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Title	Cancer incidence attributable to oral contraceptives and hormone therapy use in Alberta, Canada in 2012
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Reviewer 1	Dr. Jeffrey Bakal PhD PStat
Institution	University of Alberta, Edmonton, Alta.
General comments (author response in bold)	1. Clarify the take-away message **• Response: the take-away message has been streamlined in the last paragraph in the Interpretation section. Please see our response to Copyediting comment #16.** *16. Main findings: Summarize findings and explain what Alberta policy-makers should take away from this study.* *• Response: We include the summary text "Our analyses showed that the benefit of oral contraceptive use exceeds the potential risk among the cancer sites investigated since the number of cancers possibly reduced by oral contraceptive use was more than twice the number potentially associated with the exposure. Oral contraceptive use likely reduced the cancer burden in Alberta in 2012. In contrast, hormone therapy use was estimated to increase the cancer burden in the province by approximately 200 excess cancer cases in 2012. The risks and benefits of hormone therapies should be carefully considered prior to their use." The main finding and take-away message is summarized in last paragraph in the interpretation section (page 10)* 2. Update the references, in general **• Response: through the revision process we added and updated references when it is available.** 3. Reference the PAR **• Response: Levin 1953 paper(2) was referenced (page 5).** 4. Make sure that all the CIs are properly and similarly noted **• Response: revisions have been made in the results section to properly include CIs.** 5. In the results there are statements made which are very difficult to pull from the tables **• Response: the Results section has been restructured and revised to explain the main findings. A summary of PAR estimates is added at the end of paragraphs two and three in this section to highlight the key results. When available, we reported both estimated numeric data and percentages.** 6. Move newly stated results out of the interpretation section. **• Response: Revisions have been made and no newly results are presented in the interpretation section.**
Reviewer 2	Dr. Cheryl Peters
Institution	Department of Health Sciences, Carleton University, Ottawa, Ont.
General comments (author response in bold)	1. Page 6 line 32 – I'm confused as to why the authors mention "estimations were performed for individual sex and age groups." Aren't all of the estimations done for women in the case of these exposures? **• Response: the content has been revised and the estimations were performed by age groups only. This revision can be found in Methods section, subtitle Population Attributable Fraction, paragraph 3. (Page 5)** 2. Page 6 line 55 – the sentence starting with "Where Pe is the prevalence…" is a sentence fragment. 3. Page 7 line 6 "estimates" should be 'estimated.' 4. Page 9, first line, misspelling of ductal. 5. Please note that this paper requires a thorough proofread. There are way too many typos and grammatical errors to note, so I just stopped doing so after a while. **• Response: A thorough review has been conducted to eliminate all spelling and grammatical errors found.** 6. In Table 3, under the HRT- Current use section for breast cancer, I don't understand the sub-analyses for breast cancer subtypes. If the overall PAR for breast cancer is 9%, how can the PARs for the different subtypes be so much higher? Are these from separate data sources? The observed number of cases doesn't add up (although it's close) so maybe this is the case. In any event, this needs to be better described so that the Table is less puzzling. **• Response: The assumption used to estimate PARs for the different subtypes are correct. The much higher PARs and EACs for the subtypes of breast cancer were due to the higher RRs reported for these subtypes. However, we agree with the comment made by Dr. Peters that presenting both the overall PAR for breast cancer and the PARs for the subtypes together was confusing. Therefore, we decided to only present the overall PAR data for breast cancer to be consistent with other cancer sites presented.** 7. On Page 9, last paragraph, which continues on to page 10, the differences between the UK and Alberta studies are outlined (the differences appear to be due to differences in hormone use between the countries, such that Canadian women use

	contraceptives and HRT more than women in the UK). Then the sentence appears on page 10 line 19: "This evidence indicates that the prevalence of OC use in Canada is similar to the UK and the higher rates in ATP were likely due to over-estimation in this cohort." I think the evidence the authors presented in this section does not lead to that conclusion at all – they are presenting data sources that indicate differences in prevalence. The sentence on page 10 line 12 that has a lower prevalence of contraceptive use is only based on the previous 6 months, when they used the ATP prevalence of 92% having ever used contraceptives, which seems correct. Also why is it "unclear" if the "ATP and Parkin's study used the same definition for hormone 'ever use'"? Isn't "ever use" fairly straightforward? **• Response: In the interpretation section paragraph 2 (page 8) we added additional evidence on regional variations in hormone exposures. We also clarified that the prevalence of hormone use in our study could have been overestimated because the cohort population had higher proportion of women with higher education and income and they likely had better access to drug coverage thus more likely to use hormone preparations. This argument is supported by published evidence. In terms of definition of 'ever use', Parkin did not have information on prevalence of hormone therapy former users and it was estimated in terms of the difference of current users in population prevalence from one year to the next and the author stated that the prevalence was underestimated. Parkin also added that their estimation on past use of oral contraceptive was based on published data from other UK studies and was less accurate.** 8. Page 12 line 40: the sentence that begins "In contrast,…" How is this a contrast? You seem to be talking about lack of precision in both cases. **• Response: The wording of this section has been revised and modified (page 9)** 9. It would be interesting to note in the discussion that OCs probably lead to women having less kids (or none), and we know that this is a risk factor for breast cancer in and of itself. **• Response: Dr. Peters raised a very interesting point. However, the scope of our manuscript series did not estimate muti-factual PAR. The main focus of this manuscript was to estimate the universal population attributable risks; therefore we did not discuss the etiology of breast cancer in relation to hormone exposures and reproductive factors. Thus, regrettably, Dr. Peters recommendation was not included in our discussion in this manuscript.** Reference: 1. Cook LS, Leung AC, Swenerton K, Gallagher RP, Magliocco A, Steed H, et al. Adult lifetime alcohol consumption and invasive epithelial ovarian cancer risk in a population-based case-control study. Gynecologic oncology. 2016;140(2):277-84. 2. Levin ML. The occurrence of lung cancer in man. Acta - Unio Internationalis Contra Cancrum. 1953;9(3):531-41.