of people with melanoma reporting anxiety or depression symptoms or use of anxiolytics or antidepressants after diagnosis, in the absence of recurrence

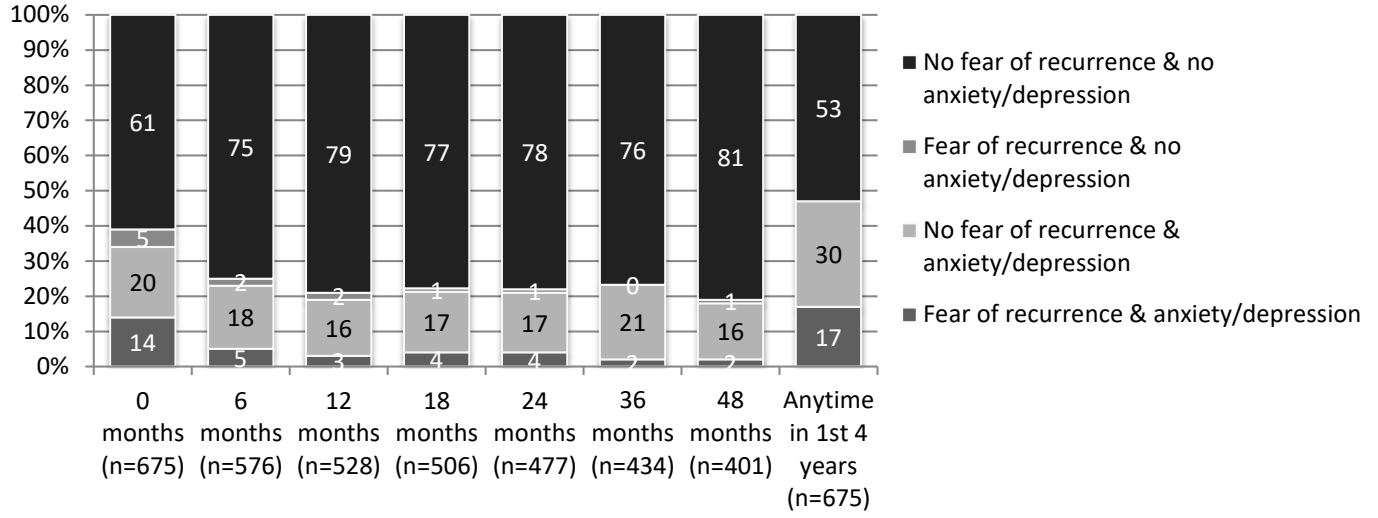


Figure 1b: Proportion of people with and without fear of melanoma recurrence among those with anxiety or depression (including those symptomatic of anxiety or depression or using anxiolytics or antidepressants)

