eLife reviews

Manuscript title: Lung cancer incidence decreases with elevation: evidence for oxygen as an inhaled carcinogen

Manuscript tracking number: 03-07-2014-RA-eLife-03894

Decision letter sent to authors on 29 August 2014.

Dear Dr. Simeonov,

Thank you for choosing to send your work entitled "Lung cancer incidence decreases with elevation: evidence for oxygen as an inhaled carcinogen" for consideration at eLife. Your full submission has been evaluated by a Senior editor, a reviewing editor and 3 peer reviewers, and the decision was reached after discussions between the reviewers. We regret to inform you that your work will not be considered further for publication.

In brief, we were concerned about the bold statement for a causal effect for oxygen in lung carcinogenesis on the basis of an ecological investigation, albeit an elegant one. Although you attempted to control for as many confounders as you could there are limits on what can be attained via this type of investigation. We recommend that you revise along the lines indicated in the reviewers' critiques and submit your paper to a specialty journal in the domain of cancer epidemiology and prevention.

eLife is highly selective, which means that the majority of submissions are rejected, but we thank you for sending your work for review and we hope you will submit toeLife again in the future.

Please note that we ask permission from reviewers to pass their referee report and identity to another journal. Such transfers will only be undertaken in response to an explicit request by the corresponding author. We have established relationships to share referee reports and identities with Biology Open (http://bio.biologists.org), BMC Biology (http://www.biomedcentral.com/bmcbiol) and the more specialized BMC-series journals (http://www.biomedcentral.com/authors/bmcseries#journallist), the four EMBO scientific publications (http://www.embo.org/publications.html), and the PLOS journals (http://www.plos.org/publications/journals/). This process can potentially help authors to avoid lengthy re-review and reduce the burden on peer reviewers. However, the editors of these journals may decide to consult additional referees on a case-by-case basis. Please also note that reviewers may not provide us with permission to share their identity with another journal.

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Best wishes,

Randy Schekman
Editor-in-Chief, eLife

Fiona Watt
Deputy Editor, eLife

Detlef Weigel
Deputy Editor, eLife

Reviewer #1

This research investigated the ecologic relationship between elevation and lung cancer incidence in the Western U.S.; strong inverse associations were reported and atmospheric oxygen was presented as the underlying biologic hypothesis. The statistical framework of this paper was well-developed and thorough. However, the authors should consider tempering their conclusions on oxygen as an inhaled carcinogen throughout the tone of the article since in this ecological analysis, oxygen was not measured. The comments below pertain mostly to clarifying concepts and methodology in epidemiology as an ecological study design was employed.

Abstract

1)Line 12 'concrete epidemiological support' for oxygen-driven tumorigenesis is an overstatement based solely on the results of this study.

Introduction

1)Page 3: Line 44-46 The word "control" has a very precise meaning in epidemiology, and the term "negative control" is not used. The use of this terminology is unclear.

2)Page 3: Line 47 to 54

The strategy underlying the literature review is unclear. Four studies are cited (Amsel 1982; Hayes 2010; Cohen 1995; van Pelt 2003). However, Hayes 2010 is a review article that the authors use to represent 7 additional studies; Cohen 1995 and Amsel 1982 is among the 7 'additional studies.' The authors should consider reviewing the original studies.

Also, the authors cite the two articles by Cohen 1995 and van Pelt 2003. For thoroughness in summarizing the literature, the authors should present the original findings by Cohen 1995, the reassessment of the data by van Pelt 2003, as well as the counter-argument presented by the original authors in Cohen, 2004.

In addition, studies conducted by Mason and Miller 1974, Hart 2013, Hart 2011 and Ezzati 2012 may be of relevance to this review.

3)Page 3: Line 57 It is unclear what the authors mean by "extraneous variation."

Methods

1)The Methods are not presented clearly. Consider reorganizing the Methods in the following sections:
A.Study population i.e. County filtering
B.Data collection and preparation
C.Exposure of interest i.e. Population-weighted mean elevation
D.Outcome of interest i.e .Cancer incidence
E.Confounders/Covariates

2)Page 9-10: Line 232-233 The use of the term outliers seems inappropriate - do the authors mean that they initially considered these counties but for these counties exposure/outcome values were outliers and thus excluded? This should be explained.

3)Why was sex not included as a covariate for colorectal cancer?

4)Page 11: Line 270-271 It is unclear why a one-tailed t-test was used; please justify? Furthermore, in Table 2 a one-tailed test was used and in Figure 2 (Figure supplement 1) a 2-tailed p-value is reported; please justify.
a. In Table 2: It is unclear which model the one-tailed p-value is referring to.

5)Page 12: Line 307 It may be more appropriate to refer to this as uncontrolled confounding, which is the standard term used in epidemiology

6)Page 13: Line 326 For collection periods that spanned multiple years - were covariates averaged over time?

7)Page 13: Line 335-337
a.Why do the N's differ for other cancers for each site in Table 1?
b.Dividing by half to obtain this 'other cancer variable' for sex-specific analysis seems inappropriate; you should obtain sex-specific incidences to calculate this variable.

