

Fear of new or recurrent melanoma after treatment for localised melanoma

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3 **FEAR OF NEW OR RECURRENT MELANOMA AFTER TREATMENT FOR**
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5 **LOCALISED MELANOMA**
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8 **Running Title: Fear of new or recurrent melanoma**
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ABSTRACT

Objective: To estimate the amount of fear of new or recurrent melanoma among people treated for localised melanoma in an Australian specialist centre.

Methods: We randomly selected 400 potential participants from all those treated for localised melanoma at the Melanoma Institute Australia during 2014 (n=902). They were asked to complete an adapted version of the Fear of Cancer Recurrence Inventory (FCRI). We calculated summary statistics for demographics, clinical variables and total FCRI and subscale scores.

Results: 215 people (54%) completed the FCRI questionnaire. The overall mean severity subscale score was 15.0 (95% CI 14.0-16.1). A high proportion of participants had scores above a proposed threshold to screen for clinical fear of cancer recurrence (77% and 63% of participants with and without new or recurrent melanoma had severity subscale scores ≥ 13). Most participants also had scores above a threshold found to have high specificity for clinical fear of cancer recurrence (65% and 48% of participants with and without new or recurrent melanoma had severity subscale scores ≥ 16). The severity subscale appeared to discriminate well between groups with differing levels of risk of new or recurrent melanoma.

Conclusions: There is a substantial amount of fear of new or recurrent melanoma among this population, despite most having a very good prognosis.

KEYWORDS

Fear, melanoma, recurrence, surveys and questionnaires, cancer, oncology

BACKGROUND

The incidence of melanoma has been increasing in at risk populations worldwide(1). In particular the incidence of localised disease (American Joint Cancer Committee [AJCC] Stages 0, I or II) has increased, largely driven by increased detection of in-situ melanomas and thin invasive melanomas (Breslow thickness < 1 mm)(1-3). People treated for localised melanoma are at risk of their melanoma recurring and have an elevated risk of both new primary melanomas (approximately 5-10 times higher risk relative to people without a melanoma history(4, 5)) and non-melanoma skin cancers (approximately 3-5 times higher risk(5)); because of this regular clinical review and lifelong surveillance are recommended (6, 7).

Notwithstanding the increased risks of developing new or recurrent melanoma and other skin cancers, this population generally have a very good prognosis. In fact, people treated for melanoma in situ have the same overall expected survival as the general population(8). Of those with localised invasive melanoma, the majority have thin melanomas (<1mm)(1), and also have a very favourable prognosis, with 20 year survival rates of 96%(9). The potential benefits of surveillance for new or recurrent melanoma in ensuring timely treatment need to be balanced against possible harms of frequent scheduled follow-up clinic visits. People who have been treated for melanoma identify the uncertainty and fear that the melanoma could return or progress as a source of anxiety and distress(10, 11), and some cite frequent clinical review as a contributor to this(12). Among people treated for cancer of a variety of different types, those attending regular scheduled follow-up had higher levels of fear than those not attending follow-up(13).

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3 Fear of cancer recurrence (FCR) has been defined as “Fear, worry, or concern relating to the
4 possibility that cancer will come back or progress”(14), and is one of the most commonly
5 reported problems by people treated for cancers of many different types, including melanoma
6 (13, 15). FCR is multidimensional in nature, comprising of cognitions, beliefs and emotions
7 which manifest along a continuum from normal reactions through to clinical manifestations
8 (16). A valid and reliable way to measure fear of cancer recurrence is using a questionnaire
9 called the Fear of Cancer Recurrence Inventory (FCRI)(16, 17). A related concept to FCR is
10 “Supportive care needs” – a person’s stated desire for some further action or resource which
11 is not currently part of their experience of support(18). People treated for localised melanoma
12 report moderate-to-high unmet needs with regards to melanoma specific information and
13 psychological concerns, with the most prevalent concern relating to FCR (10, 19).
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31 Clinical FCR is characterized by “frequent and chronic intrusive thoughts about a possible
32 recurrence, disproportionate fear in function to the actual risk of recurrence, excessive need
33 for reassurance, and functional impairment resulting from the fear”. Specifically, it may
34 include the following characteristics: “(1) high levels of preoccupation, worry, rumination, or
35 intrusive thoughts; (2) maladaptive coping; (3) functional impairments; (4) excessive distress;
36 and (5) difficulties making plans for the future”(14). A systematic review of psychological
37 responses and coping strategies found that approximately 30% of patients with melanoma
38 reported clinically relevant levels of psychological distress, with anxiety more prevalent than
39 depression, but that standard screening measures may have limited sensitivity and
40 specificity(20). The FCRI severity subscale, also known as the Fear of Cancer Recurrence
41 Inventory - Short Form (FCRI-SF), has been proposed as a screening tool for clinical levels
42 of fear of cancer recurrence which are associated with substantial psychiatric morbidity(21).
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The psychometric properties of an adapted version of the FCRI have been studied among

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3 people treated for melanoma who are at moderate and high risk of developing new primary
4 disease, and the factor structure was generally confirmed(22). There are no previous reports
5 on the total FCRI and subscale scores among people treated for localised melanoma.
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13 Our primary aim was to estimate the amount of fear of new or recurrent melanoma among
14 people recently diagnosed and treated for localised melanoma by administering the Fear of
15 Cancer Recurrence Inventory (FCRI). We used the FCRI-SF to estimate the proportion of
16 people who may have clinical FCR in this population. We also explored how well the
17 different sub-scales discriminated between people with and without new or recurrent
18 melanoma, and between people treated for stage 0, I and II melanoma.
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30 **METHODS**

31 Recruitment and participants

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34 We undertook a cross sectional study to measure fear of new or recurrent melanoma in
35 people treated for localised melanoma at the Melanoma Institute Australia (MIA) during the
36 2014 calendar year. The selection of potential participants is illustrated in Figure 1. Based on
37 MIA administrative data, there were 902 people in total who were diagnosed and treated for a
38 first primary melanoma that was stage 0, I or II (all sub-stages); 5 had died by the time of
39 data extraction leaving 897 people. Subsequent to their diagnosis, 19 people (2.1%) had been
40 diagnosed with a recurrence and 31 people (3.5%) with a new primary melanoma by the time
41 the questionnaire was administered. Of the 846 people not known to have new or recurrent
42 melanoma, 20.9% had had stage 0, 56.4% had had stage I and 22.6% had had stage II as their
43 index melanoma.
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6 We calculated that a sample size of 200 participants was required to obtain a 95% confidence
7 interval for the mean FCRI severity sub-scale score that was within 1.5 units of the true mean,
8 assuming that the score was normally distributed and that the sample mean and standard
9 deviation were 14.3 and 7.6 respectively (17). We estimated that 50% of individuals we
10 approached would agree to participate, and so approached 400 people.
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18 We planned a priori that we would report results for the group overall and separately for the
19 following subgroups: stage 0/I vs II and presence vs absence of new or recurrent melanoma.
20 We therefore used a stratified random sampling framework to ensure that there were
21 sufficient numbers of people who had had stage 0 to II melanoma and who had subsequently
22 developed new or recurrent melanoma. In order to achieve this, all patients who were known
23 to have a new or recurrent melanoma were included (n=50). We then randomly selected 177
24 patients with stage 0/I melanoma and 173 from stage II melanoma, giving a total of 400
25 potential participants.
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35 36 Procedure

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39 The 400 potential participants were sent study materials in the postal mail which included a
40 letter inviting them to participate, a patient information sheet and the paper based FCRI
41 questionnaire. The 400 people were asked to participate in both this study and a phone
42 interview study being run in parallel which asked about their experiences of follow-up. They
43 were asked to email a member of the study team if they would prefer to access the
44 questionnaire online. Potential participants who did not initially return a completed
45 questionnaire were emailed (up to three times) and sent further postal invitations (up to three
46 times). Those who participated in the phone interview being run in parallel to this study were
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3 also asked by the interviewer to complete the FCRI questionnaire. All non-participants were
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5 contacted a minimum of three times inviting them to participate.
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11 This selection process summarised in Figure 1 defined 3 sets of people, firstly all people
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13 treated for localised melanoma at MIA during 2014 (full population), secondly a set who
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15 were invited to participate (potential participants), and thirdly a set who actually participated
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17 (actual participants).
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27 Information on participant demographics and clinical characteristics of the index (first
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29 primary) melanoma were retrieved from the Melanoma Institute Australia database.
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35 We measured fear of new or recurrent melanoma using the Fear of Cancer Recurrence
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37 Inventory (FCRI), adapted for people with melanoma (17). The FCRI is a multi-dimensional
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39 validated questionnaire which measures the self-reported level of fear of cancer recurrence,
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41 along a continuum of severity. Permission was obtained to use the FCRI, and questions
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43 adapted so that 'recurrence' was defined as either a recurrence of the original melanoma or a
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45 new primary melanoma. The FCRI is comprised seven subscales, with higher scores
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47 indicative of greater fear of cancer recurrence (FCR, Item 13 - 'I believe that I am cured and
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49 the melanoma will not come back' – is the only item that must be reverse coded). The
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51 subscales are: Triggers (8 items), Severity (9 items), Psychological Distress (4 items),
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53 Functional Impairment (6 items), Insight (3 items), Reassurance (3 items) and Coping
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55 Strategies (9 items); each item is rated on a 5-point Likert scale. Previous research has
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3 demonstrated high internal consistency (α) and temporal stability (r) of the FCRI for both the
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5 original French version ($\alpha=0.95$ and $r=0.89$) (17) and more recent English version ($\alpha=0.96$
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7 and $r=0.88$)(23).
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11 Although we report results for total FCRI and the separate subscales, our primary outcome
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13 was the FCRI severity subscale score, which measures the intensity of the FCR and may most
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15 directly measure the level of fear (24). The FCRI-SF also has high internal consistency
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17 ($\alpha=0.89$ (17) / 0.88 (23)) and temporal stability ($r=0.80$ (17) / 0.87 (23)). A recent study of 60
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19 people with a history of cancer evaluated different thresholds of severity sub-scale scores
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21 against a reference standard of clinical fear of cancer recurrence (21). The authors applied the
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23 DSM-IV(25) definition of mental disorders when conducting semi-structured interviews with
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25 participants in order to determine whether or not clinical FCR was present. They found that a
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27 score of ≥ 13 has 88% sensitivity and 75% specificity, and proposed that this cut-off may be
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29 used to screen for clinical fear of cancer recurrence. The same study found that a severity
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31 subscale score of ≥ 16 has 67% sensitivity and 97% specificity for clinical fear of cancer
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33 recurrence.
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41 Analysis

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43 We first calculated summary statistics for demographic and clinical variables for: the full
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45 population (all people treated for localised melanoma at MIA during 2014), potential
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47 participants and actual participants. The following variables were examined: age at diagnosis,
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49 sex, anatomic site of primary lesion, AJCC stage at initial presentation, and diagnosis of
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51 recurrence or new primary melanoma. We reported mean and SD for age at diagnosis, and
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53 number and percentage for all other variables.
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3 We then calculated summary statistics and constructed distributional plots for the total FCRI
4 score and each of the subscales for: the total study population, stage sub-groups and people
5 who had been diagnosed with a recurrence or new primary. We reported medians and ranges
6 for total score and each subscale score and tested for statistical significance of any differences
7 using the Kruskal Wallis test. We calculated the percentage of people with scores on the
8 Severity subscale who were ≥ 13 (recommended for screening for clinical fear of cancer
9 recurrence) and ≥ 16 (high specificity for clinical fear of cancer recurrence). Finally we
10 compared the FCRI results for our study with those in published reports of FCRI among
11 people with other types of cancer. To enable this comparison we reported means and standard
12 deviations for each subscale score.
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26 All analyses were conducted in SAS 9.4. We used proc surveymeans to adjust our estimated
27 means and proportions for our sampling frame (re-weighting the estimates to account for
28 oversampling of participants with index melanoma that was stage II, and who had new or
29 recurrent melanoma).
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35 Ethics and Governance Approval

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38 The study was approved by the University of Sydney Human Research Ethics Committee
39 (Project No. 2015/226) and by the MIA Governance Committee (MIA 2015_147).
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45 **RESULTS**

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47 Of the 400 patients invited to participate in the study, 215 (54%) completed the FCRI
48 questionnaire (175 paper based and 40 online questionnaires returned). A comparison of
49 people in the full population, potential participants and actual participants is provided in
50 Table 1. Participants were similar on most characteristics to the potential participants. The
51 stratified random sampling ensured that there were more participants with stage II disease
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3 and new or recurrent melanoma compared to the full population. Participants were more
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5 likely to take part in the study if they had had a recurrence compared to a new primary
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7 melanoma.
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13 The overall mean severity subscale score, adjusted for our stratified sampling, was 15 (95%
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15 confidence interval = 14.0 - 16.1). A high proportion of participants had scores above the
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17 proposed cut-off for screening for clinical fear of cancer recurrence: 77% of participants with,
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19 and 63% without, a known new or recurrent melanoma had scores ≥ 13 (adjusted for
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21 stratified sampling). In addition, a large number of participants had scores above a threshold
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23 found to have high specificity for clinical fear of cancer recurrence: 65% of participants with,
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25 and 48% without, a known new or recurrent melanoma had scores ≥ 16 (adjusted for
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27 stratified sampling). (See Figure 2).
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35 For both people with and without known new or recurrent melanoma, the total FCRI score,
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37 and the subscale scores for Severity, Triggers and Coping Strategies were approximately
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39 normally distributed; all other subscale scores showed positive skew (tail on right side with
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41 higher scores longer than left side with lower scores). Table 2 presents the median and range
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43 for the total FCRI and subscales scores (means and standard deviations are presented in
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45 Appendix Table 1). The overall median score for total FCRI was 61 (range 0-133) and for the
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47 severity subscale was 17 (range 0-33).
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54 Scores for the total FCRI and for all the subscales were higher for participants with a new or
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56 recurrent melanoma than for those without, these reached statistical significance ($p < 0.05$) for
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3 the subscales Triggers, Insight, Reassurance and the Total score, and approached significance
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5 for severity subscale ($p=0.07$). Scores for participants with and without a new or recurrent
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7 melanoma were 72 vs 61 for total FCRI score and 19 vs 17 for severity subscale score.
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13 Among participants without known new or recurrent melanoma, there were stepwise
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15 increases in median scores for total FCRI and for severity and trigger subscales from Stage 0
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17 to Stage II. The median scores for coping strategies, psychological distress and functional
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19 impairment subscales were the same or increased from stage 0 to Stage II. The median scores
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21 for insight and reassurance subscales were the same or decreased from stage 0 to Stage II.
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23 Mean scores showed the same patterns across subscales. Differences were not statistically
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25 significant for any of the scores, but approached significance ($p<0.10$) for the subscales
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27 Severity, Psychological Distress, Reassurance and the Total score.
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35 **DISCUSSION**

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37 In this group of people who had been treated for localised melanoma, we found evidence of
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39 substantial levels of fear of new or recurrent melanoma. Nearly half of participants without,
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41 and nearly two thirds of participants with, new or recurrent melanoma had severity subscale
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43 scores ≥ 16 , which may indicate clinical levels of fear. Clinical FCR has similarities with
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45 psychological disorders (e.g., Anxiety Disorders), but appears to be a distinct entity related to
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47 cancer survivorship(26). Some level of anxiety is an expected response to the melanoma
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49 diagnosis and the fact that they are at increased risk of a new or recurrent melanoma. For
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51 some people this may helpfully motivate them to undertake regular surveillance. However the
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53 high levels of fear found in this study may have a substantial impact on quality of life.
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3 The FCRI subscale for severity appeared to have high discriminant validity than the other
4 subscales, with higher levels of fear (perceived risk) for groups with higher actual risk of new
5 or recurrent melanoma. Step-wise increases in median levels were seen for stage 0, stage I
6 and stage II, and the median levels for patients with known new or recurrent melanoma were
7 higher than for those without. The p values for differences between both types of subgroups
8 were <0.10. Further research is needed to determine if these quantitative differences between
9 sub-groups is proportionate to their higher risk of these events, or whether there are also
10 qualitatively differences.
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24 In Appendix Table 2 we compare the mean and standard deviation of scores for each of the
25 subscales in our study (limited to participants without known new or recurrent melanoma, all
26 of whom had their melanoma diagnosis less than 2 years ago and adjusted for our stratified
27 sampling) to those from other published reports in different cancer populations (a minority of
28 whom had known recurrence, and cancer diagnosis was within the last 10-13 years). Our
29 results indicate similar levels of fear of cancer recurrence for people treated for localised
30 melanoma as for people treated for breast cancer, lung cancer, colorectal cancer, and higher
31 levels of fear than for men treated for prostate cancer (17, 23).
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46 Strengths of our study include the epidemiological design for selecting potential participants
47 from all individuals undergoing treatment for localised melanoma at a large specialist centre
48 over a defined period of time (i.e. an inception cohort). This is one of the largest studies on
49 FCR among both recurrence-free melanoma survivors and those who have experienced a new
50 primary or recurrence. We adjusted estimated means and proportions for our stratified
51 random sampling frame (which meant we had a higher proportion of stage II participants and
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3 people with new or recurrent melanoma than the full inception cohort) so that our results
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5 would be representative of the full cohort. For the estimated medians reported within stage
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7 and recurrence subgroups, no adjustment was needed for these to be representative.
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13 Weaknesses include the proportion of non-respondents, which although comparative to other
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15 questionnaire studies, may mean our results are not representative of the full population
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17 treated for localised melanoma. The fact that non-participants did not differ to actual
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19 participants in terms of baseline characteristics (including stage) is reassuring. For the median
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21 scores for the group overall (i.e. not subgroups), we did not adjust estimates for sampling
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23 frame as methods are not as well established for this. The fact that the difference between the
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25 adjusted and unadjusted means on the subscales was small (ranged from +0.2 to -0.7)
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27 indicates that the unadjusted medians are unlikely to be substantial over-estimates.
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35 Caution should be exercised in interpreting the results of significance testing. Our study was
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37 not powered to detect differences between subgroups and so we may have found a false
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39 negative result when there truly was a difference. On the other hand, undertaking multiple
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41 tests increases the risk that we found a false positive result by chance. For this reason, we
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43 interpreted p values in the context of the descriptive results for each subscale. We found
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45 consistent patterns in both point estimates and p values for the severity subscale. Although
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47 we cannot not definitively rank the severity subscale as having highest validity, our findings
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49 are in keeping with the findings of others and add to the body of evidence on the usefulness
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51 of this instrument.
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3 A further limitation is that the FCRI may be less suited to people with a recent a cancer
4 diagnosis. The initial validation was performed in people diagnosed with cancer on average
5 3.8-4.9 years ago(17) and the more recent validation was done in people diagnosed on
6 average 5.9 to 6.6 years(23). Two of the possible responses for the severity subscale question
7 which asks how long the respondent has been thinking about the possibility of cancer
8 recurrence are 'a few years' and 'several years', but our participants had all been diagnosed
9 with their first melanoma under two years before the questionnaire was administered. This
10 may have resulted in under-estimation of the amount of fear of new or recurrent melanoma in
11 this population with a very recent cancer diagnosis (although we note that the answers for
12 some participants did in fact fall in both of these categories). On the other hand, our choice of
13 study population with such a recent melanoma diagnosis may mean our estimates of the
14 amount of fear of new or recurrent melanoma are higher than for people with a melanoma
15 diagnosis several years ago. However there is evidence that fear of developing a new
16 melanoma may endure for years after treatment (11, 12), which may reflect knowledge of
17 their lifelong elevated risk of a new melanoma(5-6). Moreover, the FCRI validation studies
18 (17, 23) and most other studies(16) found no relationship between FCR severity and time
19 since diagnosis.
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45 The transactional model of stress and coping has been proposed as a useful theoretical
46 framework for thinking about and exploring individual experiences of health threat, including
47 fear of new or recurrent melanoma(26). According to this model, key components of the
48 coping process include efforts to: regulate the stressor, perception of the stressor, or to use the
49 resources available. These efforts then result in increased emotional well-being and health-
50 oriented behaviours. In applying this theoretical model to our findings, we suggest some
51 important implications for clinical practice and policy. Although most people treated for
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3 localised melanoma have an excellent prognosis in terms of survival (actual stressor may not
4 be high), they have high levels of fear about the consequences should the melanoma recur or
5 a new melanoma develop (perception of stressor is high). There is evidence that frequent
6 scheduled follow-up visits may be a driver for this fear (12), and people treated for localised
7 melanoma who are not at very high risk of a recurrence or new primary may benefit from a
8 reduction in clinic visit frequency (perception of stressor may be increased by frequent
9 scheduled visits). The recent report from the MELFO trial supports this, with findings of less
10 cancer-related stress and a 45% reduction in costs at 1-year for the group randomised to
11 reduced follow-up(27).
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27 Increased education and support for people to do their own skin self-surveillance may be
28 another way of decreasing their fear of new or recurrent melanoma (using resources available
29 to decrease the threat). Only a small proportion of people treated for melanoma perform
30 regular total skin examination (a recent report estimated only 14%)(28), but doing so may
31 enable and empower individuals, with evidence that actively doing something to prevent
32 recurrence or new primary melanoma offsets some of the worry(29, 30). It is important that
33 the effects of interventions to increase self-examination on levels of melanoma associated
34 fear are tested however, as overly frequent self-examination may itself be associated with
35 higher levels of anxiety(31) (without RCT evidence it is difficult to know the direction of any
36 possible causal relationship). Increased psychological support for people diagnosed with
37 localised melanoma may be another way to decrease fear levels, as shown in a recent trial
38 among high risk patients(32).
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57 CONCLUSION

