Reviewer's report

Title: Spatial analysis of bladder, kidney, and pancreatic cancer on upper Cape Cod: An application of generalized additive models to case-control data

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Reviewer: Christopher Paciorek

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Overview

This paper uses geocoded addresses in a case-control study to assess the presence of spatial patterns in cancers on Cape Cod, with the ultimate goal of understanding potential exposures that may lead to cancer. The authors use spatial smoothing within a generalized additive modeling framework.

I found this to be a careful analysis. I liked the use of point-level data, which avoids issues with aggregated data that may obscure patterns and that prevents use of individual-level covariates. I also liked the consideration of latency, though I am concerned about the specific statistical approach taken for this issue. Otherwise, the statistical methods are appropriate and up-to-date.

As I am a statistician, I can't comment on the degree to which the substantive questions are of interest in environmental health, but it seems to me that the methods used make this analysis better than area-based disease mapping studies. I do not know if the cancers and exposures under consideration or the results obtained are of general interest in the field.

Major compulsory revisions

1.) The analyses use multiple locations for individuals who move (p. 5 talks about 'case locations' and p. 9 about multiple residences for the same individual but this is not fully clarified until p. 15 in the discussion), thereby having more 'observations' than individuals. This does not seem well justified and the authors make brief reference to the possibility of bias at the bottom of p. 9, but I felt that the statistical issues were not sufficiently addressed. For one thing, the outcomes are no longer independent. For another, individuals who move a lot are weighted more heavily than those who do not move, with weight equal to the number of residences. Accounting for residential history is a difficult problem, but creating replicates of an outcome to assign to each address does not see well-founded and needs further justification. What is the statistical underpinning of this? At the very least, I would like to see it stated clearly in the methods that the approach replicates each outcome with the same covariates but different residence for each residence.

The authors note that for bladder cancer, in using longest residence, the optimal span is much larger than when using multiple residences, raising concern that
the multiple residence results (which have a smaller span) may be biased away from the null. For the other analyses, it appears the sample size is sufficient only when using multiple residences; if the maximum residence approach does not have sufficient sample size, I am wary about analyses of the same data that rely on the multiple residence approach, which seems to artificially inflate the sample size. Does going from 37 cases to 49 case locations really make the analysis feasible with the larger size (49) but not the smaller (37)?

2.) p. 8: It seems to me that since the span selection is part of the model fitting, in doing the permutation test, one should estimate the span from the data for each of the 999 permutations. Otherwise one conditions on the the amount of smoothing selected based on the data, treating that as the correct value, when under the null, it surely is not. Could the authors either further explain their logic or consider estimating the span for each permutation? Is this a computational limitation?

Minor essential revisions

1.) Figures: The first plot (1a) shows the MMR as a separate 'town', but later plots do not indicate the MMR. I would like to see the MMR indicated on all the plots, since proximity to the MMR is a key exposure hypothesis.


3.) p. 4: Why were only cases from 1983-1986 used?

4.) p. 6: I wouldn't call $x_1$ and $x_2$ 'longitude' and 'latitude' since they are projected coordinates.

5.) p. 7: How was the number of parameters in the AIC calculation determined - is this based on an estimated degrees of freedom for the smooth term?

6.) p. 8: Strictly speaking, the permutation test is not 'with and without the smooth term' since the smooth term is in the permutation-based model fits, no? I would instead say something like 'with and without spatial structure'.

7.) p. 11: I would point out that the hotspot for kidney cancer with span 0.15 in the MMR is surely spurious as there are no addresses within the hotspot.

Discretionary revisions

1.) Figures: To my mind, given that there is a null value, I would choose a color scheme with white as an odds ratio of 1 and blue and red for values less than and greater than one. As it is, the values near zero are at an intermediate color and one has to go back and forth from the legend to the map to determine which areas are near the null value. Plotting as log odds may also be an improvement to achieve symmetry of odds ratios larger than and less than one.

2.) p. 8-9: The local permutation test does not account for multiple testing, so I'm concerned that too many areas may be detected. On the other hand, by virtue of
doing smoothing as the initial modeling step, there should be some protection against false positives (see refs below in the Bayesian context, as this is somewhat analogous to what is being done with the smoothing in the manuscript, thereby borrowing strength spatially). Is the false discovery rate approach a possibility here to be more sure about protecting against false positives? There is now a literature on using FDR techniques in the face of spatial correlation (including a paper I was involved in: Ventura et al. 2004, J of Climate 17:4343-4356). Another possibility is to use a cluster detection type algorithm such as SatScan to see if the hotspots seem robust (though I haven't looked to see if SatScan is appropriate for case-control data). At the least I'd like to see some mention of the possibility of a multiple testing problem or why the authors think this is not an issue (perhaps based on the effects of smoothing I refer to above).

3.) p. 14: Are there any mechanisms for the ground water plumes to be related to bladder cancer, such as known carcinogens in the Cape Cod plumes?

References on multiple testing in a Bayesian context:
Berry, D. A. and Hochberg, Y. (1999), "Bayesian Perspectives on Multiple Comparisons,"
Journal of Statistical Planning and Inference, 82, 215227.
(material is also probably in the new 2008 edition, but haven't looked up the page)

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests.