

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	MORTALITY (1950-1999) AND CANCER INCIDENCE (1969-1999) OF WORKERS IN THE PORT HOPE COHORT STUDY EXPOSED TO A UNIQUE COMBINATION OF RADIUM, URANIUM AND GAMMA-RAY DOSES
AUTHORS	Zablotska, Lydia; Lane, Rachel; Frost, Stanley

VERSION 1 - REVIEW

REVIEWER	Linda Walsh PhD Scientist, Federal office for Radiation Protection (BfS), Germany.
REVIEW RETURNED	23-Oct-2012

REPORTING & ETHICS	please give more details in the revision connected with Strobe item 12 c) & d)
GENERAL COMMENTS	<p>General comments.</p> <p>This paper describes a cohort of uranium refinery and processing workers and reports on the cancer risks related to exposures from uranium and radium compounds from the ore dust and to gamma (γ)-ray and radon decay products. Although the results are interesting, only a few category specific strong associations were reported (i.e., the standardised mortality ratio for hypertensive diseases and the relative risk for lung cancer incidence in the 3.5-15 & 15-50 WLM RDP exposure categories).</p> <p>The paper is well and clearly written and the dedication to the memory of their former colleague Prof. Howe is a fine tribute to him – given the care and general high quality associated with the authors work. I would like to recommend the paper for publication in BMJ open after the authors have considered a few, hopefully constructive, comments and suggestions that I hope will lead to some further improvement in the quality of the already good paper.</p> <p>I would like to see the small confusions concerning gender specific methods and results cleared up (see below) and more quantitative information concerning % loss-to-follow up and % of missing causes of death in the cohort. The cohort was probably exposed to relatively high levels of other types of dust exposure – can the authors say something about quartz or fine dust exposures in this cohort? I look forward to reading the revised version and seeing the paper online very soon.</p> <p>Specific comments and remarks.</p> <p>1. Title: The word “substantial” is subjective. I asked several of my colleagues what they thought were substantial gamma-ray doses and they all came up with different ranges! Maybe the authors should consider if they really want to keep this word in the title.</p>

	<p>2. Abstract (page 2), Design: The number of male and female cohort members totals 3,000 – but all the results given in the paper pertain to the 2,645 men. I think it would be better to make this clear in the abstract.</p> <p>3. Abstract (page 2), Outcome measures: In the second sentence I think you could delete the word “model”.</p> <p>4. Abstract (page 2), Conclusions: Please reconsider the “substantial” gamma-ray doses. I suggest deleting “substantial” and giving the mean gamma-ray dose in brackets. You also need to inform the reader about the type of gamma-dose (i.e., is it measured/estimated effective dose? the dose from film badges? (skin dose), colon dose?).</p> <p>5. Introduction (page 6): It would be interesting for a reader to be given some information on the degree of overlap between this paper under review and the earlier paper by this group (reference no. 12) – How many cases are included in both publications? Why exactly were “different analytical methods” used?</p> <p>6. Methods (page 7, line 27): Can you justify selecting sites with 5 or more deaths or cases? – Why 5? (page 7, line 37): Were there any cases of aplastic anaemia?</p> <p>7. Methods (page 8, line 39– You also need to inform the reader about the type of gamma-dose.</p> <p>8. Statistical analyses(page 9, line 48): Were adjustments really made for sex? All the values in tables 2 and 3 are male specific. Did you correct the SMRs for “missing causes of death”?</p> <p>9. Statistical analyses(page 10, line 13): What type of gamma-dose? and why did you choose age at first exposure rather than age at last exposure or age at median exposure? Also potential modification by gender should be either explained here or the reasons for not considering gender modification should be explained here.</p> <p>10. Results (page 11, line 23): Second sentence. You could make it clear that the mean values of RDP exposures are gender specific in this sentence. Line 45 – at last it is made clear to the reader that all analyses are restricted to males (please make this clear throughout the paper in a consistent way so that the reader is not as confused as I was).</p> <p>11. Table 1 - 5. Please give the ICD codes – otherwise it is unclear, for example, exactly what “stroke” is. The sub-grouping in terms of cerebrovascular diseases may be better than just “stroke” – otherwise it will be difficult to include the results in future Meta-analyses. Also given the results from a recent BMJ-open paper “A Prospective Follow-up Study of the Association of Radiation Exposure with Fatal and Non-Fatal Stroke among Atomic Bomb Survivors in Hiroshima and Nagasaki (1980-2003)” by Takahashi et al, would it be interesting to compute the SMR for stroke sub-types (ischaemic and haemorrhagic events)?</p> <p>12. Results (page 12, line 41): change “estimated SMRs included</p>
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	<p>unity” to “estimated SMR CIs included unity”</p> <p>13. Table 4: Half-way down the table in the text “RRa” – the “a” needs superscripting. The reference group only has extremely small WLMs – how do the RRs change if the reference category is changed to 0-1 WLM? The RR for lung cancer incidence is high in the 3.5-15 & 15-50 WLM categories – could this be due to confounding with quartz dust?</p> <p>14. Results (page 15, lines 4-13): It would interest me, and the readership in general, to know exactly how the non-cancer disease registry in Canada works and how complete the ascertainment is. Do you really have good ascertainment of non-cancer diseases such as nephritis, COPD and asthma ? In Germany we do not have such statistics. How strongly can you back up the statements on non-cancer diseases that you made here?</p> <p>15. Results (page 15, lines 48-53): The comparison of non-nested models should be done in terms of changes in AIC or BIC here and not just qualitatively by mentioning the “smaller deviances”. Please make this statement more quantitative by giving the differences in AIC or BIC.</p> <p>16. Discussion (page 19, line 22): Please quantify the level of ascertainment. Also please give explicitly and quantitatively the % loss-to-follow up and % of missing causes of death in the cohort.</p> <p>17. Discussion (page 20, line 25 – 29): Could the authors be more quantitative about the time periods during which exposures were either estimated or measured?</p>
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REVIEWER	<p>Dominique LAURIER Head of the Laboratory of Epidemiology Institute for Radiological Protection and Nuclear Safety France</p> <p>I certify I present no conflict of interest with the peer-review of this manuscript.</p>
REVIEW RETURNED	02-Nov-2012

THE STUDY	<p>- definition and description of the study population could be improved</p> <p>- additional recent references could be cited</p>
RESULTS & CONCLUSIONS	The present analysis do not allow evaluating the risk associated to uranium or radium exposure. Several changes could help avoiding any misinterpretation and improving the discussion regarding that point
GENERAL COMMENTS	This article presents an analysis of the mortality and cancer incidence among Port Hope workers in Canada. This is a more in-depth analysis of a subset of the Eldorado study published by Lane et al. in 2010. It is a good idea to propose a specific analysis of the population of Port Hope, as occupational exposures of these workers were different from that of the Beaverlodge and Port Radium miners. But, the present paper did not succeed in considering the specific exposures of these workers (internal

contamination by uranium and radium compounds), and only RDP and gamma exposures are considered. I think this article presents anyway a real interest in the understanding of radiation induced risks at low doses. Methods and results are well presented, but several improvements should be made to clarify the article before publication.

General comments

Even if a few modifications exist compared to the data included in the Eldorado study published by Lane et al. in 2010, the data are globally the same. It would have been interesting to provide results based on an extended follow-up. Also, the available exposure indicators are the same as those considered previously. As stated by the authors, conversely to the situation for miners, RDP exposure is not the main important one for Port Hope workers. It would have been interesting to try to consider exposures due to the handling of uranium and radium chemical compounds. I understand that the retrospective reconstruction of doses due to incorporation is out of the scope of the present paper, but other (simpler) approaches could have been considered, such as the use of a Job Exposure Matrix or at least the duration of exposure as a time dependant variable. This constitutes a major limitation of the present analysis. The possibility of additional analyses should be investigated, or at least this point should be better discussed as a limitation of the study.

The presentation of the cohort includes both men and women, whereas risk analyses are (reasonably) limited to men. I think the paper should focus on the male population only. A chapter presenting major characteristics of the female subset and justifying its exclusion could be included in the Discussion section.

Several publications were recently published dealing with either the effect of RDP or the toxicity of uranium and should be cited (UNSCEAR radon report 2009, ICRP report 115 2010, ATSDR U toxicological profile 2011). Also, several articles dealing with the reconstruction of exposures and the assessment of risks among workers of uranium processing plants were recently published in the US and in France (Anderson et al. HP 2007, JESEE 2012 ; Guseva et al. RESP 2008, IAOEH 2009, IJHEH 2009, HP 2010, CCC 2011, OEM2012).

	<p>Specific comments</p>
	<p>Title, page 1: the title may be misleading as the article provides no results regarding exposure to uranium and radium. Another writing such as “Mortality and cancer incidence of workers in the radium and uranium refining and processing plant in Port Hope” may be preferred.</p> <p>Introduction, page 5: reference to the BEIR VI report dates of 1999. More recent references on the same subject (UNSCEAR 2009, ICRP 2010) could be added. Also a new version of the ATSDR report dealing with uranium toxicity was recently released (ATSDR 2011).</p> <p>Introduction, page 6: a reference for radium dosimetry and toxicity should be provided.</p> <p>Material and methods, cohort characteristics and follow-up, page 6: it should be indicated if the inclusion criteria considered a minimal duration of employment.</p> <p>Material and methods, cohort characteristics and follow-up, page 7: the classification of workers as exposed primarily to radium or uranium is not clear. Is it based only on the year of first employment? What about workers who began with radium processing and moved to uranium processing afterward? Consideration of a time dependant variable may have been considered. At least, more details should be given.</p> <p>Material and methods, assessment of exposures, page 8: it should be indicated here that RDP exposure is expressed in WLM, and WLM should be defined.</p> <p>Material and methods, assessment of exposures, page 8: the reconstruction methods are clearly associated to important and complex measurement errors, for both RDP and gamma exposure. A paragraph on that point should be added.</p> <p>Material and methods, statistical analyses, page 9: a definition of</p>

	<p>loss to follow-up is missing.</p> <p>Material and methods, statistical analyses, page 9: other analyses of the population near Port Hope used regional reference rates. Such approach may be interesting in discussing the Healthy Worker Effect.</p> <p>Material and methods, statistical analyses, page 10: please replace “exposure” by “cumulated exposure” in the text associated to equation 1 (and everywhere needed).</p> <p>Material and methods, statistical analyses, page 10: define “WLM” at its first occurrence in the manuscript.</p> <p>Material and methods, statistical analyses, page 10: classification of the total duration of employment in 2 categories (less or more than 6 months) is surprising. Was it to be able to distinguish short duration workers (such as students for instance)? Indeed, the creation of a real time-dependant variable instead would have been helpful to provide a proxy for potential occupational exposure to uranium or radium compounds.</p> <p>Results, demographic and exposure characteristics, page 11: sentence “Radium workers had significantly higher RDP and γ-ray doses compared to workers involved in uranium refining and processing” is duplicated.</p> <p>Results, demographic and exposure characteristics, page 11: additional information should be given, either in the text or in table 1: duration of employment, age at first exposure, duration of exposure, % lost to follow-up, duration of follow-up, % of unexposed workers. Also, it would be better to have min and max values. The numbers of workers and of person-years included in the incidence follow-up are also missing.</p> <p>Results, demographic and exposure characteristics, page 11: “Thus all further analyses were restricted to males”. Therefore I think the whole article should be restricted to males.</p> <p>Results, table 1, page 12: I don’t think it is PY weighted mean</p>
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	<p>exposures, but means of cumulated individual exposures at the end of follow-up. In that case, “cumulated exposure” should be explicitly indicated, and footnote a should be removed.</p> <p>Results, table 2, page 13: the significantly decreased SMR observed for “chronic obstructive lung disease and asthma” should be discussed in the text.</p> <p>Results, table 2, page 13: for coherence, the line “All cancers” should be move above, with those related to specific cancer sites.</p> <p>Results, dose-response analysis of lung cancer risks, page 15: replace “risks” by “risk” in the section title.</p> <p>Results, dose-response analysis of lung cancer risk, page 15: unit for gamma exposure is Gy whereas Sv is used in the Methods section. Please homogenise.</p> <p>Results, dose-response analysis of lung cancer risks, page 15: I guess the presented correlation between RDP and gamma exposures is based on individual cumulated exposures at the end of follow-up. This should be clearly indicated. In that case, the duration of exposure may partially explain this high correlation.</p> <p>Results, dose-response analysis of lung cancer risks, page 15: I don't agree with the last sentence “...indicating that the observed increases in risks were primarily due to RDP exposures”. Other factors correlated to RDP exposure (such as uranium contamination of exposure to chemical, which might be also correlated to the duration of work) may explain the observed association. A more careful writing is recommended.</p> <p>Results, table 4, page 16: I guess here the exposure means are PY weighted.</p> <p>Results, table 4, page 16: replace “RRa” by “RR^a”</p> <p>Results, table 4, page 16: the high proportion of PY in the 0 WLM category is surprising. A sentence may be added in the text to</p>
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	<p>explain it.</p> <p>Results, table 4, page 16: the difference in the estimated ERR per 100 WLM observed between uranium and radium workers should be better discussed in the text (even if not significant).</p> <p>Discussion, page 18: sentence “This report presents the analysis of 50 years of mortality (1950-1999) and 31 years of cancer incidence (1969-1999) in a cohort of 3,000 Port Hope, Ontario, radium and uranium processing workers first employed sometime in 1932-1980.” is misleading as results are presented only for males. Again, I recommend restricting the article to men only.</p> <p>Discussion, page 19: mean cumulative RDP exposure (15.23 WLM) is different from the value in table 1 (15.9 WLM). Also, I agree that a lower level of exposure could explain a lower global excess (SMR) of lung cancer, but I am not convinced that it should led to a lower ERR per 100 WLM (indeed it is not the case in the U miners literature).</p> <p>Discussion, page 19: in view of the results presented in table 4, I think the sentence “Radium and uranium workers had similarly non-significantly increased risks of lung cancer” is misleading, and appear contradictory with the discussion at the end of page 20.</p> <p>Discussion, page 19: 50y and 31y are the periods of follow-up for mortality and incidence respectively, but the mean durations are about 31y and 21y respectively. Either replace “duration” by “period” in the text, or provide the mean durations of follow-up.</p> <p>Discussion, page 19: I agree that organ dose calculation is out of the scope of the present article, but other approaches exist (proxy based on the duration of work, Job Exposure Matrix) and have been used in published work. These approaches should be better discussed.</p> <p>Discussion, page 20: the discussion about uncertainties and measurement errors should be completed by some insight their putative nature and size. Also, their potential impact on the estimated ERRs should be discussed.</p>
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	<p>Discussion, page 20: replace “four-fold higher risks” by “four-fold higher association between cumulative exposure and risk”.</p> <p>Discussion, page 21: a recent analysis suggested a potential risk of CVD associated to uranium exposure (Canu et al OEM 2012). It could be mentioned in the chapter discussing CVD risk.</p>
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REVIEWER	<p>Matthias Möhner, PhD Head of the unit "Statistical Methods in Epidemiology and Biometry" Federal Institute for Occupational Safety and Health (BAuA), Berlin, Germany</p> <p>I have no competing financial interests.</p>
REVIEW RETURNED	08-Nov-2012

RESULTS & CONCLUSIONS	<p>The study is well done. But although the follow-up is 50 years the power of the study is low. Therefore, this study should be included later on in a corresponding meta-analysis of similar studies. In the results section information about lost to follow-up is missing. It should be added necessarily. In the present stage of the study it could be useful to compare the results of the internal analysis with models based on miners studies. This comparison could be added in the discussion part. In the method section is described, that total duration of employment was split at 6 months. But in the results are no further data on this topic.</p>
GENERAL COMMENTS	<p>Please change the position of "All cancers" in table 2. It should be in the second line of the table.</p>

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Linda Walsh PhD, Scientist, Federal office for Radiation Protection (BfS), Germany

Please give more details in the revision connected with Strobe item 12 c) & d)

Response: Agreed.

General comments.

This paper describes a cohort of uranium refinery and processing workers and reports on the cancer risks related to exposures from uranium and radium compounds from the ore dust and to gamma (γ)-ray and radon decay products. Although the results are interesting, only a few category specific strong associations were reported (i.e., the standardised mortality ratio for hypertensive diseases and the relative risk for lung cancer incidence in the 3.5-15 & 15-50 WLM RDP exposure categories).

The paper is well and clearly written and the dedication to the memory of their former colleague Prof. Howe is a fine tribute to him – given the care and general high quality associated with the authors work. I would like to recommend the paper for publication in BMJ open after the authors have considered a few, hopefully constructive, comments and suggestions that I hope will lead to some further improvement in the quality of the already good paper.

I would like to see the small confusions concerning gender specific methods and results cleared up (see below) and more quantitative information concerning % loss-to-follow up and % of missing

causes of death in the cohort. The cohort was probably exposed to relatively high levels of other types of dust exposure – can the authors say something about quartz or fine dust exposures in this cohort? I look forward to reading the revised version and seeing the paper online very soon.

Response: Thank you very much for your thoughtful and comprehensive input concerning our paper. Please see below our replies to specific comments. With regards to exposures to quartz or fine silica dust, a small fraction of the Port Hope employees before 1955 would have had some dust exposure but the quartz content of that dust would have been much less than that from some of the other uranium properties operating at the time.

Specific comments and remarks.

1. Title: The word “substantial” is subjective. I asked several of my colleagues what they thought were substantial gamma-ray doses and they all came up with different ranges! Maybe the authors should consider if they really want to keep this word in the title.

Response: Agreed. We removed this word from the title and from several other places in the manuscript.

2. Abstract (page 2), Design: The number of male and female cohort members totals 3,000 – but all the results given in the paper pertain to the 2,645 men. I think it would be better to make this clear in the abstract.

Response: Agreed. We clarified this fact in the Abstract and in several other places in the manuscript.

3. Abstract (page 2), Outcome measures: In the second sentence I think you could delete the word “model”.

Response: Agreed.

4. Abstract (page 2), Conclusions: Please reconsider the “substantial” gamma-ray doses. I suggest deleting “substantial” and giving the mean gamma-ray dose in brackets. You also need to inform the reader about the type of gamma-dose (i.e., is it measured/estimated effective dose? the dose from film badges? (skin dose), colon dose?).

Response: Agreed. We provided mean RDP and γ -ray doses in the Abstract and clarified that γ -ray doses were whole-body effective doses.

5. Introduction (page 6): It would be interesting for a reader to be given some information on the degree of overlap between this paper under review and the earlier paper by this group (reference no. 12) – How many cases are included in both publications? Why exactly were “different analytical methods” used?

Response: Agreed. We provided a comparison of the data used in both studies as well as a description of the differences in methods of data analysis in the section titled Cohort characteristics and follow-up.

6. Methods (page 7, line 27): Can you justify selecting sites with 5 or more deaths or cases? – Why 5?

(page 7, line 37): Were there any cases of aplastic anaemia?

Response: Agreed. We removed this sentence because we looked at all causes of death and cancer. We clarified in the Results section that causes with <5 cases produced unstable risk estimates. There were no cases of aplastic anemia in the cohort.

7. Methods (page 8, line 39– You also need to inform the reader about the type of gamma-dose.

Response: Agreed.

8. Statistical analyses (page 9, line 48): Were adjustments really made for sex? All the values in tables 2 and 3 are male specific. Did you correct the SMRs for “missing causes of death”?

Response: Agreed. We removed a reference to adjustment for sex. We did not correct SMRs for “missing causes of death” as the Canadian Mortality Data Base (CMDB), which goes back to 1950 for all Canadians (back to 1940 for fact of death), including those who died while residing in the United States, has been shown to be complete (above 98%) and accurate¹ and is routinely used to ascertain mortality in a number of cohort studies.

9. Statistical analyses (page 10, line 13): What type of gamma-dose? and why did you choose age at first exposure rather than age at last exposure or age at median exposure? Also potential modification by gender should be either explained here or the reasons for not considering gender modification

should be explained here.

Response: Agreed. We clarified in the text that we used whole-body gamma doses. Age at first exposure was chosen as a stratification factor because of suspected cohort effects in mortality and cancer incidence.

10. Results (page 11, line 23): Second sentence. You could make it clear that the mean values of RDP exposures are gender specific in this sentence. Line 45 – at last it is made clear to the reader that all analyses are restricted to males (please make this clear throughout the paper in a consistent way so that the reader is not as confused as I was).

Response: Agreed.

11. Table 1 - 5. Please give the ICD codes – otherwise it is unclear, for example, exactly what “stroke” is. The sub-grouping in terms of cerebrovascular diseases may be better than just “stroke” – otherwise it will be difficult to include the results in future Meta-analyses.

Also given the results from a recent BMJ-open paper “A Prospective Follow-up Study of the Association of Radiation Exposure with Fatal and Non-Fatal Stroke among Atomic Bomb Survivors in Hiroshima and Nagasaki (1980-2003)” by Takahashi et al, would it be interesting to compute the SMR for stroke sub-types (ischaemic and haemorrhagic events)?

Response: Agreed. We included ICD-9 codes in Table 2. With regards to stroke, Takahashi et al.² is based on the Adult Health Study (AHS) of survivors of atomic bombings in Hiroshima. Subjects in the AHS study were screened biennially, which provided important clinical information which could be used to supplement death certificates and tumor registry data. The authors noted that they had neuroimaging data for 50% of their stroke cases.² In a much larger mortality study of atomic bomb survivors,³ which only relied on death certificates, stroke diagnoses could not be separated into ischemic and hemorrhagic events. Currently, there is lack of consensus on how to identify ischemic stroke diagnoses based on death certificates (www.queri.research.va.gov/tools/stroke-quality/ICD9.doc). Therefore, we did not separate our stroke diagnoses into ischaemic and hemorrhagic events.

12. Results (page 12, line 41): change “estimated SMRs included unity” to “estimated SMR CIs included unity”

Response: Agreed.

13. Table 4: Half-way down the table in the text “RR_a” – the “a” needs superscripting.

Response: Agreed.

The reference group only has extremely small WLMs – how do the RRs change if the reference category is changed to 0-1 WLM? The RR for lung cancer incidence is high in the 3.5-15 & 15-50 WLM categories – could this be due to confounding with quartz dust?

Response: We repeated our analyses in Table 4 using those with RDP 0-1 WLM as a reference category. The estimated RRs were similar to the analyses presented in Table 4 (RRs of 0.68 (95% CI: 0.35, 1.33), 1.74 (1.04, 2.90), 1.39 (0.65, 2.99) and 1.44 (0.58, 3.55), p-linear trend=0.55 for mortality and RRs of 0.77 (0.40, 1.46), 1.80 (1.08, 3.00), 2.24 (1.12, 4.46), and 2.01 (0.82, 4.90), p-linear trend=0.21 for incidence analysis, respectively). In addition, our cut-points were chosen a priori to evenly distribute cases between RDP exposure categories. Based on these additional results, which were similar to the results presented in Table 4, we did not make any changes to the manuscript.

14. Results (page 15, lines 4-13): It would interest me, and the readership in general, to know exactly how the non-cancer disease registry in Canada works and how complete the ascertainment is. Do you really have good ascertainment of non-cancer diseases such as nephritis, COPD and asthma? In Germany we do not have such statistics. How strongly can you back up the statements on non-cancer diseases that you made here?

Response: Agreed. We included the following supplemental information in the manuscript: The Canadian Mortality Database (CMDDB) is a computerized file of all deaths registered in Canada, as well as voluntarily reported deaths of Canadian residence occurring in the United States. Data in the CMDDB are obtained through the vital statistics system for national reporting of vital statistics data. Since the registration of deaths is a legal requirement through the Vital Statistics Acts (or equivalent legislation) in each Canadian province and territory, reporting is virtually complete. Death records

originate with the provincial and territorial registrars of vital statistics and are provided regularly to Statistics Canada. Under coverage is thought to be minimal, but is being monitored.¹

15. Results (page 15, lines 48-53): The comparison of non-nested models should be done in terms of changes in AIC or BIC here and not just qualitatively by mentioning the “smaller deviances”.

Please make this statement more quantitative by giving the differences in AIC or BIC.

Response: We presented the results of our quantitative analysis using likelihood ratio test in the sentence above: “Addition of γ -ray dose term to the model with RDP exposures did not significantly improve the model fit ($p=0.71$ for mortality and $p=0.54$ for incidence, not shown).” We revised the text to clarify this point.

16. Discussion (page 19, line 22): Please quantify the level of ascertainment. Also please give explicitly and quantitatively the % loss-to-follow up and % of missing causes of death in the cohort.

Response: Agreed. We provided the requested information in the section titled Cohort characteristics and follow-up.

17. Discussion (page 20, line 25 – 29): Could the authors be more quantitative about the time periods during which exposures were either estimated or measured?

Response: Agreed. We provided the requested information in the section titled Assessment of exposure.

Reviewer 2: Dominique LAURIER, Head of the Laboratory of Epidemiology, Institute for Radiological Protection and Nuclear Safety, France

- definition and description of the study population could be improved

Response: Agreed. We have provided additional information about the cohort in the section titled Cohort characteristics and follow-up.

- additional recent references could be cited

Response: Agreed. We have added several new references.

the present analysis do not allow evaluating the risk associated to uranium or radium exposure. Several changes could help avoiding any misinterpretation and improving the discussion regarding that point

Response: Disagree. We had data from employment records at Port Hope which allowed us to exclude those with any mining experience and to separate those primarily exposed to radium and those primarily exposed to uranium. We used these data to estimate ERR/100 WLM and ERR/Sv separately for two groups of workers (see Table 4).

This article presents an analysis of the mortality and cancer incidence among Port Hope workers in Canada. This is a more in-depth analysis of a subset of the Eldorado study published by Lane et al. in 2010. It is a good idea to propose a specific analysis of the population of Port Hope, as occupational exposures of these workers were different from that of the Beaverlodge and Port Radium miners. But, the present paper did not succeed in considering the specific exposures of these workers (internal contamination by uranium and radium compounds), and only RDP and gamma exposures are considered. I think this article presents anyway a real interest in the understanding of radiation induced risks at low doses. Methods and results are well presented, but several improvements should be made to clarify the article before publication.

Response: Thank you very much for your thoughtful and comprehensive input concerning our paper. Please see below for our replies to general and specific comments.

General comments

Even if a few modifications exist compared to the data included in the Eldorado study published by Lane et al. in 2010, the data are globally the same. It would have been interesting to provide results based on an extended follow-up. Also, the available exposure indicators are the same as those considered previously. As stated by the authors, conversely to the situation for miners, RDP exposure is not the main important one for Port Hope workers. It would have been interesting to try to consider

exposures due to the handling of uranium and radium chemical compounds. I understand that the retrospective reconstruction of doses due to incorporation is out of the scope of the present paper, but other (simpler) approaches could have been considered, such as the use of a Job Exposure Matrix or at least the duration of exposure as a time dependant variable. This constitutes a major limitation of the present analysis. The possibility of additional analyses should be investigated, or at least this point should be better discussed as a limitation of the study.

Response: Although the current analysis did not have extended follow-up compared to Lane et al.,⁴ we used additional exposure information which was not available in that analysis. Specifically, we had data from employment records at Port Hope which allowed us to exclude those with any mining experience and to separate those primarily exposed to radium and those primarily exposed to uranium. In addition, we included additional 39 workers who were previously classified as having worked at “other sites.”

Although urinalysis tests were performed since mid-1960s, we did not have adequate data for JEM use. This information was presented in the Methods section. We moved this discussion of internal exposures to soluble uranium to the Discussion section and supplemented it with a reference to a recent study of French uranium processors.⁵

The presentation of the cohort includes both men and women, whereas risk analyses are (reasonably) limited to men. I think the paper should focus on the male population only. A chapter presenting major characteristics of the female subset and justifying its exclusion could be included in the Discussion section.

Response: Agreed. We have revised the text in several places to reflect this change.

Several publications were recently published dealing with either the effect of RDP or the toxicity of uranium and should be cited (UNSCEAR radon report 2009, ICRP report 115 2010, ATSDR U toxicological profile 2011). Also, several articles dealing with the reconstruction of exposures and the assessment of risks among workers of uranium processing plants were recently published in the US and in France (Anderson et al. HP 2007, JESEE 2012 ; Guseva et al. RESP 2008, IAOEH 2009, IJHEH 2009, HP 2010, CCC 2011, OEM2012).

Response: Agreed. We would like to thank the Reviewer for this suggestion. We added several of the recommended references to the revised manuscript.

Specific comments

Title, page 1: the title may be misleading as the article provides no results regarding exposure to uranium and radium. Another writing such as “Mortality and cancer incidence of workers in the radium and uranium refining and processing plant in Port Hope” may be preferred.

Response: Disagree. The title does not state that we estimated risks from radium and uranium, only that workers were exposed to radium and uranium and γ -ray doses.

Introduction, page 5: reference to the BEIR VI report dates of 1999. More recent references on the same subject (UNSCEAR 2009, ICRP 2010) could be added. Also a new version of the ATSDR report dealing with uranium toxicity was recently released (ATSDR 2011).

Response: Agreed.

Introduction, page 6: a reference for radium dosimetry and toxicity should be provided.

Response: Agreed.

Material and methods, cohort characteristics and follow-up, page 6: it should be indicated if the inclusion criteria considered a minimal duration of employment.

Response: Agreed. The inclusion criteria did not consider duration of employment.

Material and methods, cohort characteristics and follow-up, page 7: the classification of workers as

exposed primarily to radium or uranium is not clear. Is it based only on the year of first employment? What about workers who began with radium processing and moved to uranium processing afterward? Consideration of a time dependant variable may have been considered. At least, more details should be given.

Response: Agreed. We clarified in the Methods section that workers who had worked in radium operations at any time were classified as radium workers, while all other workers who had never worked in radium operations were classified as uranium workers. A time-dependent variable for duration of exposure was considered in the analysis and was determined to be a significant confounder. Because we were able to separate those primarily exposed to radium from those primarily exposed to uranium, time-dependent duration of exposure is directly relevant to these exposures.

Material and methods, assessment of exposures, page 8: it should be indicated here that RDP exposure is expressed in WLM, and WLM should be defined.

Response: Agreed.

Material and methods, assessment of exposures, page 8: the reconstruction methods are clearly associated to important and complex measurement errors, for both RDP and gamma exposure. A paragraph on that point should be added.

Response: Agreed. We significantly expanded a discussion of this issue in the Discussion section.

Material and methods, statistical analyses, page 9: a definition of loss to follow-up is missing.

Response: Agreed. We provided additional information about the cohort in the section titled Cohort characteristics and follow-up.

Material and methods, statistical analyses, page 9: other analyses of the population near Port Hope used regional reference rates. Such approach may be interesting in discussing the Healthy Worker Effect.

Response: This study is the part of a larger study of all Eldorado Ltd. employees who had worked at multiple locations in three provinces and one territory. Further, it had been noted that many retired employees moved to other locations. Therefore, the decision was made to compare the Eldorado cohort with the population of Canada. In the Port Hope case, a comparison with the population of Ontario could be useful but this would risk losing potential matches to employees who were known to have moved out of Ontario.

Material and methods, statistical analyses, page 10: please replace “exposure” by “cumulated exposure” in the text associated to equation 1 (and everywhere needed).

Response: Disagree. We used a time-dependent variable for RDP exposures, such that workers contributed to person-time at various stages of their work, not only at cumulative stage.

Material and methods, statistical analyses, page 10: define “WLM” at its first occurrence in the manuscript.

Response: We provided an explanation for WLM methodology in the section titled Assessment of exposure.

Material and methods, statistical analyses, page 10: classification of the total duration of employment in 2 categories (less or more than 6 months) is surprising. Was it to be able to distinguish short duration workers (such as students for instance)? Indeed, the creation of a real time-dependant variable instead would have been helpful to provide a proxy for potential occupational exposure to uranium or radium compounds.

Response: We categorized duration of exposure into <6 mos and 6+ mos, because we observed that risks of lung cancer dropped after 6 months but remained constant afterward. Whether this was due to short-time employees such as students and summer interns or due to higher mortality of short-time

workers, is not known. Similar phenomena have been observed previously in other studies.⁶

Results, demographic and exposure characteristics, page 11: sentence “Radium workers had significantly higher RDP and γ -ray doses compared to workers involved in uranium refining and processing” is duplicated.

Response: Agreed.

Results, demographic and exposure characteristics, page 11: additional information should be given, either in the text or in table 1: duration of employment, age at first exposure, duration of exposure, % lost to follow-up, duration of follow-up, % of unexposed workers. Also, it would be better to have min and max values. The numbers of workers and of person-years included in the incidence follow-up are also missing.

Response: Agreed.

Results, demographic and exposure characteristics, page 11: “Thus all further analyses were restricted to males”. Therefore I think the whole article should be restricted to males.

Response: Agreed. We clarified this in various places in the manuscript.

Results, table 1, page 12: I don't think it is PY weighted mean exposures, but means of cumulated individual exposures at the end of follow-up. In that case, “cumulated exposure” should be explicitly indicated, and footnote a should be removed.

Response: Disagree. In Table 1 we presented PY-weighted mean doses which were calculated from summary PY experience cross-classified by various confounders as described in the Methods section.

Results, table 2, page 13: the significantly decreased SMR observed for “chronic obstructive lung disease and asthma” should be discussed in the text.

Response: Agreed.

Results, table 2, page 13: for coherence, the line “All cancers” should be move above, with those related to specific cancer sites.

Response: Agreed.

Results, dose-response analysis of lung cancer risks, page 15: replace “risks” by “risk” in the section title.

Response: Agreed.

Results, dose-response analysis of lung cancer risk, page 15: unit for gamma exposure is Gy whereas Sv is used in the Methods section. Please homogenise.

Response: Agreed.

Results, dose-response analysis of lung cancer risks, page 15: I guess the presented correlation between RDP and gamma exposures is based on individual cumulated exposures at the end of follow-up. This should be clearly indicated. In that case, the duration of exposure may partially explain this high correlation.

Response: RDP and gamma exposures were correlated not just at the end of follow-up but throughout follow-up. We used PY-weighted means for this analysis.

Results, dose-response analysis of lung cancer risks, page 15: I don't agree with the last sentence “...indicating that the observed increases in risks were primarily due to RDP exposures”. Other factors correlated to RDP exposure (such as uranium contamination of exposure to chemical, which might be also correlated to the duration of work) may explain the observed association. A more careful writing

is recommended.
Response: Agree.

Results, table 4, page 16: I guess here the exposure means are PY weighted.
Response: Yes, throughout the manuscript we used PY-weighted means of exposures.

Results, table 4, page 16: replace “RRa” by “RRa”
Response: Agreed.

Results, table 4, page 16: the high proportion of PY in the 0 WLM category is surprising. A sentence may be added in the text to explain it.
Response: We added information on high proportion on RDP-unexposed in the Results sub-section titled Demographic and exposure characteristics.

Results, table 4, page 16: the difference in the estimated ERR per 100 WLM observed between uranium and radium workers should be better discussed in the text (even if not significant).
Response: Agreed.

Discussion, page 18: sentence “This report presents the analysis of 50 years of mortality (1950-1999) and 31 years of cancer incidence (1969-1999) in a cohort of 3,000 Port Hope, Ontario, radium and uranium processing workers first employed sometime in 1932-1980.” is misleading as results are presented only for males. Again, I recommend restricting the article to men only.
Response: Agreed.

Discussion, page 19: mean cumulative RDP exposure (15.23 WLM) is different from the value in table 1 (15.9 WLM). Also, I agree that a lower level of exposure could explain a lower global excess (SMR) of lung cancer, but I am not convinced that it should led to a lower ERR per 100 WLM (indeed it is not the case in the U miners literature).
Response: Agreed. We clarified that lower doses were probably associated with lower statistical power to detect any association with risk of lung cancer.

Discussion, page 19: in view of the results presented in table 4, I think the sentence “Radium and uranium workers had similarly non-significantly increased risks of lung cancer” is misleading, and appear contradictory with the discussion at the end of page 20.
Response: Agreed.

Discussion, page 19: 50y and 31y are the periods of follow-up for mortality and incidence respectively, but the mean durations are about 31y and 21y respectively. Either replace “duration” by “period” in the text, or provide the mean durations of follow-up.
Response: Agreed.

Discussion, page 19: I agree that organ dose calculation is out of the scope of the present article, but other approaches exist (proxy based on the duration of work, Job Exposure Matrix) and have been used in published work. These approaches should be better discussed.
Response: Agreed. We discussed this limitation in the Discussion section.

Discussion, page 20: the discussion about uncertainties and measurement errors should be completed by some insight their putative nature and size. Also, their potential impact on the estimated ERRs should be discussed.
Response: Agreed. We provided an extensive discussion of the possible effects of uncertainties and measurement errors on risk estimates in the Discussion section.

Discussion, page 20: replace “four-fold higher risks” by “four-fold higher association between cumulative exposure and risk”.

Response: Agreed.

Discussion, page 21: a recent analysis suggested a potential risk of CVD associated to uranium exposure (Canu et al OEM 2012). It could be mentioned in the chapter discussing CVD risk.

Response: Agreed. We significantly expanded a discussion of our results with regards to radiation-related risks of CVD as well as included most recent references in the Discussion section.

Reviewer 3: Matthias Möhner, PhD, Head of the unit "Statistical Methods in Epidemiology and Biometry," Federal Institute for Occupational Safety and Health (BAuA), Berlin, Germany
The study is well done. But although the follow-up is 50 years the power of the study is low. Therefore, this study should be included later on in a corresponding meta-analysis of similar studies.

Response: We agree with Reviewer's comments and are making efforts to pool the data from our study with the data from the three Canadian cohorts of uranium miners, and eventually with the European cohorts of uranium miners.

In the results section information about lost to follow-up is missing. It should be added necessarily.

Response: Agreed. We provided this information in the section titled Cohort characteristics and follow-up.

In the present stage of the study it could be useful to compare the results of the internal analysis with models based on miners studies. This comparison could be added in the discussion part.

Response: Agreed. We expanded the Discussion section by including a comparison of our study findings with other published studies.

In the method section is described, that total duration of employment was split at 6 months. But in the results are no further data on this topic.

Response: Duration of employment was found to be a significant confounder and was used, along with age at risk and calendar year at risk, to stratify background rates.

Please change the position of "All cancers" in table 2. It should be in the second line of the table.

Response: Agreed.

References

1. Goldberg MS, Carpenter M, Theriault G, Fair M. The accuracy of ascertaining vital status in a historical cohort study of synthetic textiles workers using computerized record linkage to the Canadian Mortality Data Base. *Can J Public Health.* 1993;84(3):201-4. PMID: 8358698.
2. Takahashi I, Abbott RD, Ohshita T, Takahashi T, Ozasa K, Akahoshi M, et al. A prospective follow-up study of the association of radiation exposure with fatal and non-fatal stroke among atomic bomb survivors in Hiroshima and Nagasaki (1980-2003). *BMJ open.* 2012;2(1):e000654. PMID: PMC3274709.
3. Shimizu Y, Kodama K, Nishi N, Kasagi F, Suyama A, Soda M, et al. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. *BMJ.* 2010;340:b5349. PMID: PMC2806940.
4. Lane RS, Frost SE, Howe GR, Zablotska LB. Mortality (1950-1999) and cancer incidence (1969-1999) in the cohort of Eldorado uranium workers. *Radiat Res.* 2010;174(6):773-85. PMID: 21128801.
5. Guseva Canu I, Jacob S, Cardis E, Wild P, Caer S, Auriol B, et al. Uranium carcinogenicity in humans might depend on the physical and chemical nature of uranium and its isotopic composition: results from pilot epidemiological study of French nuclear workers. *Cancer Causes Control.* 2011;22(10):1007-15. PMID: 21874522.

6. Howe GR, Chiarelli AM, Lindsay JP. Components and modifiers of the healthy worker effect: evidence from three occupational cohorts and implications for industrial compensation. *Am J Epidemiol.* 1988;128(6):1364-75. PMID: 2973746.