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3 In conclusion, we found evidence of substantial amounts of fear in a population of people
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5 treated for localised melanoma, most of who have a very good prognosis and are unlikely to
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7 die from the disease. Future research is needed on levels of fear among people with a less
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9 recent diagnosis of localised melanoma and the effects of decreasing scheduled visits,
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11 increasing support for self-surveillance and increasing psychological support, on levels of
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13 distress and wellbeing in this population.
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33 independent from NHMRC and the funder had no role in the study design; in the collection,
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35 analysis, and interpretation of data; in the writing of the report; and in the decision to submit
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37 the article for publication.
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For Peer Review

Table 1: Baseline characteristics of all people treated for localised melanoma at MIA in 2014, potential participants and actual participants

Characteristics	NO RECURRENCE OR NEW PRIMARY			RECURRENCE OR NEW PRIMARY	
	All people treated at MIA in 2014 (N=846)	Potential Participants (N=350)	Actual Participants (N=183)	All people treated at MIA in 2014 (N=50)	Actual Participants (N=32)
SEX N (%)					
Female	358 (42)	135 (39)	69 (38)	15 (30)	9 (28)
Male	488 (58)	215 (61)	114 (62)	35 (70)	23 (72)
AGE Mean (SD) [Range]					
At time of diagnosis	61 (16)	63 (16) [21-102]	63 (14) [27-98]	64 (16) [31-90]	64 (15) [31-88]
At time of study			65 (14) [29-100]		65 (15) [32-89]
YEARS SINCE DIAGNOSIS Mean (SD) [Range]		1.3 (0.2) [0.8-1.7]	1.3 (0.2) [0.8-1.7]	1.3 (0.2) [0.9-1.7]	1.4 (0.2) [1.0-1.7]
AJCC SUBSTAGE N (%)†					
Stage 0	177 (21)	52 (15)	27 (15)	8(16)	4(13)
Stage Ia	189 (22)	50 (14)	25 (14)	6(12)	4(13)
Stage Ib	288 (34)	75 (21)	45 (25)	11(22)	8(25)
Stage IIa	95 (11)	83 (24)	44 (24)	12(24)	8(25)
Stage IIb/ IIc	96 (11)	90 (26)	42 (23)	13(26)	8(25)
RECURRENCE/ NEW PRIMARY N (%)					
Recurrence	-	-	-	19 (38)	15 (47)
New Primary	-	-	-	31 (62)	17 (53)

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PRIMARY SITE N (%)					
Legs and arms	386 (46)	155 (44)	79 (43)	23 (46)	15 (47)
Trunk	283 (33)	115 (33)	66 (36)	17 (34)	8 (25)
Head and neck	177 (21)	80 (23)	38 (21)	10 (20)	9 (28)

* Number of participants known to have recurrence or new primary at time of data extraction. A further 7 participants had been diagnosed with recurrence or new primary by the time the questionnaire was administered (index melanoma was substage IA for 1, IB for 1, IIA for 1 and IIB for 3 and unknown for 1).

†AJCC= American Joint Committee on Cancer. Sub-stage was unknown for one person treated at MIA in 2014 but not included in the study

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Table 2: Median and range (in brackets) of adapted FCRI subscales scores for 183 participants without, and 32 participants with, new or recurrent melanoma*

FCRI Subscale			NO RECURRENCE OR NEW PRIMARY				RECURRENCE OR NEW PRIMARY	ALL	
Subscale	No. of items	Possible Range	Stage 0 (N=27)	Stage I (N=70)	Stage II (N=86)	P value [‡]	Total [†] (N=183)	Total (N=32)	P value [‡] (with vs without Recurrence or New Primary) (N=216)
Severity [‡]	9	0-36	13(3-25)	15(0-26)	18(0-33)	0.08	17(0-33)	19 (1-33)	0.07
Triggers	8	0-32	12.5(2-19)	13(0-29)	16(0-32)	0.16	14(0-32)	18 (0-31)	0.03
Psychological Distress	4	0-16	3 (0-8)	3 (0-15)	4(0-16)	0.05	3 (0-16)	5 (0-16)	0.12
Coping strategies	9	0-36	13(0-29)	15(0-28)	15 (0-34)	0.66	15(0-34)	16 (0-34)	0.14
Functioning impairments	6	0-24	0.5 (0-14)	2(0-15)	2(0-24)	0.19	2(0-24)	3.5 (0-24)	0.24
Insight	3	0-12	0(0-6)	0(0-9)	0(0-12)	0.52	0(0-12)	1 (0-12)	0.04
Reassurance	3	0-12	4.5(0-12)	4(0-12)	3(0-12)	0.07	3(0-12)	5.5 (0-12)	0.02
Total	42	0-168	46 (17-92)	60(0-122)	68(11-131)	0.08	59(0-131)	75 (16-133)	0.02

*Exact number of participants with data for each subscale and total score differs

† Not adjusted for stratified sampling from total inception cohort

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5 ‡ P Value for differences based on Kruskal Wallis test
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7 ¥ Severity subscale is also used as Fear of Cancer Recurrence Inventory-short form (FCRI-SF)(21)
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Appendix Table 1: Mean and SD (in brackets) of adapted FCRI subscales scores for 183 participants without, and 32 participants with, new or recurrent melanoma

FCRI Subscale			NO RECURRENCE OR NEW PRIMARY				RECURRENCE OR NEW PRIMARY
Subscale	No. of items	Possible Range	Stage 0 (N=27)	Stage I (N=70)	Stage II (N=86)	Total [†] (N=183)	Total (N=32)
Severity[‡]	9	0-36	13.4 (6.8)	15.0 (6.7)	16.7 (7.8)	15.0 (6.9)	19.0 (8.0)
Triggers	8	0-32	11.7 (4.4)	13.4 (6.5)	14.6 (8.1)	13.3 (6.3)	17.6 (6.7)
Psychological Distress	4	0-16	2.6 (2.2)	4.0 (3.8)	4.8 (4.0)	3.9 (3.6)	5.4 (3.9)
Coping strategies	9	0-36	12.8 (8.2)	13.3 (7.9)	14.1 (8.2)	13.3 (8.2)	16.9 (8.6)
Functioning impairments	6	0-24	2.6 (4.4)	3.4 (4.3)	4.3 (5.5)	3.4 (4.5)	5.9 (6.5)
Insight	3	0-12	0.9 (1.6)	1.3 (2.0)	1.5 (2.4)	1.3 (2.0)	2.5 (2.8)
Reassurance	3	0-12	5.2 (3.4)	4.0 (2.9)	3.6 (3.2)	4.2 (3.2)	5.7 (3.6)
Total	42	0-168	48.3 (22.7)	54.4 (27.6)	62.3 (29.9)	54.3 (26.9)	74.5 (29.4)

*Exact number of participants with data for each subscale and total score differs

[†] Adjusted for stratified sampling from total inception cohort

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5 ¥ Severity subscale is also used as Fear of Cancer Recurrence Inventory-short form (FCRI-SF)(21)
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Appendix Table 2: FCRI subscale scores for people with melanoma in the current study and for other types of cancer

	CURRENT STUDY 2016	SIMARD AND SAVARD 2009 (17)				LEBEL 2016(23)			
	Melanoma (N=183*)	Breast (N=227)	Prostate (N=246)	Colorectal (N=78)	Lung (N=49)	Breast (N=140)	Prostate (N=147)	Colorectal (N=42)	Lung (N=21)
Subscales	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Severity†	15.0 (6.9)	14.3 (7.6)	10.7 (7.3)	13.8 (8.4)	14.6 (7.7)	15.8 (8.4)	11.9 (6.8)	13.5 (7.7)	14.0 (9.3)
Trigger	13.3 (6.3)	13.6 (6.9)	9.4 (6.9)	12.7 (7.9)	12.5 (7.5)	14.2 (8.1)	9.5 (6.8)	10.9 (8.7)	10.6 (8.1)
Psychological	3.9 (3.6)	5.4 (3.8)	3.3 (3.5)	6 (4.8)	5.3 (4.2)	5.1 (4.3)	2.9 (2.9)	3.4 (3.4)	4.6 (5.1)
Coping	13.3 (8.2)	19.3 (7.5)	11.2 (8.5)	17.6 (8.7)	17.3 (8.9)	16.4 (9.5)	10.1 (8.8)	14.3 (10)	12.4 (10.7)
Function	3.4 (4.5)	3.1 (4.1)	2.7 (4.3)	4.5 (5.6)	5.1 (6.5)	3.6 (5.6)	2.5 (4.4)	2.0 (3.3)	4 (5.8)
Insight	1.3 (2.0)	1.7 (2.4)	1.5 (2.3)	2 (2.8)	2.1 (2.8)	1.1 (2.1)	0.5 (1.4)	0.8 (1.8)	1.4 (2.6)
Reassurance	4.2 (3.2)	3.2 (2.9)	1.0 (1.8)	2.3 (2.9)	2.0 (2.6)	2.5 (2.8)	0.8 (1.4)	1.3 (2.2)	0.8 (1.4)

*Study participants in current study without new or recurrent melanoma and adjusted for stratified sampling from total inception cohort

†Severity subscale is also used as Fear of Cancer Recurrence Inventory-short form (FCRI-SF)(21)

FIGURE LEGENDS

Figure 1: Selection of participants in study from 902 consecutive people treated for localized melanoma at Melanoma Institute Australia in 2014.

