EMBARGOED until January 13th 2015: 7 am EDT; 12 midday UK time

Your Peers, Your Science
Academic Publishing is Evolving

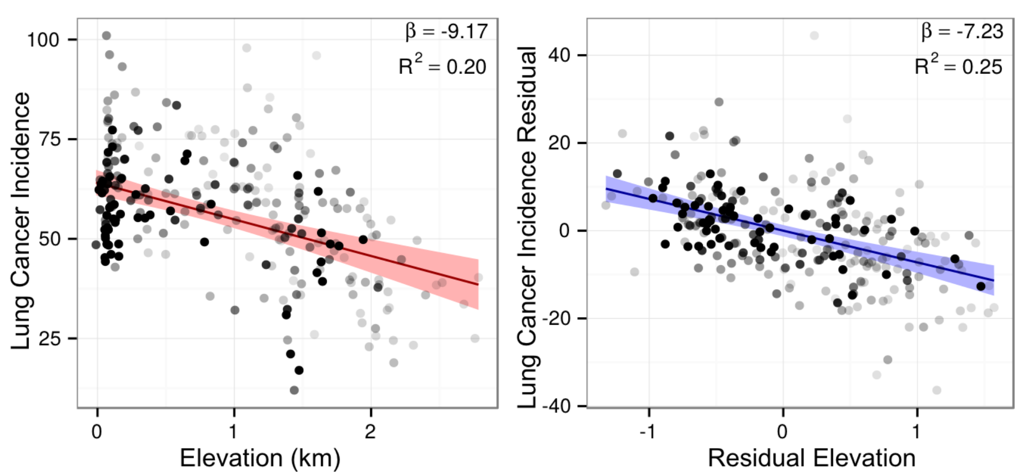
Can inhaled oxygen cause cancer?
Lung cancer rates fall dramatically with increasing elevation in the Western U.S.

The ancient physician/alchemist, Paracelsus, said: "The dose makes the poison." According to a new study published in *PeerJ*, even oxygen may fall prey to the above adage. While essential to human life, aspects of oxygen metabolism may promote cancer. Capitalizing on the inverse relationship of oxygen concentration with elevation, researchers found lower rates of lung cancer at higher elevations, a trend that did not extend to non-respiratory cancers, suggesting that carcinogen exposure occurs via inhalation.

In the United States, lung cancer is responsible for 27% of all cancer deaths, claiming an estimated 160,000 lives per year [1]. While smoking is linked to as many as 90% of lung cancer cases, this new study suggests that atmospheric oxygen may play a role in lung carcinogenesis.

Oxygen is highly reactive and even when it is carefully and quickly consumed by our cells, it results in reactive oxygen species (ROS) which can lead to cellular damage and mutation. While oxygen composes 21% of the overall atmosphere, lower pressure at higher elevations results in less inhaled oxygen - an effect which notoriously frustrates athletes at high altitudes. For example, across United States counties, elevation differences account for a 34.9% decrease in oxygen from Imperial County, California (-11 m) to San Juan County, Colorado (3473 m).

To investigate whether inhaled oxygen could be a human carcinogen, two researchers compared cancer incidence rates across counties of the elevation-varying Western US. They found that as county elevation increased, lung cancer incidence decreased. The effect was dramatic with incidence decreasing by 7.23 cases per 100,000 individuals for every 1,000 meter (3,281 feet) rise in elevation, equating to approximately 13% of the mean lung cancer incidence of 56.8 cases per 100,000 individuals. A variety of statistical techniques attested that the association was not due to chance.



Caption: *In the left hand panel, lung cancer incidence is plotted against elevation for Western US counties. Darker counties have higher populations and thus lower observational errors. The right hand panel shows the association when accounting for additional factors, such as smoking and education.*

The observed association does not prove that oxygen causes lung cancer. The study looked at groups of people rather than individuals and many variables in addition to oxygen levels are correlated with elevation. Accordingly the researchers performed a thorough analysis to investigate confounding potentials. Their model accounted for important risk and demographic variables, such as smoking prevalence and education. The association was consistent across population subgroups, states, and models that included a range of additional factors.

The researchers also evaluated breast, colorectal, and prostate cancer: the remaining three most common cancers in the United States. Elevation's association with these non-respiratory cancers was either weak or absent, supporting the hypothesis of an inhaled risk factor. Furthermore, environmental correlates of elevation, such as sun exposure and fine particulate matter (a measure of pollution), produced vastly inferior predictions of lung cancer incidence compared to elevation itself.

Two past epidemiological reports, looking at elevation as a confounder, proposed that elevation-dependent oxygen variation was responsible for lower cancer mortality at high elevation [2, 3]. Unlike the two previous studies, the current study was specifically designed to assess the effect of elevation and benefited from a recent proliferation of high-quality county-level data. In total, the study relied on over 30 variables with sufficient coverage and precision to enable the inclusion of ~250 Western US counties. Using high resolution census data, the researchers calculated elevation values that reflected population dispersion within each county, thereby more accurately estimating the atmospheric exposure of each county's populace. All resources were public, underscoring the importance of open data for future scientific discovery.

