PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between cigarette smoking, cancer screening, and cancer stage: A prospective study of the Women's Health Initiative Observational Cohort
AUTHORS	Eng, Victor; David, Sean; Li, Shufeng; Ally, Mina; Stefanick, Marcia; Tang, Jean

VERSION 1 – REVIEW

REVIEWER	Alejandra Castanon King's College London, United Kingdom
REVIEW RETURNED	13-Mar-2020

GENERAL COMMENTS	Major comments 1. Presence of known cardiovascular comorbidity may dissuade a clinician from prescribing over age 60yrs. – Given this specific age cut off mentioned in the introduction why is it not reflected in the analysis or in the discussion. Could it be that more affluent areas also have younger populations? Would it be possible to add practice list size in 5year age groups to the multivariable analysis? 2. Understandable, the authors focus on the result for IMDscore adjusted for all other factors, however the results in supplementary table 3 are interesting and need to be discussed. In particular higher prevalence of cardiovascular disease is related to higher rates of HRT prescribing in lower IMD practices. 3. Although the ratio of oral to transdermal is sig higher in lower IMD practices, IMD was not an independent predictor of transdermal prescription. This could indicate less acceptance of the female population in lower IMD areas or it could be related to the cardiovascular results discussed in point 2. Therefore, I felt the last sentence in the discussion/summary was misleading. 4. A table (like suppl table 3) for the oral vs transdermal analysis should be provided. 5. The very strong relationship between proportion with diabetes and lower prescribing rates (34%) and given that the unadjusted and adjusted estimates are very similar it suggests that the decision to prescribe may be driven by this co-morbidity more than any other. This could explain the higher oral prescribing in lower deprivation. Those that would benefit from transdermal may also have diabetes and this may result in no prescription. I accept that I may be reading into the results more than is appropriate. However, as a non- subject expert these were the questions running through my mind whilst reading the manuscript. Minor comments Supplementary Table 2. There is a mistake as the lower confidence

	interval in the table for all estimates is the same as the point estimate (not what is seen in Figure 1) How this fits in – I think 29% lower HRT prescribing rate should be replaced by 18% (figure once all other variables were adjusted for). Dear Editor, I read with interested the manuscript by Tang et al. There concluding message 'clinicians should emphasize the promotion of both smoking cessation and cancer screening' is important and not often addressed. I have the following major comments which I hope will help the authors improve the manuscript. 1. There needs to be a more detailed description of the analysis for stage at presentation. The analysis is actually the odds of having late stage cancer among those who have never been screened compared to those screened - stratified by smoking status. 2. How was the decision to assess colorectal screening over 5yrs arrived at? FOBT is recommended at yrly intervals. This is probably due to the fact that coloscopy and sigmoidoscopy is recommended every 5yrs. This should be clarified. I would assume more screens were FoBT than endoscopy therefore it may be worth an analysis with shorter intervals between tests? 3. Page 15 (discussion). Mammograms detect cancer at an early stage (NOT precancer – that's cervical screening). However colorectal cancer screening does both – detect adenoma and prevents cancer but also early stage cancer reducing mortality. This is probably why no effect on late stage was seen other than in smokers, there is lots of screen detected cancer when individuals are screened specially with such a long interval (5yrs) between tests. 4. From table 2, The key point of discussion should be the increased risk among smokers' non-attenders (2.95) compared to never smokers (1.59) non-attenders. We know that those who don't attend will have higher stage what is new here is that those that are current smokers are at an even greater risk than that associated with not attending screening. I didn't think this came across in the discussion. 5. Recall bias is only mentioned for smoking but also applies to the screening exposure data. This bias would work in different directions for smoking than screening: people are probably likely to report less smoking than actually occurred whereas with screening it is more screening than actually occurred. Would they cancel out? In light of my comments above the conclusion paragraph should be revisited.