Figure 2: Distribution of scores on the severity subscale (Figure 2A – in people without new or recurrent melanoma; Figure 2B – in people with new or recurrent melanoma)

Caption: Yellow box: A threshold of ≥ 13 has 88% sensitivity and 75% specificity for clinically important fear of cancer recurrence; Green box: A threshold of ≥ 16 has 67% sensitivity and 97% specificity for clinically important fear of cancer recurrence (21).

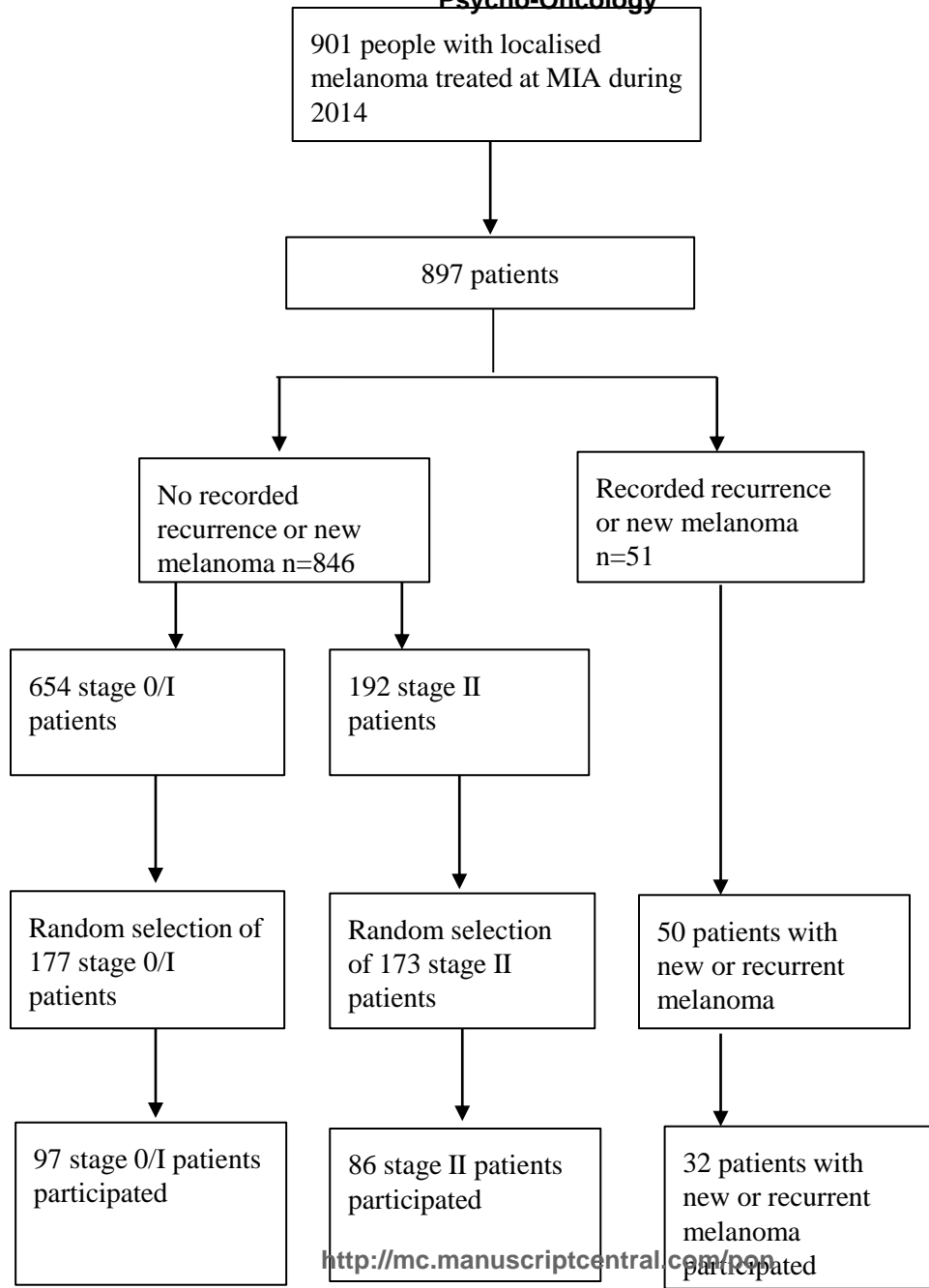
Psycho-Oncology

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All people treated at MIA in 2014 still alive n=897

Potential participants n=400

Actual participants n=215



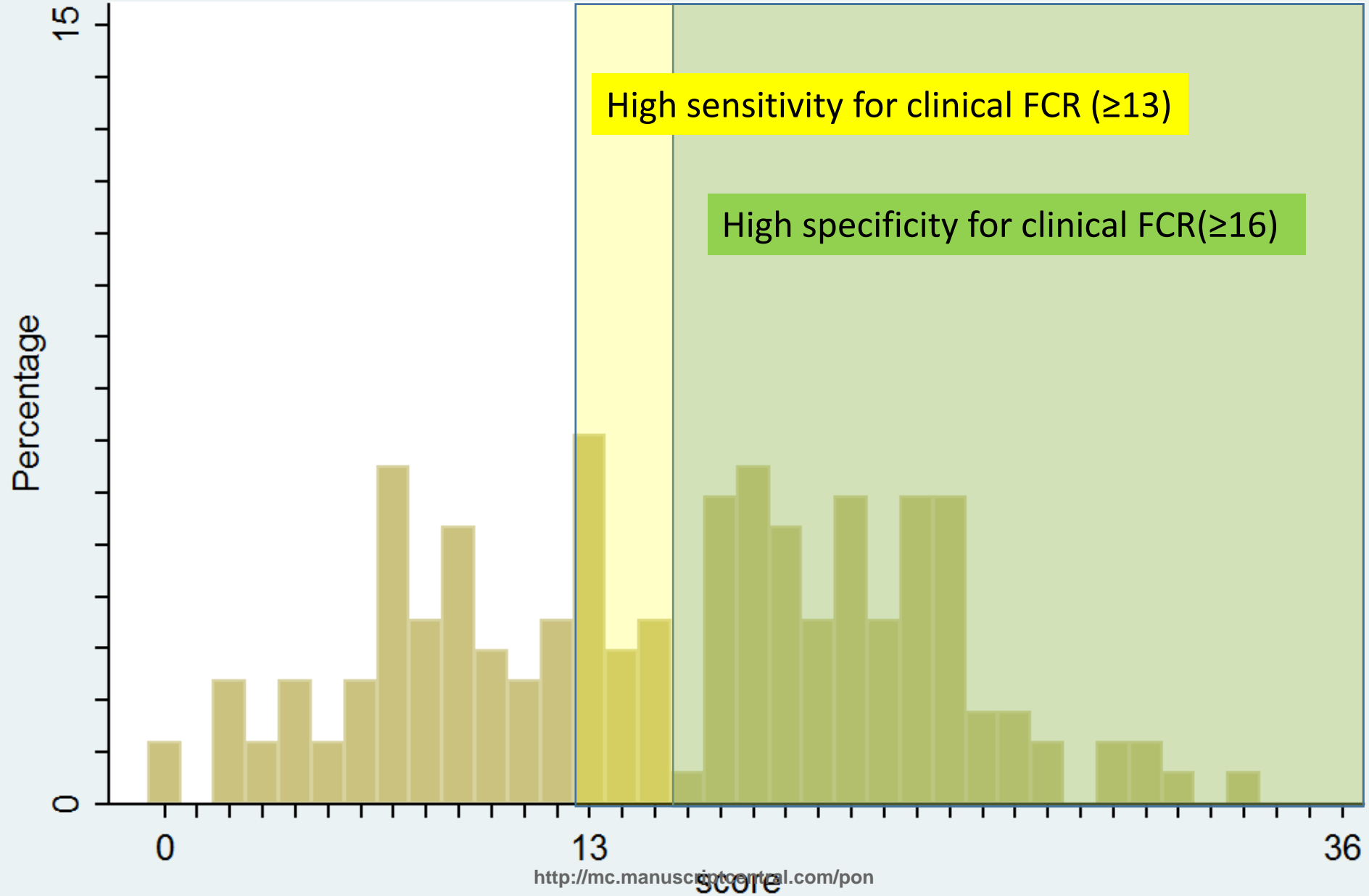
People not included at each step of selection process

