

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The magnitude of the association between smoking and the risk of developing cancer in Brazil: a multicenter study
<b>AUTHORS</b>	Moura, Marcione; Bergmann, Anke; Aguiar, Suzana; Thuler, Luiz

### VERSION 1 - REVIEW

<b>REVIEWER</b>	David Levy, Research Professor Georgetown University, Washington, DC, USA
<b>REVIEW RETURNED</b>	14-Oct-2013

<b>GENERAL COMMENTS</b>	<p>The paper should end with a summary paragraph, instead of just the limitations. What is now the last sentence is poorly worded.</p> <p>This study examines the effect of smoking on different types of cancer using secondary data collected from a large number of cancer treatment centers. The methods used to analyze the data are appropriate and the authors clearly present the results. The importance of this study is that it is conducted in a middle income nation with a diverse culture, and that data is collected on alcohol use along with smoking.</p> <p>The authors should explain how tobacco and alcohol consumption were measured. Do they distinguish quantity or just whether tobacco or alcohol were consumed. It would have also be useful to know how the inclusion of alcohol consumption affected the results, especially for breast cancer.</p> <p>It was not clear how the non-melanoma skin cancers were used as a case control. please explain.</p> <p>Given the varied population of Brazil, it would have been useful to know more about how the effects varied by population. The authors separately consider males and females, but it would have been useful to know how the effects varied by other characteristics. In particular, the authors present data distinguishing by race, region and schooling, but they do not include any of these variables in their equations distinguishing the effect of tobacco. The authors should explain why these variables are omitted, and how their inclusion affects the results or their reason for excluding these variables.</p> <p>The authors suggest that the effect of lung cancer is greater among women than men, but the confidence intervals overlap. Without further exploration, their claims seem unfounded. Have the authors considered how gender variations may depend on age, alcohol consumption or other factors?</p> <p>In summary, this is an important study, and it would be useful to expand the results to help understand how the effect of smoking on</p>
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	cancer may depend on other factors. At present, most of the studies of the relationship of smoking to cancers are for high income nations, and it would be useful to know how the effects might differ for a middle income nation. The Discussion section could be expanded to discuss if there are distinctions in the effect of smoking in high income nations relative to low and middle income nations.
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<b>REVIEWER</b>	Gulnar Azevedo e Silva Departamento de Epidemiologia, Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro, Brasil
<b>REVIEW RETURNED</b>	30-Oct-2013

<b>GENERAL COMMENTS</b>	<p>In a new version, some considerations might be reviewed and informed by the authors based in the following points.</p> <p><b>Methods</b></p> <p>1. Source of data: necessary to describe what kind of hospitals are included is this information System (“secondary data from Cancer Hospital Registries (CHR), provided by the Brazilian NCI through the Integrator CHR System”) and how is their distribution in these 24 Brazilian states (are there equal proportions between the Brazilian regions?).</p> <p>2. The authors mention that they have “adopted a case-case study design” where cancer cases from 32 sites were compared to cases of non-melanoma skin cancer. This doesn’t configure a case-case study. This type of approach may be more characterized as a case-control study based on secondary which as cases, they included patients diagnosed with the 32 sites of cancer and as controls to cases of non-melanoma skin cancer.</p> <p>3. The information about tobacco use must be described. How was the exposure considered (ever/never? Ever means that the patient was still smoking at the moment of the diagnosis?)</p> <p><b>Discussion</b></p> <p>1. The composition of control group should be addressed as one limitation. The authors used as controls cases of non-melanoma skin cancer that may be different from cases considering skin color, ethnic origin and geographical precedence (once fair skin population in Brazil is concentrated in the South region).</p> <p>2. Considering the limitations of the study the results should be regarded with caution and the authors should state clearly that condition.</p>
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<b>REVIEWER</b>	Vera Luiza da Costa e Silva Center for Studies on Tobacco and Health National Public Health School Oswaldo Cruz Foundation Brazil
<b>REVIEW RETURNED</b>	30-Oct-2013