REVIEWER	Silvano Gallus Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
REVIEW RETURNED	18-Mar-2020

GENERAL COMMENTS	This is a well-written manuscript showing findings from a large prospective study on postmenopausal women showing that smoking is strongly associated with a decreased participation to cancer screening and that smokers have more advanced cancer stage at

	the time of diagnosis compared with never smokers. Data are important, conclusions are interesting and recommendations are potentially relevant from a public health perspective. Authors should consider a few minor points to improve the presentation of findings: 1) Please, mention also in the Abstract that the reference category for the ORs is never smokers. 2) Please, check all the estimates provided in the Results: for example, the OR for the preast cancer screening in the Abstract should be 0.55 and not 0.49. 3) Please, revise the entire text for the presence of a few typos, also in the Abstract (last line of the Results section: “OR 2.2556”?) 4) I suggest to provide also in the Results of the Abstract the proportion of never, ex- and current smokers. In this population of postmenopausal women, current smokers are only 6.4%. It is possible that this subpopulation has baseline characteristics that could explain at least in part the results. However, the OR estimates are carefully adjusted for age. 5) In the headings of Table 1, mention “breast cancer”, “cervical cancer” and “colorectal cancer”. 6) I suggest to keep 2 (and 2 only!) decimals for ORs, also when the second decimal is 0 (e.g., Table 1 lines 46-47, or when the estimate is at borderline significance (see the third decimal at; e.g., Table 1 line 38

VERSION 1 – AUTHOR RESPONSE

Reviewer Comment R1

We thank the editors and reviewers for the opportunity to revise our manuscript. We have carefully considered each feedback and made revisions to the manuscript as recommended.

Please include a statement relating to the ethical approval obtained for your study. If ethics approval was not required, please provide a full justification to explain why.

Data used in this study were previously collected by Women’s Health Initiative, . All data provided to the authors were completely deidentified. Studies that use deidentified third-party data is exempt from the Stanford IRB review process. We have added this statement to the Methods section.

Please modify your Data Sharing Statement to include full details of permissions to access the data used in your study, including whether the data was provided already anonymised. In this statement, please clarify how others can access the data used in your study, who the 3rd party is, and where readers may access the data.

We have modified our Data Sharing Statement as recommended. Data used in this study is hosted by the Women’s Health Initiative and was fully deidentified and anonymized prior to receipt by the study authors. Eligible researchers may download the study protocol, study procedures, data collection forms, and deidentified participant data directly at the WHI online resource (https://www.whi.org/researchers/data/Pages/Home.aspx). Other researchers may download the publicly available data through BioLINCC (https://biolincc.nhlbi.nih.gov/studies/whict).

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name

Alejandra Castanon

Institution and Country

King's College London, United Kingdom

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below

Dear Editor,
I read with interested the manuscript by Tang et al. There concluding message ‘clinicians should emphasize the promotion of both smoking cessation and cancer screening’ is important and not often addressed.

I have the following major comments which I hope will help the authors improve the manuscript.

1. There needs to be a more detailed description of the analysis for stage at presentation. The analysis is actually the odds of having late stage cancer among those who have never been screened compared to those screened - stratified by smoking status.

We have clarified this in the Abstract and Introduction sections, and rephrased the findings in the Results section: “The odds of late-stage cancer diagnoses among patients with adequate versus inadequate screening as stratified by smoking status were also calculated.” “The present cross-sectional study will investigate use of cancer screening by smoking status, and determine whether the stage of cancer at the time of diagnosis varies based on smoking status among a nationally representative sample of women from the Women’s Health Initiative-Observational Cohort (WHI-OS).”

2. How was the decision to assess colorectal screening over 5yrs arrived at? FOBT is recommended at yrly intervals. This is probably due to the fact that coloscopy and sigmoidoscopy is recommended every 5yrs. This should be clarified. I would assume more screens were FoBT than endoscopy therefore it may be worth an analysis with shorter intervals between tests?

In the WHI dataset, colorectal screening was determined as having had an FOBT or endoscopy within the past 5 years. FOBT was not categorized separately and, thus, we are limited from analyzing FOBT vs. endoscopy separately. We have added this study limitation to the Discussion section.

3. Page 15 (discussion). Mammograms detect cancer at an early stage (NOT precancer – that’s cervical screening). However colorectal cancer screening does both – detect adenoma and prevents cancer but also early stage cancer reducing mortality. This is probably why no effect on late stage was seen other than in smokers, there is lots of screen detected cancer when individuals are screened specially with such a long interval (5yrs) between tests.

We agree with the distinction that colorectal screening detects precancerous adenomas in addition to cancer, and have added this interpretation to the Discussion section. We also revised our statement on mammograms to clarify that they detect early-stage cancer, not precancerous lesions.

4. From table 2, The key point of discussion should be the increased risk among smokers' non-attenders (2.95) compared to never smokers (1.59) non-attenders. We know that those who don't attend will have higher stage. what is new here is that those that are current smokers are at an even greater risk than that associated with not attending screening. I didn't think this came across in the discussion.

We have strengthened the discussion of this important finding on page 15.(paste the sentence below…)

5. Recall bias is only mentioned for smoking but also applies to the screening exposure data. This bias would work in different directions for smoking than screening: people are probably likely to report less smoking than actually occurred whereas with screening it is more screening than actually occurred. Would they cancel out?

This is a definite possibility. Unfortunately, we are unable to quantify the recall bias or social desirability bias for either smoking or cancer screening. Thus, we cannot determine if these effects cancel out. This limitation has been added to the Discussion section.

In light of my comments above the conclusion paragraph should be revisited.

We have revised the conclusion to emphasize the higher odds of advanced/late-stage cancers in non-attenders with active smoking status.

Reviewer: 2

Reviewer Name

Silvano Gallus

Institution and Country

Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
This is a well-written manuscript showing findings from a large prospective study on postmenopausal women showing that smoking is strongly associated with a decreased participation to cancer screening and that smokers have more advanced cancer stage at the time of diagnosis compared with never smokers. Data are important, conclusions are interesting and recommendations are potentially relevant from a public health perspective. Authors should consider a few minor points to improve the presentation of findings:

1) Please, mention also in the Abstract that the reference category for the ORs is never smokers.

We have added never smokers as the reference group in the Abstract.

2) Please, check all the estimates provided in the Results: for example, the OR for the preast cancer screening in the Abstract should be 0.55 and not 0.49.

We made the change as noted. We have also verified the numbers throughout the manuscript for accuracy.

3) Please, revise the entire text for the presence of a few typos, also in the Abstract (last line of the Results section: “OR 2.2556”?)

We have revised this typo in the Abstract.

4) I suggest to provide also in the Results of the Abstract the proportion of never, ex- and current smokers. In this population of postmenopausal women, current smokers are only 6.4%. It is possible that this subpopulation has baseline characteristics that could explain at least in part the results. However, the OR estimates are carefully adjusted for age.

We have added these proportions to the results of the Abstract.

5) In the headings of Table 1, mention “breast cancer”, “cervical cancer” and “colorectal cancer”.

We have added the cancers screened for to the heading of Table 1.

6) I suggest to keep 2 (and 2 only!) decimals for ORs, also when the second decimal is 0 (e.g., Table 1 lines 46-47, or when the estimate is at borderline significance (see the third decimal at; e.g., Table 1 line 38

Calculations were performed to the fourth decimal. We will round to the nearest thousandth place for results that were borderline significant. For all other results, we will round to the nearest hundredth place.

VERSION 2 – REVIEW

REVIEWER	Alejandra Castanon King's College London, United Kingdom
REVIEW RETURNED	01-May-2020

GENERAL COMMENTS	I thank the authors for addressing in full all the comment from my first review. I am satisfied that they have been fully addressed in the revised manuscript.

REVIEWER	Silvano Gallus Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
REVIEW RETURNED	24-Apr-2020

GENERAL COMMENTS	The Authors satisfactorily addressed all the points I raised in my previous report.