5 people had died at time of data extraction not included in analysis

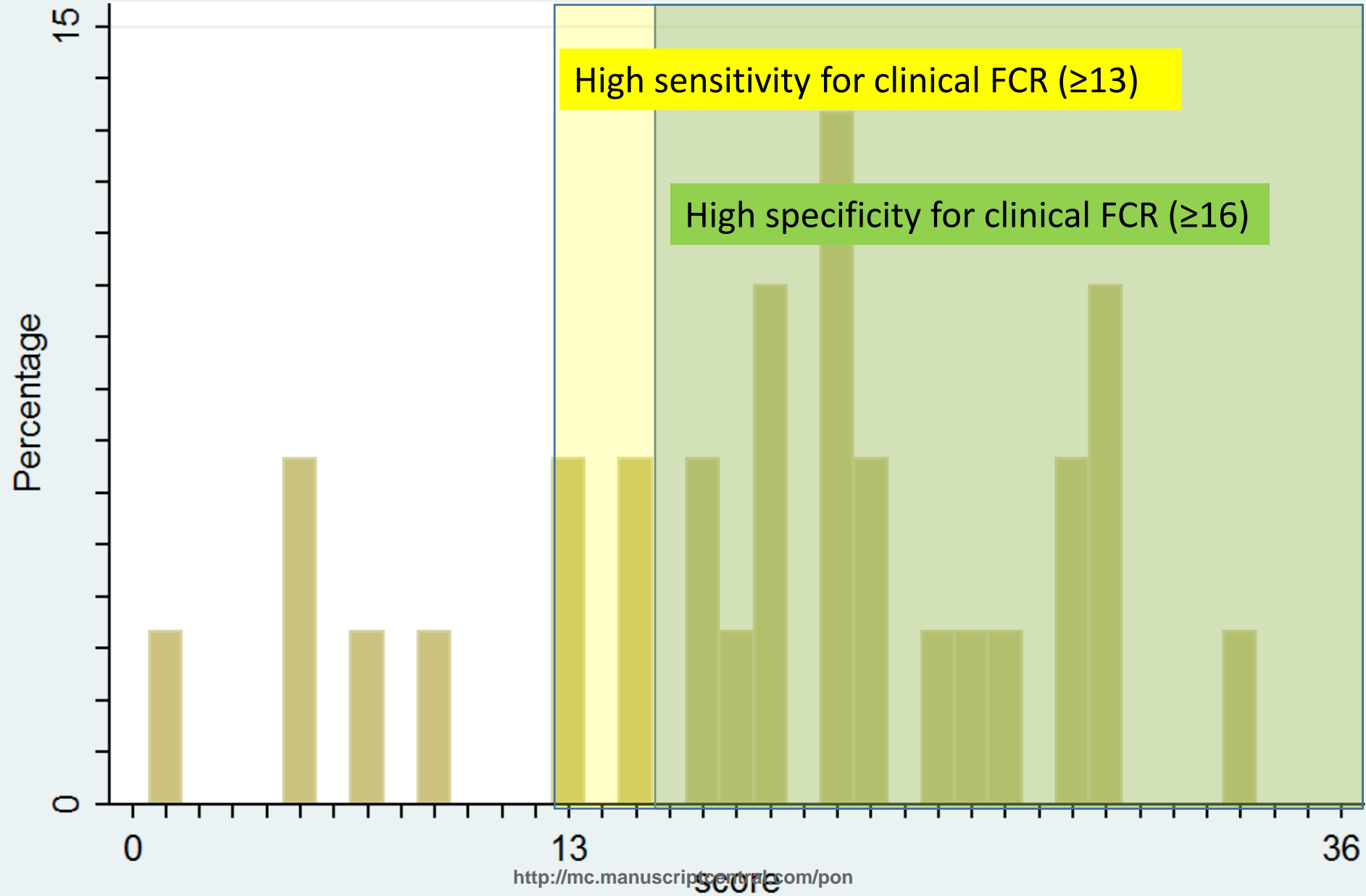
497 people not included in random sampling
496 people without new or recurrent melanoma
- 477 stage 0/I not included
- 19 stage II not included
1 person with a new primary not recorded in database at time of original data extraction and not included in potential participants

185 people didn't participate:
122 people without new or recurrent melanoma
- 80 stage 0/I didn't participate
- 86 stage II didn't participate
- 1 stage II excluded as index melanoma before 2014
18 people with new or recurrent melanoma didn't participate

No Recurrence or New Primary



Recurrence or New Primary



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**FEAR OF NEW OR RECURRENT MELANOMA AFTER TREATMENT FOR
LOCALISED MELANOMA**

Running Title: Fear of new or recurrent melanoma

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ABSTRACT

Objective: To estimate the amount of fear of new or recurrent melanoma among people treated for localised melanoma in an Australian specialist centre.

Methods: We randomly selected 400 potential participants from all those treated for localised melanoma at the Melanoma Institute Australia during 2014 (n=902). They were asked to complete a ~~modified~~ adapted version of the Fear of Cancer Recurrence Inventory (FCRI). We calculated summary statistics for demographics, clinical variables and total FCRI and subscale scores.

Results: 215 people (54%) completed the FCRI questionnaire. The overall mean severity subscale score was 15.0 (95% CI 14.0-16.1). A high proportion of participants had scores above a proposed threshold to screen for clinical fear of cancer recurrence (77% and 63% of participants with and without new or recurrent melanoma had severity subscale scores ≥ 13). Most participants also had scores above a threshold found to have high specificity for clinical fear of cancer recurrence (65% and 48% of participants with and without new or recurrent melanoma had severity subscale scores ≥ 16). The severity subscale appeared to discriminate well between groups with differing levels of risk of new or recurrent melanoma.

Conclusions: There is a substantial amount of fear of new or recurrent melanoma among this population, despite most having a very good prognosis.

KEYWORDS

Fear, melanoma, recurrence, surveys and questionnaires, cancer, oncology

BACKGROUND

The incidence of melanoma has been increasing in at risk populations worldwide(1). In particular the incidence of localised disease (American Joint Cancer Committee [AJCC] Stages 0, I or II) has increased, largely driven by increased detection of in-situ melanomas and thin invasive melanomas (Breslow thickness < 1 mm)(1-3). ~~This increased early detection may be a result of: increased melanoma awareness in the population leading to more people undergoing skin checks; increasing use of dermoscopy at skin checks, and increasing biopsy rates(4). People with localised melanoma are treated with wide local excision with or without sentinel lymph node biopsy to determine lymph node metastasis. Because they. People treated for localised melanoma~~ are at risk of their melanoma recurring and have an elevated risk of both new primary melanomas (approximately 5-10 times higher risk relative to people without a melanoma history(4, 5, 6)) and non-melanoma skin cancers (approximately 3-5 times higher risk(65)); ~~because of this~~ regular clinical review and lifelong surveillance are recommended (7, 8)(6, 7).

Notwithstanding the increased risks of developing new or recurrent melanoma and other skin cancers, this population generally have a very good prognosis. In fact, people treated for melanoma in situ have the same overall expected survival as the general population(9)(8). Of those with localised invasive melanoma, the majority have thin melanomas (<1mm)(1), and also have a very favourable prognosis, with 20 year survival rates of 96%(10). ~~Overall people treated for localised invasive melanoma have estimated 5 year survival rates of 97% for stage I and 72% for stage II disease. Once a person survives 5 years, their prognosis from that time forward is 98 and 86%, for stage I and stage II respectively (11)(9).~~ The potential benefits of surveillance for new or recurrent melanoma in ensuring timely treatment need to be balanced against possible harms of frequent scheduled follow-up clinic visits. People who have been

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7 treated for melanoma identify the uncertainty and fear that the melanoma could return or
8 progress as a source of anxiety and distress(~~12, 13~~10, 11), and some cite frequent clinical
9 review as a contributor to this(~~4~~12). Among people treated for cancer of a variety of
10 different types, those attending regular scheduled follow-up had higher levels of fear than
11 those not attending follow-up(~~15~~13).

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20 Fear of cancer recurrence (FCR) has been defined as “Fear, worry, or concern relating to the
21 possibility that cancer will come back or progress”(~~16~~(14)), and is one of the most commonly
22 reported problems by people treated for cancers of many different types, including melanoma
23 (13, 15, 17). FCR is multidimensional in nature, comprising of cognitions, beliefs and
24 emotions which manifest along a continuum from normal reactions through to clinical
25 manifestations (16). A valid and reliable way to measure fear of cancer recurrence is using a
26 questionnaire called the Fear of Cancer Recurrence Inventory (FCRI)(~~18, 19~~16, 17). A
27 related concept to FCR is “Supportive care needs” – a person’s stated desire for some further
28 action or resource which is not currently part of their experience of support(~~20~~(18)). People
29 treated for localised melanoma report moderate-to-high unmet needs with regards to
30 melanoma specific information and psychological concerns, with the most prevalent concern
31 relating to FCR (~~12, 21~~10, 19).

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46 Clinical FCR Clinical FCR is characterized by “frequent and chronic intrusive thoughts about
47 a possible recurrence, disproportionate fear in function to the actual risk of recurrence,
48 excessive need for reassurance, and functional impairment resulting from the fear”.
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50 Specifically, it may include the following characteristics: “(1) high levels of preoccupation,
51 worry, rumination, or intrusive thoughts; (2) maladaptive coping; (3) functional impairments;
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7 (4) excessive distress; and (5) difficulties making plans for the future”~~(16)-(14)~~. A systematic
8 review of psychological responses and coping strategies found that approximately 30% of
9 patients with melanoma reported clinically relevant levels of psychological distress, with
10 anxiety more prevalent than depression, but that standard screening measures may have
11 limited sensitivity and specificity~~(22)-(20)~~. The FCRI severity subscale, also known as the
12 Fear of Cancer Recurrence Inventory - Short Form (FCRI-SF), has been proposed as a
13 screening tool for clinical levels of fear of cancer recurrence which are associated with
14 substantial psychiatric morbidity~~(23)~~. ~~The psychometric properties of a modified(21)~~. ~~The~~
15 ~~psychometric properties of an adapted~~ version of the FCRI have been studied among people
16 treated for melanoma who are at moderate and high risk of developing new primary disease,
17 and the factor structure was generally confirmed~~(24)-(22)~~. There are no previous reports on
18 the total FCRI and subscale scores among people treated for localised melanoma.
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33 Our primary aim was to estimate the amount of fear of new or recurrent melanoma among
34 people recently diagnosed and treated for localised melanoma by administering the Fear of
35 Cancer Recurrence Inventory (FCRI). We used the FCRI-SF to estimate the proportion of
36 people who may have clinical FCR in this population. We also explored how well the
37 different sub-scales discriminated between people with and without new or recurrent
38 melanoma, and between people treated for stage 0, I and II melanoma.
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48 **METHODS**

49 Recruitment and participants

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7 We undertook a cross sectional study to measure fear of new or recurrent melanoma in
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9 people treated for localised melanoma at the Melanoma Institute Australia (MIA) during the
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11 2014 calendar year. The selection of potential participants is illustrated in Figure 1. Based on
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13 MIA administrative data, there were 902 people in total who were diagnosed and treated for a
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15 first primary melanoma that was stage 0, I or II (all sub-stages); 5 had died by the time of
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17 data extraction leaving 897 people. Subsequent to their diagnosis, 19 people (2.1%) had been
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19 diagnosed with a recurrence and ~~3231~~ people (3.65%) with a new primary melanoma by the
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21 time the questionnaire was administered. Of the 846 people not known to have new or
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23 recurrent melanoma, 20.69% had had stage 0, 56.24% had had stage I and ~~23.1~~22.6% had had
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25 stage II as their index melanoma.