<b>GENERAL COMMENTS</b>	<p>This case-control study aimed to estimate the magnitude of association and the etiologic fraction (EF) attributable to smoking in the development of different types of cancers in Brazil. The study population consists of 204 131 cancer cases relating to 30 topographies and 26 971 cases of non-melanoma skin</p> <p>The study was well conducted and the manuscript was well prepared. The issue approached in the study is an important for</p>
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	<p>Brazil .</p> <p>Some minor comments:</p> <p>Introduction :</p> <p>Page 4 line 32 a 39-2 paragraph – There are more recent estimates of attributable mortality in the following references.</p> <p>The Brazil SimSmoke policy simulation model: the effect of strong tobacco control policies on smoking prevalence and smoking-attributable deaths in a middle income nation.</p> <p>Levy D, de Almeida LM, Szklo A. PLoS Med. 2012;9(11):e1001336. doi: 10.1371/journal.pmed.1001336. Epub 2012 Nov 6.</p> <p>Cancer mortality attributable to tobacco by selected countries based on the WHO Global Report.</p> <p>Katanoda K, Yako-Suketomo H. Jpn J Clin Oncol. 2012 Sep;42(9):866. doi: 10.1093/jjco/hys134. No abstract available.</p> <p>Mortality attributable to tobacco by selected countries based on the WHO Global Report.</p> <p>Katanoda K, Yako-Suketomo H. Jpn J Clin Oncol. 2012 Jun;42(6):561-2. doi: 10.1093/jjco/hys083.</p> <p>Methods</p> <p>The author should insert references to the formula used in calculating the attributable mortality using Odds Ratio (OR) as a measure of association instead of Relative Risk (RR) .</p> <p>We suggest authors succinctly describe the instrument for data collection used in the Hospitalar Cancer Registry of Brazil .</p> <p>Results</p> <p>We recommend authors Include the number and percentage of cases and controls with information ignored for categories analyzed in table 2</p> <p>Authors should note that the percentage of smokers among the controls is considerably higher than the general population of Brazil, suggesting some selection bias. Somehow this data suggests that smoking influences patients hospitalization on selected as controls.</p> <p>Discussion :</p> <p>The author should mention the limitations of case-control studies for estimates of relative risk (to use odds ratio as an estimator of relative risk)</p>
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### VERSION 1 – AUTHOR RESPONSE

#### REVIEWER DAVID LEVY

The paper should end with a summary paragraph, instead of just the limitations. What is now the last sentence is poorly worded

Was included "This study confirms a high risk of developing cancer of the hypopharynx, bronchi and lung, larynx, hypopharynx, oropharynx and oral cavity, esophagus and bladder cancer among smokers and establishes the EF attributable to smoking in the development of different types of cancer in Brazil"

The authors should explain how tobacco and alcohol consumption were measured.

Was included "The exposure variable was the report of habitual tobacco use and its derivatives at the time of hospital enrollment, categorized as yes or not." and "...current alcohol consumption (more than three times per week, independent of amount consumed)"

It was not clear how the non-melanoma skin cancers were used as a case control. please explain.

Was included "as they are not related to tobacco use and information were available in the database."

The authors should explain why these variables are omitted, and how their inclusion affects the results or their reason for excluding these variables.

Was included "In order to control for confounding factors or interactions, an adjusted analysis was performed considering age, gender and alcohol consumption, factors associated with both exposure and outcome. Variables completely outside the system of interest and variables only associated with the exposure or outcome were not included in the final model in order to avoid unnecessary regression adjustment and improve precision of estimators."

The authors suggest that the effect of lung cancer is greater among women than men, but the confidence intervals overlap. Without further exploration, their claims seem unfounded. Have the authors considered how gender variations may depend on age, alcohol consumption or other factors? We performed modifications in the text in order to better describe these results "Stratification of the risk of developing cancer by gender showed that in men the highest risk were observed in the piriform sinus, bronchi and lung, hypopharynx, oropharynx, and larynx (Table 4). On the other hand, for women, the highest risk were for larynx, piriform sinus, bronchi and lung, oropharynx and oral cavity (Table 5)".

The Discussion section could be expanded to discuss if there are distinctions in the effect of smoking in high income nations relative to low and middle income nations.

Was included "...the magnitude of the risk varies between studies according to race and income nation." and "In Brazil, a survey conducted before the beginning of this study, covering urban and rural areas, estimated the smoking prevalence at 34.8% (43.3% among men and 27.0% among women). Surveys carried out in subsequent periods have shown lower prevalence, which is consistent with the figures obtained among controls in the present study"

REVIEWER GULNAR AZEVEDO E SILVA

Source of data: necessary to describe what kind of hospitals are included is this information System ("secondary data from Cancer Hospital Registries (CHR), provided by the Brazilian NCI through the Integrator CHR System") and how is their distribution in these 24 Brazilian states (are there equal proportions between the Brazilian regions?).

