Peer Review File

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Reviewer A

1. The Abstract includes conflicting statements and abbreviations that not spelled out when first used. As a result, it is really confusing, and the message of the paper is not clear at all.

Reply 1: We have revised the abstract to improve the message about what our study focused on as well as the implications of our findings. (see Page 1, lines 48-69).

2. Why did you only look at the features you did? i.e time in the sun and SES?

Reply 2: Our literature review of factors associated with melanoma of the skin and stage at diagnosis, delays in diagnosis, and etiological factors identified the following ones:

(a) Education level, SES, Employment, Age, Obesity, Family history, Smoking status, sunburn history, Marital status, Gender, Race, Urban vs. rural place of residence, Physical activity including occupational physical activity and time spent outdoors for recreational activities,

(b) Delay in seeking medical attention, Skin self-examination history, Specific lesion symptoms, Melanoma awareness, Tumor subtype and Anatomic location of lesion.

Based on this list, we then determined which factors were also measured using the Health and Lifestyle Questionnaire (HLQ) that had been completed by the cohort participants at enrollment. These were the factors in list (a), where SES was defined using family income, Race was defined using untanned skin color of inner upper arm skin color, and Obesity was defined using body mass index. In addition to the factors identified in our literature review, we also evaluated other lifestyle factors collected from these participants including health-related (e.g., self-rated health, family history of melanoma skin cancer and any cancer), psychosocial factors (e.g., stress, social support), and health practices (e.g., cancer screening, physical activity), dietary intake (from the Canadian Diet History Questionnaire I), and body measurements.

We have added sentences in the Methods section to more clearly explain our rationale and list all factors considered in the statistical analysis plan (see Page 5, lines 200-201, 212-215; supplementary materials).

3. Why was the incidence of melanoma so low; only 0.2% of your cohort in the period of study and follow -up. Should be much higher.

Reply 3: We are uncertain about the exact reasons but speculate that it is in part because of the relatively young age of this cohort. About half of the cases in our

study data set were < 60 years of age, so additional cases will be expected as the participants age. . For example, the average age at diagnosis is 66.9 years in 2018 according to Statistics Canada (https://www150.statcan.gc.ca/n1/daily-quotidien/210519/dq210519b-eng.htm).

We evaluated whether the percentage of melanoma cases out of all cancer cases could shed light on whether the incidence was exceptionally low. Based on the Canadian Cancer Statistics* estimated for 2023, melanoma accounts for 4.06% of all incident cancers (9700/239,100 x 100% = 4.06%). In our data set, there were 159 cases of skin melanoma (note that most lacked stage or HLQ information so were excluded in our study) out of 3359 cancer cases, which is about 4.74%. Thus, in the absence of additional information, the incidence of melanoma did not seem unusually low.

* 2023_cancer-specific-stats.pdf, obtained from: https://cancer.ca/en/research/cancer-statistics/canadian-cancer-statistics

4. You are comparing a huge group (32,000) to a small group (62) and subsets within that small group. The chance for type II error is astronomical, and explains some of your findings, such as risk of melanoma not correlating with skin type (Table 2).

Reply 4: We completely agree with this assessment about low statistical power resulting in high probability of Type II errors. We had noted the small sample size as a major limitation of the study on page 7, line 305. We have revised that sentence to point out this would limit statistical power to identify associations (page 7, line 305-306). We also corrected Table 2 to clarify that participants only had light or medium colored skin, so the lack of participants with dark skin, and only 12 with medium colored skin, might also explain that lack of an association. (page 7-8, lines 306 – 308).

However, we note this was a case-only study, not a nested case-control or case-cohort study. So, the only comparisons were within the cases by stage at diagnosis.

Reviewer B

This study analyzes melanoma stage versus lifestyle/socioeconomic factors in Canada. Though a small cohort, I applaud the authors for this detailed analysis and well-written paper.

Reply 0: We thank this reviewer for their positive assessment of our manuscript and for their thoughtful and constructive comments that improved its presentation.

My questions/suggestions are below.

Major:

1) Why grade melanoma based on TMN stage rather than breakdown by Breslow

depth, as is more common in the literature? (AJCC 7/8: T0, T1a/b, T2a/b).

Reply 1a: To ensure it was available for the entire cohort, which initiated in 2000, TNM was used. The Alberta Cancer Registry uses the Grade Manual (Schemas | SSDI Data | (naaccr.org)) for coding grade since 2018+. For AJCC systems (pre-2018) for which there is no recommended grading system (for Melanoma of the Skin), the generic cancer registry grade categories used historically will align and will be used for all four grade fields. Breslow Tumor Thickness was collected 2018+ but is inconsistent prior to this time.

In follow up - why was T0, or melanoma in situ not analyzed in depth? Or is this included in the author's stage 1 cohort and what are the MIS numbers?

Reply 1b: In situ melanoma was not included in the study as there is inconsistency in its reporting to cancer registries. In situ are frequently identified and removed in primary care with incomplete submission for pathology. Additionally, cancer registries only record the first registration for each body part (e.g. 1 on arm even if multiple identified). To avoid bias, in situ were excluded from the cohort.