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29 We calculated that a sample size of 200 participants was required to obtain a 95% confidence
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31 interval for the mean FCRI severity sub-scale score that was within 1.5 units of the true mean,
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33 assuming that the score was normally distributed and that the sample mean and standard
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35 deviation were 14.3 and 7.6 respectively (~~4917~~). We estimated that 50% of individuals we
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37 approached would agree to participate, and so approached 400 people.

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39 We planned a priori that we would report results for the group overall and separately for the
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41 following subgroups: stage 0/I vs II and presence vs absence of new or recurrent melanoma.

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43 We therefore used a stratified random sampling framework to ensure that there were
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45 sufficient numbers of people who had had stage 0 to II melanoma and who had subsequently
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47 developed new or recurrent melanoma. In order to achieve this, all patients who were known
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49 to have a new or recurrent melanoma were included (n=50). We then randomly selected 177
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51 patients with stage 0/I melanoma and 173 from stage II melanoma, giving a total of 400
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53 potential participants.

Procedure

The 400 potential participants were sent study materials in the postal mail which included a letter inviting them to participate, a patient information sheet and the paper based FCRI questionnaire. The 400 people were asked to participate in both this study and a phone interview study being run in parallel which asked about their experiences of follow-up. They were asked to email a member of the study team if they would prefer to access the questionnaire online. Potential participants who did not initially return a completed questionnaire were emailed (up to three times) and sent further postal invitations (up to three times). Those who participated in the phone interview being run in parallel to this study were also asked by the interviewer to complete the FCRI questionnaire. All non-participants were contacted a minimum of three times inviting them to participate.

This selection process summarised in Figure 1 defined 3 sets of people, firstly all people treated for localised melanoma at MIA during 2014 (full population), secondly a set who were invited to participate (potential participants), and thirdly a set who actually participated (actual participants).

Measures

Information on participant demographics and clinical characteristics of the index (first primary) melanoma were retrieved from the Melanoma Institute Australia database.

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7 We measured fear of new or recurrent melanoma using the Fear of Cancer Recurrence
8 Inventory (FCRI), ~~modified~~adapted for people with melanoma (~~1917~~). The FCRI is a multi-
9 dimensional validated questionnaire which measures the self-reported level of fear of cancer
10 recurrence, along a continuum of severity. Permission was obtained to use the FCRI, and
11 questions ~~modified~~adapted so that 'recurrence' was defined as either a recurrence of the
12 original melanoma or a new primary melanoma. The FCRI is comprised seven subscales,
13 with higher scores indicative of greater fear of cancer recurrence (FCR, Item 13 - 'I believe
14 that I am cured and the melanoma will not come back' – is the only item that must be reverse
15 coded). The subscales are: Triggers (8 items), Severity (9 items), Psychological Distress (4
16 items), Functional Impairment (6 items), Insight (3 items), Reassurance (3 items) and Coping
17 Strategies (9 items); each item is rated on a 5-point Likert scale. Previous research has
18 demonstrated high internal consistency (α) and temporal stability (r) of the FCRI for both the
19 original French version ($\alpha=0.95$ and $r=0.89$) (~~1917~~) and more recent English version ($\alpha=0.96$
20 and $r=0.88$) (~~2523~~).
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36 Although we report results for total FCRI and the separate subscales, our primary outcome
37 was the FCRI severity subscale score, which ~~is thought to most appropriately represent~~
38 ~~fear(26)-measures the intensity of the FCR and may most directly measure the level of fear~~
39 ~~(24)~~. The FCRI-SF also has high internal consistency ($\alpha=0.89$ (~~1917~~) / 0.88 (~~2523~~)) and
40 temporal stability ($r=0.80$ (~~1917~~) / 0.87 (~~2523~~)). A recent study of 60 people with a history of
41 cancer evaluated different thresholds of severity sub-scale scores against a reference standard
42 of clinical fear of cancer recurrence (~~23~~). ~~The authors~~ (~~21~~). ~~The authors applied the DSM-~~
43 ~~IV(25) definition of mental disorders when conducting semi-structured interviews with~~
44 ~~participants in order to determine whether or not clinical FCR was present. They~~ found that a
45 score of ≥ 13 has 88% sensitivity and 75% specificity, and proposed that this cut-off may be
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6 used to screen for clinical fear of cancer recurrence. The same study found that a severity
7 subscale score of ≥ 16 has 67% sensitivity and 97% specificity for clinical fear of cancer
8 recurrence.
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11 Analysis

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14 We first calculated summary statistics for demographic and clinical variables for: the full
15 population (all people treated for localised melanoma at MIA during 2014), potential
16 participants and actual participants. The following variables were examined: age at diagnosis,
17 sex, anatomic site of primary lesion, AJCC stage at initial presentation, and diagnosis of
18 recurrence or new primary melanoma. We reported mean and SD for age at diagnosis, and
19 number and percentage for all other variables.
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32 We then calculated summary statistics and constructed distributional plots for the total FCRI
33 score and each of the subscales for: the total study population, stage sub-groups and people
34 who had been diagnosed with a recurrence or new primary. We reported medians and ranges
35 for total score and each subscale score and tested for statistical significance of any differences
36 using the Kruskal Wallis test. We calculated the percentage of people with scores on the
37 Severity subscale who were ≥ 13 (recommended for screening for clinical fear of cancer
38 recurrence) and ≥ 16 (high specificity for clinical fear of cancer recurrence). Finally we
39 compared the FCRI results for our study with those in published reports of FCRI among
40 people with other types of cancer. To enable this comparison we reported means and standard
41 deviations for each subscale score.
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51 All analyses were conducted in SAS 9.4. We used proc surveymeans to adjust our estimated
52 means and proportions for our sampling frame (re-weighting the estimates to account for
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oversampling of participants with index melanoma that was stage II, and who had new or
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recurrent melanoma).

Ethics and Governance Approval

The study was approved by the University of Sydney Human Research Ethics Committee (Project No. 2015/226) and by the MIA Governance Committee (MIA 2015_147).

RESULTS

Of the 400 patients invited to participate in the study, 215 (54%) completed the FCRI questionnaire (~~176~~175 paper based and 40 online questionnaires returned). A comparison of people in the full population, potential participants and actual participants is provided in Table 1. Participants were similar on most characteristics to the potential participants. The stratified random sampling ensured that there were more participants with stage II disease and new or recurrent melanoma compared to the full population. Participants were more likely to take part in the study if they had had a recurrence compared to a new primary melanoma.

The overall mean severity subscale score, adjusted for our stratified sampling, was 15 (95% confidence interval = 14.0 - 16.1). A high proportion of participants had scores above the proposed cut-off for screening for clinical fear of cancer recurrence: 77% of participants with, and 63% without, a known new or recurrent melanoma had scores ≥ 13 (adjusted for stratified sampling). In addition, a large number of participants had scores above a threshold found to have high specificity for clinical fear of cancer recurrence: 65% of participants with, and 48% without, a known new or recurrent melanoma had scores ≥ 16 (adjusted for stratified sampling). (See Figure 2).

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9 For both people with and without known new or recurrent melanoma, the total FCRI score,
10 and the subscale scores for Severity, Triggers and Coping Strategies were approximately
11 normally distributed; all other subscale scores showed positive skew (tail on right side with
12 higher scores longer than left side with lower scores). Table 2 presents the median and range
13 for the total FCRI and subscales scores- (means and standard deviations are presented in
14 Appendix Table 1). The overall median score for total FCRI was 61 (range 0-133) and for the
15 severity subscale was 17 (range 0-33).
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26 Scores for the total FCRI and for all the subscales were higher for participants with a new or
27 recurrent melanoma than for those without, these reached statistical significance ($p < 0.05$) for
28 the subscales Triggers, Insight, Reassurance and the Total score, and approached significance
29 for severity subscale ($p = 0.07$). Scores for participants with and without a new or recurrent
30 melanoma were 72 vs 61 for total FCRI score and 19 vs 17 for severity subscale score.
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39 Among participants without known new or recurrent melanoma, there were stepwise
40 increases in median scores for total FCRI and for severity and trigger subscales from Stage 0
41 to Stage II. The median scores for coping strategies, psychological distress and functional
42 impairment subscales were the same or increased from stage 0 to Stage II. The median scores
43 for insight and reassurance subscales were the same or decreased from stage 0 to Stage II.
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48 Mean scores showed the same patterns across subscales. Differences were not statistically
49 significant for any of the scores, but approached significance ($p < 0.10$) for the subscales
50 Severity, Psychological Distress, Reassurance and the Total score.
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DISCUSSION

In this group of people who had been treated for localised melanoma, we found evidence of substantial levels of fear of new or recurrent melanoma. Nearly half of participants without, and nearly two thirds of participants with, new or recurrent melanoma had severity subscale scores ≥ 16 , which may indicate clinical levels of fear. ~~Clinical FCR is characterised by: “intrusive thoughts, distress and impact on functioning, death related thoughts, feeling alone, and belief that the cancer will return”.~~(27) ~~Despite similarities with psychological disorders (e.g., Anxiety Disorders) it appears to be a distinct entity related to cancer survivorship.~~ Clinical FCR has similarities with psychological disorders (e.g., Anxiety Disorders), but appears to be a distinct entity related to cancer survivorship(26). Some level of anxiety is an expected response to the melanoma diagnosis and the fact that they are at increased risk of a new or recurrent melanoma. For some people this may helpfully motivate them to undertake regular surveillance. However the high levels of fear found in this study may have a substantial impact on quality of life.

