Reviewer’s report

Title: Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis

Version: 0 Date: 26 Sep 2015

Reviewer: Stephen Schwarz

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Note: The references to page numbers below is based on the numbers at the bottom of the original manuscript.

Page 2, lines 22-24: The part of this sentence that refers to the "three published studies" should be deleted since it is already clear from the "Methods" section of the abstract that the meta-analysis is based on three studies.

Page 2, lines 27-31: This sentence has multiple problems. First, it is not clear what the authors mean by "focus on measurement of cannabis exposure." They should revise the sentence to be more precise. Second, the recommendation to investigate the "likely timing of meaningful cannabis exposure" is also vague, particularly given that the extant studies showed evidence that the increased risk was among current users. Finally, by referring to the possibility that important exposure might happen in the prenatal period or in early childhood implies that exposure is occurring secondarily through smoking/consumption by the mother or other adults in the household. This should be clarified in a revised sentence to help the reader.

Page 3, line 12: "prevalence rates" is an incorrect term because measures of prevalence and measures of rates are two different entities. What is described in this sentence appears to be proportions of the population that consume cannabis, so the proper term is most likely "prevalence."

Page 3, line 28: The wording of this sentence gives more weight to the results of these studies than is probably justified. Please revise to say "...at least three case-control studies reported associations between...

Page 3, line 31: The authors need to provide a citation for this "recent meta-analysis" somewhere in this sentence.

Page 7, line 34: It is not clear what the authors mean by "consistent." Does it just mean that all three studies used age matching, or that the age matching was done in the same way in all three studies? The latter seems unlikely, since the authors later say that one study used individual matching and the other two studies used frequency matching. The authors should avoid using general words and instead convey precise information.

Page 7, lines 45-47: It is not clear how the authors can first say that the participants in all three studies were 18-50 years of age, and then say one of the studies only included persons 18-35
years of age. It is also not correct that all three studies included 18-50 year olds, since one study (Daling et al.) restricted its study population to men diagnosed at ages 18-44 years of age. Note also that this statement contradicts what the authors have written on the subsequent page.

Page 8, lines 25-27: It is not clear how the authors arrived at this conclusion based on the information presented in the published papers. In Daling et al., for example, the Methods section does not mention anything about "independent validation." And in Lacson et al., it is not clear that there was any independent review was performed, just that histologic type was coded based on the original pathology reports (a step that is normally done by the cancer registry from which the cases were identified for the study).

Page 8, line 30: None of the studies involved a cohort. Please revise.

Page 9, lines 2-3: The authors are incorrect in asserting that these studies matched controls to cases on history of cryptorchidism. This would be almost impossible to do given how infrequent this characteristic is in the general population of men.

Page 9, line 8: The authors should refer to these as "response proportions" since they are not "rates" in the way that this term is normally interpreted in epidemiologic research.

Page 10, line 29: Sometimes the authors use the abbreviation "TC" and sometimes they use the abbreviation "TGCT". They should be consistent. Since virtually all TC are TGCT, and if in the three studies included in this meta-analysis the authors limited their case eligibility to TGCT, then that term should be used.

Page 11, lines 1-2: The authors should follow this sentence with a few well-considered remarks about the evidence that dysregulation of testicular function is relevant to TGCT etiology. Certainly the evidence that aberration in testosterone itself (specifically, low testosterone) is a risk factor is fairly weak. Further, the authors must also acknowledge what is known about the effects of THC (or other cannabinoids) and/or signaling through cannabinoid receptors on other types of cancer. For example, there is a strong series of studies showing anti-tumor effects in colon cancer models. Thus, overall, it is not at all clear that cannabis use should have net carcinogenic effects in any particular tissue.

Page 11, lines 15-16: I don't think that this argument makes sense, at least as articulated by the authors. If cannabis is as likely to cause seminomas and non-seminomas, there is no reason why the age at diagnosis per se should matter in a study (whether due to the indolence of one type or some other reason) in which the age distribution of the cases is wide enough to include the ages at which both diseases typically occur. A better explanation might be differences in statistical power to detect associations for each TGCT type. Specifically, if "current" (i.e., close to diagnosis) cannabis use is the important exposure, then a larger proportion of younger (more at risk for non-seminomas) as opposed to older men (more at risk for seminomas) will be exposed, which generally leads to more statistical power. Even so, because there is considerable overlap in the age distributions for non-seminoma and seminoma, even the "difference in statistical power" explanation seems unlikely to be the reason for the difference in the associations (if seminomas were truly caused by cannabis). Finally, if the authors truly wish to ruminate in this manuscript
on the possible reasons for an association with non-seminomas but not seminomas, then they probably should spend some time reviewing the literature that discusses the molecular and pathophysiologic bases for these two histologic types.