Melanoma in situ incidence, especially on the head and neck, can be significantly impacted by sun exposure and lifestyle factors. The authors also combine stage 2-4 melanomas due to small numbers but note that stage 2 melanomas differ significantly from stage 3,4 melanomas as they often lack lymph node involvement. I would recommend the authors include a table breakdown of how many of their cohort had melanoma in situ versus invasive melanoma as well as details of their classification (such as ulceration/mitotic rate, if available) by **AJCC 8th edition staging** for better author understanding.

Reply 1c: All of the participants had invasive melanoma for the reasons detailed above. We have noted this in the Methods section (Page 3, Line 181). The TNM stages were based on AJCC 7 and no one had staging by AJCC 8. The ulcerative and mitotic information is only available for 2018 + and so is absent for these study participants. We have noted this as an additional limitation in the Discussion section (Page 6, Line 308-309).

2) In the methods section, the authors include a paragraph (lines 163-174) that explain their final model. Can the authors please better detail in this paragraph what factors were eliminated / included in the final analysis? Are these all the factors in Table 2?

Reply 2a: We have revised the Methods section paragraph to clarify what factors were considered based on our literature review as well as were available in the ATP dataset. We are also including our statistical analysis plan that lists the variables considered in the analyses and which ones were eliminated at the univariate stage or from the multivariable model. (Page 5, Lines 200-201, 212-215, supplementary materials)

Further, were there any differences in subcohort analysis of education/ethnicity, for

example, (Table 1) or were those factors excluded?

Reply 2b: All of the 62 participants diagnosed with melanoma in this study self-identified as Caucasian. As they were recruited from 2000-2008, the adult population in Alberta at that time was over 85% Caucasian, so this is not a surprising result. The cohort has grown to be more representative of the Alberta population since then but this is a limitation of our study.

We had assessed whether education level achieved was associated with stage of disease but it was not statistically significant. For those participants with ≤ high school education, 8/23 or 35% had higher stage disease compared to 31% (12/39) for those participants with some or completed post-secondary education. Reproduced from Table 2 are the following counts, percentages and p-value from Fisher's Exact test:

Factor	**Stage I (N=42)**	**Stage II+III+IV (N=20)**	**Total (N=62)**	***p*- value Stage I vs. Stages II+III+IV**
	N (percent)	**N (percent)**	**N (percent)**	
Education				0.784
≤ High school	15 (24.2)	8 (12.9)	23 (37.1)	
Some or completed post-secondary	27 (43.5)	12 (19.4)	39 (62.9)	

3) The authors describe that family history was low for melanoma (line 189), but higher for any other types of cancer. I note in Table 1, that breast cancer stage was analyzed. What other types of cancers were surveyed?

Reply 3: Breast cancer stage should have been denoted as melanoma cancer stage in Table 1. We have now corrected Table 1 by replacing the word 'breast' with 'melanoma skin.' In our logistic regression model analyses, we evaluated whether family history of melanoma and family (first degree relative) history of any cancer were associated with melanoma skin cancer stage at diagnoses. We could not evaluate other family histories of specific cancers, such as breast, prostate, lung, colorectal, etc., because the counts of a positive history were too low.

4) A person's occupation may provide insight into other socioeconomic variables and may be a surrogate marker for income, health literacy, etc, not only increased sun exposure. What occupations were included in this group? Can the authors provide a list of occupations surveyed which included higher MET-hours associated with later stage of diagnosis (line 222)?

Reply 4: We agree that having occupational histories could provide important insights about relevant exposures beyond sun exposures. Unfortunately, we do

not have this information as it was collected in a subsequent survey (Survey 2008) not the Health and Lifestyle Questionnaire (HLQ) used at baseline. The HLQ did have an open-ended question asking about the participant's current job title, but very few people provided this information.

5) In Table 2, I would encourage the authors to examine sun exposure in more detailed categories such as <1, 1-3, 3-5 hours, for example. As we know, melanoma types (such as nodular, superficial spreading, lentigo maligna and their associated genetic drivers and incidence) are significantly impacted short, repetitive exposure, versus prolonged sun exposure. Can the authors provide a more detailed analysis of this breakdown? This would provide better understanding of the true odds ratio between categories.

Reply 5: We had considered using more categories in evaluating this variable but chose the cutoff of <1 hour and ≥ 1 hour based on having sufficient counts in each subgroup. We have now revised our analyses using three categories of sun exposure during the summer months of < 1, ≥ 1 - 2 hours, and ≥ 2 hours. Our conclusions do not change with using three rather than two categories in our analyses but the consistency of the effect of more sun exposure than less than an hour per day is more apparent. Unfortunately, we cannot provide a more detailed analysis due to the limitations of the available data.

Minor:

1) Typo on line 239 - "ofinformation" .

Reply 1: Typo has been corrected (see Page 7, line 300).

2) Typo on line 240 "Lastly, The" .

Reply 2: Typo has been corrected (see Page 7, line 300-301).