The FCRI subscale for severity appeared to have ~~higher~~high discriminant validity than the other subscales, with higher levels of fear (perceived risk) for groups with higher actual risk of new or recurrent melanoma. Step-wise increases in median levels were seen for stage 0, stage I and stage II, and the median levels for patients with known new or recurrent melanoma were higher than for those without. The p values for differences between both types of subgroups were <0.10 . ~~The other subscales also had higher median scores for patients with known new or recurrent melanoma, and most were also higher in people with stage II melanoma, but were less likely to show stepwise increases from stage 0 to stage I.~~

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7 Further research is needed to determine if these quantitative differences between sub-groups
8 is proportionate to their higher risk of these events, or whether there are also qualitatively
9 differences. ~~The finding that the Severity subscale may be most useful out of the subscales is~~
10 ~~consistent with the findings of another recent study in people treated for melanoma which~~
11 ~~used an item response theory approach to assess discrimination(24). A recent review of the~~
12 ~~FCRI scale lends further support, with the authors writing that the “severity sub-scale seems~~
13 ~~to most appropriately represent fear... The remaining sub-scales may more accurately~~
14 ~~represent antecedents (e.g. triggers), modifiers (e.g. coping strategies) or consequences (e.g.~~
15 ~~functioning impairments).”(26)~~
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27 In ~~the~~ Appendix Table 2 we compare the mean and standard deviation of scores for each of
28 the subscales in our study (limited to participants without known new or recurrent melanoma,
29 all of whom had their melanoma diagnosis less than 2 years ago and adjusted for our
30 stratified sampling) to those from other published reports in different cancer populations
31 (~~without~~ a minority of whom had known recurrence, and cancer diagnosis was within the last
32 10-13 years). Our results indicate similar levels of fear of cancer recurrence for people treated
33 for localised melanoma as for people treated for breast cancer, lung cancer, colorectal cancer,
34 and higher levels of fear than for men treated for prostate cancer (~~19, 25, 17, 23~~).
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46 Strengths of our study include the epidemiological design for selecting potential participants
47 from all individuals undergoing treatment for localised melanoma at a large specialist centre
48 over a defined period of time (i.e. an inception cohort). This is one of the largest studies on
49 FCR among both recurrence-free melanoma survivors and those who have experienced a new
50 primary or recurrence. We adjusted estimated means and proportions for our stratified
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7 random sampling frame (which meant we had a higher proportion of stage II participants and
8 people with new or recurrent melanoma than the full inception cohort) so that our results
9 would be representative of the full cohort. For the estimated medians reported within stage
10 and recurrence subgroups, no adjustment was needed for these to be representative.
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18 Weaknesses include the proportion of non-respondents, which although comparative to other
19 questionnaire studies, may mean our results are not representative of the full population
20 treated for localised melanoma. The fact that non-participants did not differ to actual
21 participants in terms of baseline characteristics (including stage) is reassuring. For the median
22 scores for the group overall (i.e. not subgroups), we did not adjust estimates for sampling
23 frame as methods are not as well established for this. The fact that the difference between the
24 adjusted and unadjusted means on the subscales was small (ranged from +0.2 to -0.7)
25 indicates that the unadjusted medians are unlikely to be substantial over-estimates.
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36 Caution should be exercised in interpreting the results of significance testing. Our study was
37 not powered to detect differences between subgroups and so we may have found a false
38 negative result when there truly was a difference. On the other hand, undertaking multiple
39 tests increases the risk that we found a false positive result by chance. For this reason, we
40 interpreted p values in the context of the descriptive results for each subscale. We found
41 consistent patterns in both point estimates and p values for the severity subscale. Although
42 we cannot not definitively rank the severity subscale as having highest validity, our findings
43 are in keeping with the findings of others and add to the body of evidence on the usefulness
44 of this instrument.
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9 A further limitation is that the FCRI may be less suited to people with a recent a cancer
10 diagnosis. The initial validation was performed in people diagnosed with cancer on average
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12 3.8-4.9 years ago([19](#)[17](#)) and the more recent validation was done in people diagnosed on
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14 average 5.9 to 6.6 years([25](#)[23](#)). Two of the possible responses for the severity subscale
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16 question which asks how long the respondent has been thinking about the possibility of
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18 cancer recurrence are 'a few years' and 'several years', but our participants had all been
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20 diagnosed with their first melanoma under two years before the questionnaire was
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22 administered. This may have resulted in under-estimation of the amount of fear of new or
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24 recurrent melanoma in this population with a very recent cancer diagnosis (although we note
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26 that the answers for some participants did in fact fall in both of these categories). On the other
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28 hand, our choice of study population with such a recent melanoma diagnosis may mean our
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30 estimates of the amount of fear of new or recurrent melanoma are higher than for people with
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32 a melanoma diagnosis several years ago. However there is evidence that fear of developing a
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34 new melanoma may endure for years after treatment ~~completion~~ ([13](#), [14](#)[11](#), [12](#)), which may
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36 reflect knowledge of their lifelong elevated risk of a new melanoma([5](#)-[6](#)). Moreover, the
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38 FCRI validation studies ([19](#), [25](#)[17](#), [23](#)) and most other studies([18](#))([16](#)) found no relationship
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40 between FCR severity and time since diagnosis.
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46 The transactional model of stress and coping has been proposed as a useful theoretical
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48 framework for thinking about and exploring individual experiences of health threat, including
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50 fear of new or recurrent melanoma([26](#)). According to this model, key components of the
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52 coping process include: efforts to regulate the stressor, perception of the stressor, or to use
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54 the resources available. These efforts then result in increased emotional well-being and
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7 health-oriented behaviours. In applying this theoretical model to our findings, we suggest
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9 some important implications for clinical practice and policy. Although most people treated
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11 for localised melanoma have an excellent prognosis in terms of survival (actual stressor may
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13 not be high), they have high levels of fear about the consequences should the melanoma recur
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15 or a new melanoma develop (perception of stressor is high). There is evidence that frequent
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17 scheduled follow-up visits may be a driver for this fear (~~44~~12), and people treated for
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19 localised melanoma who are not at very high risk of a recurrence or new primary may benefit
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21 from a reduction in clinic visit frequency (perception of stressor may be increased by frequent
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23 scheduled visits). The recent report from the MELFO trial supports this, with findings of less
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25 cancer-related stress and a 45% reduction in costs at 1-year for the group randomised to
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27 reduced follow-up(~~28~~27).

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31 Increased education and support for people to do their own skin self-surveillance may be
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33 another way of decreasing their fear of new or recurrent melanoma (using resources available
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35 to decrease the threat). Only a small proportion of people treated for melanoma perform
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37 regular total skin examination (a recent report estimated only 14%)(~~29~~(28), but doing so may
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39 enable and empower individuals, with evidence that actively doing something to prevent
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41 recurrence or new primary melanoma offsets some of the worry(~~29~~, 30, ~~34~~). It is important
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43 that the effects of interventions to increase self-examination on levels of melanoma
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45 associated fear are tested however, as overly frequent self-examination may itself be
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47 associated with higher levels of anxiety(~~32~~(31) (without RCT evidence it is difficult to know
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49 the direction of any possible causal relationship). Increased psychological support for people
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51 diagnosed with localised melanoma may be another way to decrease fear levels, as shown in
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53 a recent trial among high risk patients(~~33~~32).

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CONCLUSION

In conclusion, we found evidence of substantial amounts of fear in a population of people treated for localised melanoma, most of who have a very good prognosis and are unlikely to die from the disease. Future research is needed on levels of fear among people with a less recent diagnosis of localised melanoma and the effects of decreasing scheduled visits, increasing support for self-surveillance and increasing psychological support, on levels of distress and wellbeing in this population.

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Table 1: Baseline characteristics of all people treated for localised melanoma at MIA in 2014, potential participants and actual participants

Characteristics	NO RECURRENCE OR NEW PRIMARY			RECURRENCE OR NEW PRIMARY	
	All people treated at MIA in 2014 (N=846)	Potential Participants (N=350)	Actual Participants (N=183)	All people treated at MIA in 2014 (N= 51 50)	Actual Participants (N=32)
SEX N (%)					
Female	358 (42)	135 (39)	69 (38)	16 (31 15 (30))	9 (28)
Male	488 (58)	215 (61)	114 (62)	35 (69 70)	23 (72)
AGE Mean (SD) [Range]					
At time of diagnosis	61 (16)	63 (16) [<u>21-102</u>]	63 (14) [<u>27-98</u>]	65 64 (16) [<u>31-90</u>]	64 (15) [<u>31-88</u>]
At time of study			65 (14) [<u>29-100</u>]		65 (15) [<u>32-89</u>]
YEARS SINCE DIAGNOSIS Mean (SD) [Range]		1.3 (0.2) [<u>0.8-1.7</u>]	1.3 (0.2) [<u>0.8-1.7</u>]	1.3 (0.2) [<u>0.9-1.7</u>]	1.4 (0.2) [<u>1.0-1.7</u>]
AJCC SUBSTAGE N (%)†					
Stage 0	177 (21)	52 (15)	27 (15)	8(16)	4(13)
Stage Ia	189 (22)	50 (14)	25 (14)	6(12)	4(13)
Stage Ib	288 (34)	75 (21)	45 (25)	11(22)	8(25)
Stage IIa	95 (11)	83 (24)	44 (24)	12(24)	8(25)
Stage IIb/ IIc	96 (11)	90 (26)	42 (23)	14 (27 13(26))	8(25)
RECURRENCE/ NEW PRIMARY N (%)					
Recurrence	-	-	-	19 (37 38)	15 (47)
New Primary	-	-	-	32 (63 31 (62))	17 (53)

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PRIMARY SITE N (%)					
Legs and arms	386 (46)	155 (44)	79 (43)	23 (45 46)	15 (47)
Trunk	283 (33)	115 (33)	66 (36)	17 (33 34)	8 (25)
Head and neck	177 (21)	80 (23)	38 (21)	11 (22 10) (20)	9 (28)

* Number of participants known to have recurrence or new primary at time of data extraction. A further 7 participants had been diagnosed with recurrence or new primary by the time the questionnaire was administered (index melanoma was substage IA for 1, IB for 1, IIA for 1 and IIB for 3 and unknown for 1).