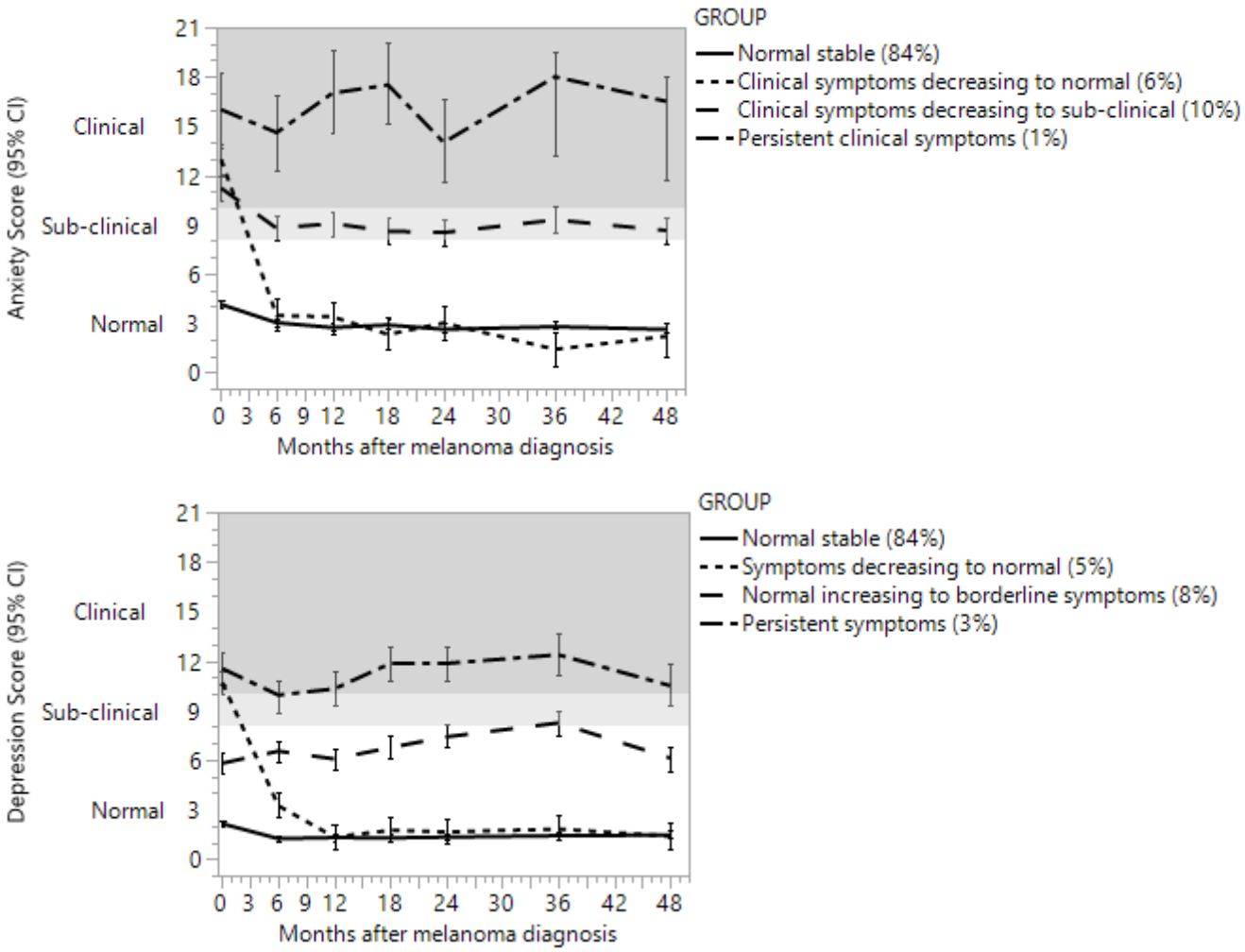
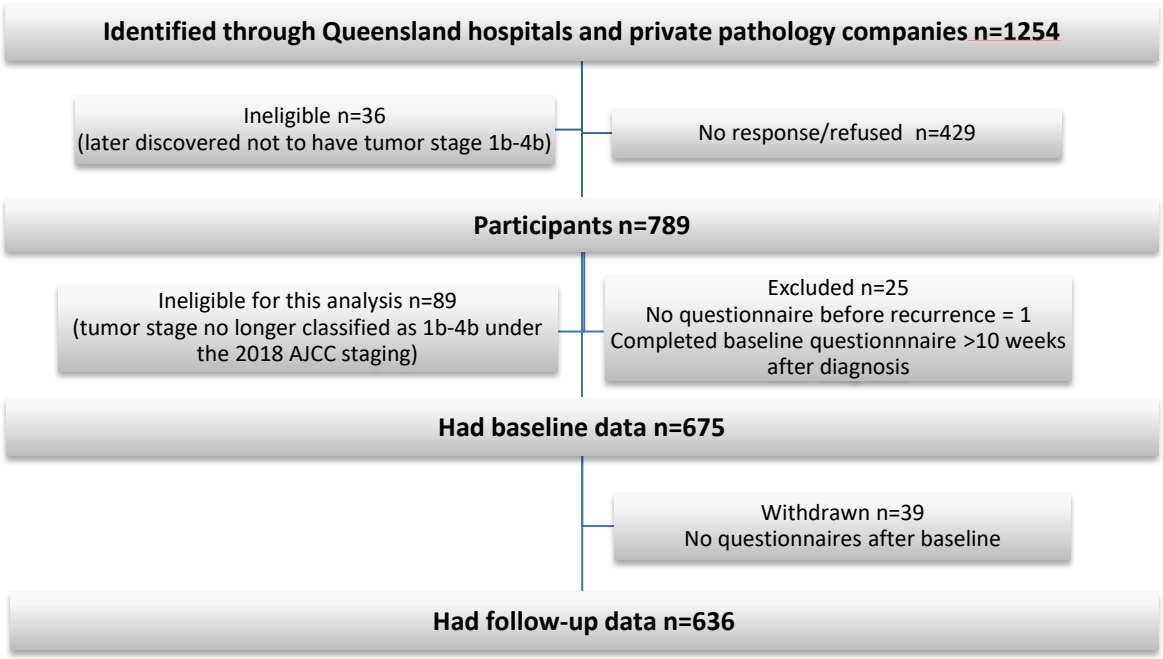


Figure 2. Group-based trajectory profiles for new-onset anxiety and depression over 48 months after melanoma diagnosis and up until 48 months or until recurrence (n=525; excludes participants who reported diagnosis of anxiety or depression within 5 years prior to index melanoma diagnosis n=95 and participants without at least one follow-up questionnaire before recurrence n=55).



Supplementary Figure. Flow of participants through the Primary Melanoma Project (PMP)