The research was published today in the peer-reviewed open access journal *PeerJ* (http://peerj.com). Both authors are strong advocates for transparent science and open-access publishing and in addition to the full release of the dataset and analysis, the peer review history is also being made available by *PeerJ*---a nascent practice that is gaining popularity.

The authors hope additional researchers will focus their efforts on oxygen's role in human carcinogenesis. Analysis of diverse regions and individual-level datasets would contribute further epidemiological evidence. Ultimately, completely-controlled, experimental investigation using models of carcinogenesis will be critical to our understanding of the phenomenon.

If future analyses confirm oxygen-driven tumorigenesis, the medical implications could be large. For example, as the authors explain, “were the entire United States situated at the elevation of San Juan County, CO (3473 m), we estimate 65,496 fewer new lung cancer cases would arise per year." While the authors do not expect or recommend individuals to relocate based on this finding, identifying a universal and major risk factor could provide new insights into lung cancer etiology. From these insights, better treatments and preventative measures may arise.

Citations

[1] Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics, 2014. CA: a cancer journal for clinicians. doi:10.3322/caac.21208

[2] Weinberg CR, Brown KG, Hoel DG (1987) Altitude, radiation, and mortality from cancer and heart disease. Radiation Research. doi:10.2307/3577265

[3] Van Pelt WR (2003) Epidemiological associations among lung cancer, radon exposure and elevation above sea level. Health Physics. pubmed:13678279

###

EMBARGOED until January 13th 2015: 7 am EST; 12 midday UK time (i.e. the date of publication)

PDF of this Press Release:
http://static.peerj.com/pressReleases/2015/PressReleasePeerJ_Simeonov.pdf

Link to the Press Preview of the Original Article (this link should only be used BEFORE the embargo ends): http://static.peerj.com/press/previews/2015/01/705.pdf (note: this is an author proof and so may change slightly before publication)

Link to the Published Version of the article (quote this link in your story – the link will ONLY work **after** the embargo lifts): https://peerj.com/articles/705 - your readers will be able to **freely** access this article at this URL.

Citation to the article: Simeonov KP, Himmelstein DS. (2015) Lung cancer incidence decreases with elevation: evidence for oxygen as an inhaled carcinogen. PeerJ 2:e705
http://dx.doi.org/10.7717/peerj.705

###

About PeerJ

PeerJ is an Open Access publisher of peer reviewed articles, which offers researchers a lifetime publication plan, for a single low price, providing them with the ability to openly publish all future articles for free. PeerJ is based in San Francisco, CA and London, UK and can be accessed at https://peerj.com/. PeerJ's mission is to help the world efficiently publish its knowledge.

All works published in PeerJ are Open Access and published using a Creative Commons license (CC-BY 4.0). Everything is immediately available—to read, download, redistribute, include in databases and otherwise use—without cost to anyone, anywhere, subject only to the condition that the original authors and source are properly attributed.

PeerJ has an Editorial Board of almost 1,000 respected academics, including 5 Nobel Laureates. PeerJ was the recipient of the 2013 ALPSP Award for Publishing Innovation.

PeerJ Media Resources (including logos) can be found at: https://peerj.com/about/press/

###

Media Contacts

Note: If you would like to join the PeerJ Press Release list, visit: http://bit.ly/PressList

For the authors: Kamen Simeonov, Perelman School of Medicine, University of Pennsylvania. kamen.simeonov@gmail.com, Tel: +1 304 685 3206

F*or PeerJ:* email: press@peerj.com , https://peerj.com/about/press/

###

Abstract (from the article):

The level of atmospheric oxygen, a driver of free radical damage and tumorigenesis, decreases sharply with rising elevation. To understand whether ambient oxygen plays a role in human carcinogenesis, we characterized age-adjusted cancer incidence (compiled by the National Cancer Institute from 2005 to 2009) across counties of the elevation-varying Western United States and compared trends displayed by respiratory cancer (lung) and non-respiratory cancers (breast, colorectal, and prostate). To adjust for important demographic and cancer-risk factors, 8–12 covariates were considered for each cancer. We produced regression models that captured known risks. Models demonstrated that elevation is strongly, negatively associated with lung cancer incidence (p < 10^−16), but not with the incidence of non-respiratory cancers. For every 1,000 m rise in elevation, lung cancer incidence decreased by 7.23 99% CI [5.18–9.29] cases per 100,000 individuals, equivalent to 12.7% of the mean incidence, 56.8. As a predictor of lung cancer incidence, elevation was second only to smoking prevalence in terms of significance and effect size. Furthermore, no evidence of ecological fallacy or of confounding arising from evaluated factors was detected: the lung cancer association was robust to varying regression models, county stratification, and population subgrouping; additionally seven environmental correlates of elevation, such as exposure to sunlight and fine particulate matter, could not capture the association. Overall, our findings suggest the presence of an inhaled carcinogen inherently and inversely tied to elevation, offering epidemiological support for oxygen-driven tumorigenesis. Finally, highlighting the need to consider elevation in studies of lung cancer, we demonstrated that previously reported inverse lung cancer associations with radon and UVB became insignificant after accounting for elevation.