Discussion

1)Page 9 Line 184-185 It is unclear which result the authors are referring to in this statement

2)Page 9 Paragraph on Confounding effect of elevation
a.This paragraph should be moved before Limitations and future directions
b.This paragraph is confusing. It tries to make varying points on elevation as a possible confounder in other environmental risk factor-lung cancer relationship. But additionally adds that lung cancer should not be used as a proxy for smoking. These are distinct points that should be separated.
c.Page 9 Line 209-210 This sentence is an overstatement of the results of this study. The authors cannot 'wholly attribute' the findings of previous papers on elevation.

Minor Comments

Introduction

1)Page 3: Line 63-64 "We compared elevation's association with lung cancer versus its association with breast, colon and prostate cancer for oxygen-independent elevation effects." This sentence is a bit confusing consider rewording.

Methods

1)Page 10: Line 251 Consider specifying that it is the exposure that has been converted to z-scores

2)Page 11: What are the environmental variables? Only 5 are listed in Table 1 (Should particulate and radon should also be labeled 'env' in Table 1?)

3)Page 13: Line 327 Define FIPS

4)Page 13-14: Line 339-344 Provide references for all surveys

Results

1)Page 4: Line 86-87 Incomplete sentence

Reviewer #2

Overall comments
I thought this to be a well-written paper that examines the influence of a novel risk factor on the incidence of lung cancer. Though well written the study design (cross-sectional), despite their assertions to the contrary, is not well suited to investigating the possible role of elevation

as an etiological factor for lung cancer. The methods do not adequately describe the types of data used in the analyses including where the data are drawn from, nor the other variables that were incorporated into the analyses (smoking, radon, etc). I feel strongly this paper should be rejected. This type of study design should not be applied to attempt to make a determination about causality for a novel risk factor.

More specific comments:
Abstract:
1. Bearing in mind most individuals interested in the paper read only the abstract (and not the full paper) the abstract should clearly describe the methods used. This abstract make no mention of the data used to derive the incidence rates, nor the time frame. These mention that there is a 25.2% decrease in lung cancer incidence but the author has not way of determine what change in altitude produces this decrease in risk. No mention is made of the other environmental factors used in the analyses, nor how they were collected. Given that smoking is estimated to cause ~ 90% of lung cancers this is fairly important to address. There is no way of telling whether risk estimates were adjusted for differences in age - which is critical. The authors indicate their findings in the abstract before telling the reader what methods were used. This is akin to telling a reader the ending of the story at the beginning of a book - it does not follow the standard scientific approach.
Introduction
1. The strengths and limitations of the previous epidemiological studies are not well described.
2. Some comment is made on the inverse associations between radon and lung cancer, with the statement that Van Pelt attributes some of this correlation to the confounding influence of elevation- dependent oxygen. While this may be true, this does not mean that Van Pelt was correct, and a number of others have implicated ecological fallacy as a driver of inverse associations between radon and lung cancer rates at a county level. So much so, that this example is taught in many introductory epidemiological. The authors need to acknowledge this.
3. The authors skip from an Introductory section straight to the Result section. There is no methods and materials section. Therefore the reader is never really provided the details needed to understand the nature of the data used in this study. What data were used to derive cancer incidence rates? How complete were they? What about smoking, radon, and other risk factors like age and sex? What calendar period was involved? Air pollution is a recognized risk factor for lung cancer, was some attempt made to model these effects which surely vary by altitude?
4. Results section, the authors indicate they dropped from 414 counties to 260 counties after quality control. The reader needs to be told what these quality control efforts entailed. The authors described that they avoided redundant factors and covariates but the reader is never told what the list of covariates were, nor how redundant factors were dropped.

Discussion
1. In my view, there is no way that ecological fallacy can be dismissed with this study design.

Materials and methods

1. It is not common, nor in my view desirable, to describe the methods after the results and discussion. In all my years of reviewing papers, I have never seen this
2. Page 10, some mention is made of the risk factors considered, but no attempt to explain where the data were obtained from.
3. Unclear how stable the smoking rates were for the areas given no description of the denominators in the BRFSS and NHIS data
4. No description of the quality of radon data, just a reference is provided.

Figure 4:

1. it would be worth adjusting comparisons of lung cancer incidence by sex. It is interesting to note that for UTAH, a state of low smoking prevalence due to large number of Mormons, there is virtually no association between elevation and lung cancer risk. The figure needs to describe adjustment factors included.

Reviewer #3

This is a very important and high quality epidemiological paper and deserves publication.

The inclusion of only the highest altitude (Western US) counties puzzles me. The larger range of altitude obtained by including counties at all altitudes would seem to make for a greater chance of finding an oxygen association. The overt choice to include counties only within a narrow range of altitudes (i.e., higher altitudes) needs to be explained. The 2003 study by Van Pelt clearly showed the inverse relation between lung cancer and altitude for 1601 counties.

The abstract claims a "25.2 point decrease". The paper uses the term "point" several times. "Point" is not a valid unit of measure. It should be clearly defined in the context of cancer incidence.

At line 184: "Notably, we found that elevation's large and unanticipated impact on lung cancer had confounded reported lung cancer associations [23, 24]." This effect was anticipated by Van Pelt (your ref 25) who reached almost identical conclusions.

Minor Comments

at line 86-87 there needs to be a grammar adjustment.