Was included "seen in 168 reference centers for cancer treatment, accredited by the Brazilian Government, in 24 Brazilian states"

The authors mention that they have "adopted a case-case study design" where cancer cases from 32 sites were compared to cases of non-melanoma skin cancer. This doesn't configure a case-case study. This type of approach may be more characterized as a case-control study based on secondary which as cases, they included patients diagnosed with the 32 sites of cancer and as controls to cases of non-melanoma skin cancer.

The type of study was changed to "case-control"

The information about tobacco use must be described. How was the exposure considered (ever/never? Ever means that the patient was still smoking at the moment of the diagnosis?)

Was included "The exposure variable was the report of habitual tobacco use and its derivatives at the time of hospital enrollment, categorized as yes or not." and "...current alcohol consumption (more than three times per week, independent of amount consumed)"

The composition of control group should be addressed as one limitation. The authors used as controls cases of non-melanoma skin cancer that may be different from cases considering skin color, ethnic origin and geographical precedence (once fair skin population in Brazil is concentrated in the South region).

Was included "Another limitation is that we used as control non-melanoma skin cancers that may have different behaviors in cases and controls taking into consideration skin color, ethnic origin and geographical precedence"

Considering the limitations of the study the results should be regarded with caution and the authors should state clearly that condition.

The paragraph concerning limitations of the study was reformulated.

REVIEWER VERA LUIZA DA COSTA E SILVA

Page 4 line 32 a 39-2 paragraph – There are more recent estimates of attributable mortality in the following references.

The following references were added:

ü Levy D, Almeida LM, Szklo A. The Brazil SimSmoke Policy Simulation Model: The effect of strong tobacco control policies on smoking prevalence and smoking-attributable deaths in a middle income nation. *PLoS Med* 2012; 9(11): e1001336. doi: 10.1371/journal.pmed.1001336.

ü Almeida L, Szklo A, Sampaio M, et al. Global adult tobacco survey data as a tool to monitor the WHO Framework Convention on Tobacco Control (WHO FCTC) Implementation: The Brazilian Case. *Int J Environ Res Public Health* 2012; 9(7):2520-36. doi: 10.3390/ijerph9072520.

The author should insert references to the formula used in calculating the attributable mortality using Odds Ratio (OR) as a measure of association instead of Relative Risk (RR)

The author should mention the limitations of case-control studies for estimates of relative risk (to use odds ratio as an estimator of relative risk)

This reference was included: Rosenthal. JA. (1996) Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21:37-59

Was included "Once relative risk (RR) was replaced by OR the computing formula will approximate the excess fraction only insofar as the odds ratio approximates the relative risk".

We suggest authors succinctly describe the instrument for data collection used in the Hospitalar Cancer Registry of Brazil

Was included "The data set collected in each case includes variables such as demographics, tumor characteristics (cancer type, extent, location, etc.), initial treatments. and history of current alcohol consumption (more than three times per week, independent of amount consumed). The exposure variable was the report of habitual tobacco use and its derivatives at the time of hospital enrollment, categorized as yes or not".

We recommend authors include the number and percentage of cases and controls with information ignored for categories analyzed in table 2

Was included in Material and Methods section: "Percentages were calculated based on valid data (i.e., missing data were excluded)".

Authors should note that the percentage of smokers among the controls is considerably higher than the general population of Brazil, suggesting some selection bias. Somehow this data suggests that smoking influences patients hospitalization on selected as controls.

Was included: "In Brazil, a survey conducted before the beginning of this study, covering urban and rural areas, estimated the smoking prevalence at 34.8% (43.3% among men and 27.0% among women). Surveys carried out in subsequent periods have shown lower prevalences, which is consistent with the figures obtained among controls in the present study".

## VERSION 2 – REVIEW

<b>REVIEWER</b>	David Levy Georgetown University, USA
<b>REVIEW RETURNED</b>	15-Dec-2013

<b>GENERAL COMMENTS</b>	<p>In the second paragraph, it is written&lt;"In Brazil, according to data released by the Brazilian National Cancer Institute (INCA), tobacco use kills about 200 000 people per year." Please provide a reference</p> <p>In describing the measure of tobacco consumption, the authors describe it as "yes or not" rather than "yes or no"</p>
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## VERSION 2 – AUTHOR RESPONSE

The following changes were performed in the text:

1. competing interests - 'None declared': None
2. A reference was provided to the sentence <"In Brazil, according to data released by the Brazilian National Cancer Institute (INCA), tobacco use kills about 200 000 people per year."
3. In describing the measure of tobacco consumption, "yes or not" was changed to "yes or no".