Page 11, line 59: The evidence that it is "hormonal development" that is disrupted in utero is extremely weak. The authors should be more careful in their assessment of the research in this area.

Page 12, line 26: The report by Trabert et al. was a hospital-based, not population-based study.

Page 12, line 29: As noted earlier, not all of the studies used this process.

Page 11, line 51: Please change "outcome" to "case or control". Also, the authors should amend this section to note that there is a major argument against this source of bias (as well as recall bias), and that is the fact that the association appears to be limited to a certain set of histologic types. It is unlikely that in these three studies that the interviewers would have known the histology of the cases they were interviewing, and even if they did, it is difficult to fathom why interviewers would preferentially encourage certain answers for non-seminoma cases as opposed seminoma cases.

Page 12, line 53: Recall bias is not something that arises from lack of blinding of the interviewers to the case/control status of the subjects. It arises from the fact that the subjects themselves are not blinded to their own status. Please revise this paragraph accordingly.

Page 13, line 17: The authors do not provide a justification for this assertion. Possibly they believe that because cannabis use was illegal in the regions in which the three studies were conducted, young men would tend to deny its use even if that were truly users. But some have argued that young men tend to be boastful about their activities, and might well overestimate their use of drugs (as well as other supposedly socially undesirable activities, such as sexual activity). I think the authors should consider what is really known about reporting of cannabis use and cite appropriate references. Even so, the issue at hand is the extent of misclassification of exposure due to self-report, and whether or not the misclassification is differential between cases and controls. If there is underreporting of exposure relative to the truth, and the underreporting is the same in cases and controls, then the ORs will be attenuated compared to the true association. Similar effects on the OR would happen if the cases and controls are equally over-reporting cannabis use. But if the misclassification is differential, then the ORs would not necessarily be attenuated. Importantly, the associations observed in the three studies could have occurred if the cases reported their cannabis use accurately but controls under-reported their cannabis use. Of course, as with the issue of differential response proportions (see below), for the results of these studies to have occurred, it would also have to be true that seminoma cases under-report cannabis use while non-seminoma cases accurately report such use. What reasoning could explain why patients with TGCT would differentially report cannabis use depending on their histology?

All of the aforementioned issues need to be considered by the authors in order to improve their assessment of the validity of the extant studies.
Page 13, line 28: This sentence is only partially correct. To be correct, the authors need to add the following after "who did not": "...and if the same differential is not present for the cases who responded and cases who did not respond,..."

Page 13, line 28: The cannabis use data in these studies are not "rates" but rather, proportions or percentages.

Page 13, line 47: I recommend that the authors revise this sentence to say "...the different potential sources of selection bias."

Page 14, line 1: Each of the three studies provided data presented on quantity of cannabis use, and at least one of the studies showed that more frequent use (among current users) was more strongly related to risk than less frequent use. At the same time, the studies also show that high frequency users are not common in the population. Thus, there is already information in the published studies that addresses the concerns expressed by the authors in this sentence. For this reason, the authors need to revise this sentence.

Page 14, lines 29-33: Most of the issues raised in this sentence have already been addressed to some extent by the published studies. For example, each study adjusted for potential confounders. In this respect, the authors have not made any cogent arguments that suggest that adjustment for confounding was a problem in the studies. This is also the first time in the manuscript that the authors use the term "mediators" and I recommend that they clarify what they mean (i.e., specific factors that they think are mediators, and/or why this is important to do). Also in this sentence, the mention of "use an evidence-based conceptualization" does not connect at all with anything else in the manuscript, and so it is unclear what the authors mean by it. In short, this sentence needs to be heavily revised.

Table 2: The title of this table is lacking in important detail, such as what this particular meta-analysis is all about!

Table 2: The meaning of the abbreviation in the "study design" column needs to be described in a footnote.

Table 3: See comment regarding Table 2, as it also applies to this table.

Additional file 1: The title of this table has the same problem as the titles of tables 2 and 3.

Additional File 1: The authors must show the full citation for each paper so that a reader can access them if he or she wishes. This could be done by including a reference list specific to this table.

Additional file 2: The title of this "file" has the same problems as the titles of Tables 2 and 3 and additional file 1.

Figure 1: It is unclear from this figure how the number of papers decreased from 16 to 3. The figure needs to be revised accordingly.
Figure 2a as well as other figures: Please spell out "Seminoma" and "Non-seminoma"

Figure 2a: Please replace "Total" with "All histologic types."

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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