VERSION 2 – REVIEW

REVIEWER	Linda Walsh PhD Scientist, Federal Office for Radiation Protection, Germany
REVIEW RETURNED	19-Dec-2012

GENERAL COMMENTS	The authors have carefully considered my previous comments and included all of my suggested changes. The revisions have clarified several points and lead to a very good paper. I would like to strongly recommend the revised paper for publication in <i>BMJ open</i> .
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REVIEWER	Dominique Laurier Head of the Laboratory of Epidemiology Institute for radiological Protection and Nuclear Safety FRANCE I declare having no conflict of interest in reviewing this manuscript.
REVIEW RETURNED	29-Dec-2012

GENERAL COMMENTS	<p>The revised version improved substantially, especially regarding the description of the material and methods and the discussion of the results. I only have one last point of correction related to “cumulative exposure” based on the answers to the points listed in the first review, (see below).</p> <p>I think the paper is now acceptable for publication. My last comments listed below are minors ones, and just intend to improve the clarity of the paper. I think they can be considered by the authors without requesting a new review.</p> <ul style="list-style-type: none"> • Of course, the Poison regression is based on PY weighted means based on cross-classified cells. But for each PY, the data considered is the exposure cumulated since the first year of exposure of the worker. Indeed, “cumulative” do not only apply to the last year of follow-up of each worker. That is the reason why I suggested to use “cumulative exposure” instead of “exposure” in the text associated to equation 1 (Material and Methods Section) and everywhere needed. For example, on page 12, I suggest to replace “The person-year weighted mean dose in each cross-classified cell was used in the regression analysis.” by “The person-year weighted mean cumulative exposure in each cross-classified cell was used in the regression analysis.” • I understand that table 1 presents PY weighted mean values. To avoid any misinterpretation with mean annual exposure or with mean exposure cumulated up to the end of follow-up, I suggest changing the line titles to “PY weighted mean cumulative exposure”. • I think the authors should provide in addition to table 1 the mean of the individual exposure cumulated up to the end of follow-up, for both RDP and gamma. Indeed, this indicator may be very different from the PY weighted mean, especially in cases like the present one in which the proportion of PY with zero exposure is close to 40%. This indicator is classically presented in this kind of analysis, and is of importance if the reader wants to compare with the literature.
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	<p>Also, the minimum and maximum values are important information, and should be provided.</p> <ul style="list-style-type: none"> • In the abstract, the sentence “mean cumulative RDP exposure was 15.9 working-level-months (WLM) and mean cumulative whole-body γ-ray dose was 134.4 millisievert” is misleading, as it refers to PY weighted means. I think the mean of individual cumulated exposure at the end of follow-up should be provided there instead. • In the discussion section, the comparison of cumulative exposure between different studies must rely on the same indicators to be valid. On page 20, the indicator provided in Villeneuve et al. 2007 is the mean of lifetime cumulative RDP exposure. Therefore, this value should not be compared to the PY weighted mean but to the mean of cumulated exposure at the end of follow-up.
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VERSION 2 – AUTHOR RESPONSE

Reviewer 1: Linda Walsh PhD, Scientist, Federal office for Radiation Protection (BfS), Germany

The authors have carefully considered my previous comments and included all of my suggested changes. The revisions have clarified several points and lead to a very good paper. I would like to strongly recommend the revised paper for publication in BMJ open.

Reviewer 2: Dominique LAURIER, Head of the Laboratory of Epidemiology, Institute for Radiological Protection and Nuclear Safety, France

The revised version improved substantially, especially regarding the description of the material and methods and the discussion of the results. I only have one last point of correction related to “cumulative exposure” based on the answers to the points listed in the first review, (see below). I think the paper is now acceptable for publication. My last comments listed below are minors ones, and just intend to improve the clarity of the paper. I think they can be considered by the authors without requesting a new review.

- Of course, the Poison regression is based on PY weighted means based on cross-classified cells. But for each PY, the data considered is the exposure cumulated since the first year of exposure of the worker. Indeed, “cumulative” do not only apply to the last year of follow-up of each worker. That is the reason why I suggested to use “cumulative exposure” instead of “exposure” in the text associated to equation 1 (Material and Methods Section) and everywhere needed. For example, on page 12, I suggest to replace “The person-year weighted mean dose in each cross-classified cell was used in the regression analysis.” by “The person-year weighted mean cumulative exposure in each cross-classified cell was used in the regression analysis.”

Response: Agreed.

- I understand that table 1 presents PY weighted mean values. To avoid any misinterpretation with mean annual exposure or with mean exposure cumulated up to the end of follow-up, I suggest changing the line titles to “PY weighted mean cumulative exposure”.

Response: Agreed. We revised Table 1 to include lifetime exposures cumulated to the end of follow-up for all workers together and separately for males and females and radium and uranium workers. We also provided ranges and standard deviations.

- I think the authors should provide in addition to table 1 the mean of the individual exposure cumulated up to the end of follow-up, for both RDP and gamma. Indeed, this indicator may be very different from the PY weighted mean, especially in cases like the present one in which the proportion

of PY with zero exposure is close to 40%. This indicator is classically presented in this kind of analysis, and is of importance if the reader wants to compare with the literature. Also, the minimum and maximum values are important information, and should be provided.

Response: Agreed. This information is now presented in Table 1. Information about person-year weighted mean cumulative RDP and gamma-ray exposures is now presented in the text on page 16.

- In the abstract, the sentence “mean cumulative RDP exposure was 15.9 working-level-months (WLM) and mean cumulative whole-body γ -ray dose was 134.4 millisievert” is misleading, as it refers to PY weighted means. I think the mean of individual cumulated exposure at the end of follow-up should be provided there instead.

Response: We clarified in the text of the Abstract that presented values are person-year weighted mean cumulative exposures.

- In the discussion section, the comparison of cumulative exposure between different studies must rely on the same indicators to be valid. On page 20, the indicator provided in Villeneuve et al. 2007 is the mean of lifetime cumulative RDP exposure. Therefore, this value should not be compared to the PY weighted mean but to the mean of cumulated exposure at the end of follow-up.

Response: Agreed.