†AJCC= American Joint Committee on Cancer. Sub-stage was unknown for one person treated at MIA in 2014 but not included in the study

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Table 2: Median and range (in brackets) of ~~modified~~adapted FCRI subscales scores for 183 participants without, and 32 participants with, new or recurrent melanoma*

FCRI Subscale			NO RECURRENCE OR NEW PRIMARY					RECURRENCE OR NEW PRIMARY	ALL
Subscale	No. of items	Possible Range	Stage 0	Stage I	Stage II	P value [‡]	Total †	Total	P value [‡] (with vs without Recurrence or New Primary)
			(N=27)	(N=70)	(N=86)		(N=183)	(N=32)	(N=216)
Severity [‡]	9	0-36	13(3-25)	15(0-26)	18(0-33)	0.08	17(0-33)	19 (1-33)	0.07
Triggers	8	0-32	12.5(2-19)	13(0-29)	16(0-32)	0.16	14(0-32)	18 (0-31)	0.03
Psychological Distress	4	0-16	3 (0-8)	3 (0-15)	4(0-16)	0.05	3 (0-16)	5 (0-16)	0.12
Coping strategies	9	0-36	13(0-29)	15(0-28)	15 (0-34)	0.66	15(0-34)	16 (0-34)	0.14
Functioning impairments	6	0-24	0.5 (0-14)	2(0-15)	2(0-24)	0.19	2(0-24)	3.5 (0-24)	0.24
Insight	3	0-12	0(0-6)	0(0-9)	0(0-12)	0.52	0(0-12)	1 (0-12)	0.04
Reassurance	3	0-12	4.5(0-12)	4(0-12)	3(0-12)	0.07	3(0-12)	5.5 (0-12)	0.02
Total	42	0-168	46 (17-92)	60(0-122)	68(11-131)	0.08	59(0-131)	75 (16-133)	0.02

*Exact number of participants with data for each subscale and total score differs

† Not adjusted for stratified sampling from total inception cohort

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‡ P Value for differences based on Kruskal Wallis test

~~Severity subscale is also used as Fear of Cancer Recurrence Inventory short form (FCRI-SF)(23)~~

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Appendix Table 1 Severity subscale is also used as Fear of Cancer Recurrence Inventory-short form (FCRI-SF)(21)

For Peer Review

Appendix Table 1: Mean and SD (in brackets) of adapted FCRI subscales scores for 183 participants without, and 32 participants with, new or recurrent melanoma

FCRI Subscale			NO RECURRENCE OR NEW PRIMARY				RECURRENCE OR NEW PRIMARY
<u>Subscale</u>	<u>No. of items</u>	<u>Possible Range</u>	<u>Stage 0</u>	<u>Stage I</u>	<u>Stage II</u>	<u>Total[†]</u>	<u>Total</u>
			(N=27)	(N=70)	(N=86)	(N=183)	(N=32)
<u>Severity[‡]</u>	<u>9</u>	<u>0-36</u>	<u>13.4 (6.8)</u>	<u>15.0 (6.7)</u>	<u>16.7 (7.8)</u>	<u>15.0 (6.9)</u>	<u>19.0 (8.0)</u>
<u>Triggers</u>	<u>8</u>	<u>0-32</u>	<u>11.7 (4.4)</u>	<u>13.4 (6.5)</u>	<u>14.6 (8.1)</u>	<u>13.3 (6.3)</u>	<u>17.6 (6.7)</u>
<u>Psychological Distress</u>	<u>4</u>	<u>0-16</u>	<u>2.6 (2.2)</u>	<u>4.0 (3.8)</u>	<u>4.8 (4.0)</u>	<u>3.9 (3.6)</u>	<u>5.4 (3.9)</u>
<u>Coping strategies</u>	<u>9</u>	<u>0-36</u>	<u>12.8 (8.2)</u>	<u>13.3 (7.9)</u>	<u>14.1 (8.2)</u>	<u>13.3 (8.2)</u>	<u>16.9 (8.6)</u>
<u>Functioning impairments</u>	<u>6</u>	<u>0-24</u>	<u>2.6 (4.4)</u>	<u>3.4 (4.3)</u>	<u>4.3 (5.5)</u>	<u>3.4 (4.5)</u>	<u>5.9 (6.5)</u>
<u>Insight</u>	<u>3</u>	<u>0-12</u>	<u>0.9 (1.6)</u>	<u>1.3 (2.0)</u>	<u>1.5 (2.4)</u>	<u>1.3 (2.0)</u>	<u>2.5 (2.8)</u>
<u>Reassurance</u>	<u>3</u>	<u>0-12</u>	<u>5.2 (3.4)</u>	<u>4.0 (2.9)</u>	<u>3.6 (3.2)</u>	<u>4.2 (3.2)</u>	<u>5.7 (3.6)</u>
<u>Total</u>	<u>42</u>	<u>0-168</u>	<u>48.3 (22.7)</u>	<u>54.4 (27.6)</u>	<u>62.3 (29.9)</u>	<u>54.3 (26.9)</u>	<u>74.5 (29.4)</u>

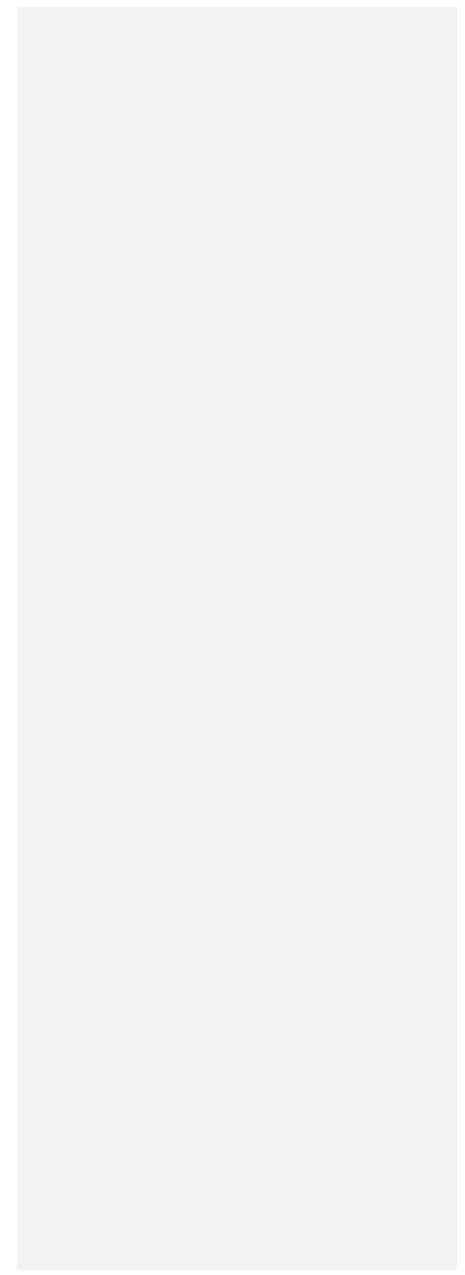
*Exact number of participants with data for each subscale and total score differs

† Adjusted for stratified sampling from total inception cohort

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¥ Severity subscale is also used as Fear of Cancer Recurrence Inventory-short form (FCRI-SF)(21)

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Appendix Table 2: FCRI subscale scores for people with melanoma in the current study and for other types of cancer

	CURRENT STUDY 2016	SIMARD AND SAVARD 2009 (1917)				LEBEL 2016(2523)			
	Melanoma (N=183*)	Breast (N=227)	Prostate (N=246)	Colorectal (N=78)	Lung (N=49)	Breast (N=140)	Prostate (N=147)	Colorectal (N=42)	Lung (N=21)
Subscales	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Severity†	15.0 (6.9)	14.3 (7.6)	10.7 (7.3)	13.8 (8.4)	14.6 (7.7)	15.8 (8.4)	11.9 (6.8)	13.5 (7.7)	14.0 (9.3)
Trigger	13.3 (6.3)	13.6 (6.9)	9.4 (6.9)	12.7 (7.9)	12.5 (7.5)	14.2 (8.1)	9.5 (6.8)	10.9 (8.7)	10.6 (8.1)
Psychological	3.9 (3.6)	5.4 (3.8)	3.3 (3.5)	6 (4.8)	5.3 (4.2)	5.1 (4.3)	2.9 (2.9)	3.4 (3.4)	4.6 (5.1)
Coping	13.3 (8.2)	19.3 (7.5)	11.2 (8.5)	17.6 (8.7)	17.3 (8.9)	16.4 (9.5)	10.1 (8.8)	14.3 (10)	12.4 (10.7)
Function	3.4 (4.5)	3.1 (4.1)	2.7 (4.3)	4.5 (5.6)	5.1 (6.5)	3.6 (5.6)	2.5 (4.4)	2.0 (3.3)	4 (5.8)
Insight	1.3 (2.0)	1.7 (2.4)	1.5 (2.3)	2 (2.8)	2.1 (2.8)	1.1 (2.1)	0.5 (1.4)	0.8 (1.8)	1.4 (2.6)
Reassurance	4.2 (3.2)	3.2 (2.9)	1.0 (1.8)	2.3 (2.9)	2.0 (2.6)	2.5 (2.8)	0.8 (1.4)	1.3 (2.2)	0.8 (1.4)

*Study participants in current study without new or recurrent melanoma and adjusted for stratified sampling from total inception cohort

†Severity subscale is also used as Fear of Cancer Recurrence Inventory-short form (FCRI-SF)(23)†Severity subscale is also used as Fear of Cancer Recurrence Inventory-short form (FCRI-SF)(21)

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FIGURE LEGENDS

Figure 1: Selection of participants in study from 902 consecutive people treated for localized melanoma at Melanoma Institute Australia in 2014.

Figure 2: Distribution of scores on the severity subscale (Figure 2A – in people without new or recurrent melanoma; Figure 2B – in people with new or recurrent melanoma)

Caption: Yellow box: A threshold of ≥ 13 has 88% sensitivity and 75% specificity for clinically important fear of cancer recurrence; Green box: A threshold of ≥ 16 has 67% sensitivity and 97% specificity for clinically important fear of cancer recurrence (~~2321~~).

Field Code Changed

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