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The Authors Respond

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To the Editor:

We appreciate the opportunity to clarify the conclusions of our study and address the criticisms raised by Kinlen and Peto.[1]

Although the studies highlighted by Kinlen and Peto describe situations that they refer to as "national in scope", none of these adopted the region-wide analysis we recommend. Rather, these studies have focused on rural areas with small populations experiencing extreme levels of inward-migration that had been selected from larger regions/nation states. To definitively avoid bias, our study points to the need for comparisons of areas with varying levels of inward-migration, either by comparing all areas within an entire region/nation state or random subsets thereof.[2]

Kinlen and Peto report that the work introducing the population mixing hypothesis originated from the observation of a "cluster" of childhood leukemia cases around the Sellafield nuclear complex and that "subsequent studies were designed to test [this hypothesis]".[3] Subsequent studies investigated similar area types, i.e. those that were rural, with a low initial population density, and that subsequently experienced a large population influx. Our analysis of simulated and observational data demonstrated that such non-random sampling of areas is prone to substantial bias where selection invokes any aspect of the outcome. It is not possible for us to ascertain whether apparent clusters'of childhood leukemia led to the initiation of these studies but if these studies were in any way informed by such knowledge they would experience bias due to conditioning on the outcome. We therefore remain confident in our assertion that the risk of selection bias can only be overcome by either analyzing all areas within a region or nation, or a random sample thereof, and advise that the existing evidence be revisited accordingly. Kinlen and Peto appear to agree in their comment that our study "confirms the trivial fact that 'statistical significance' (as indicated by p-values) is inflated

when applied to high local cancer rates selected post hoc", but apparently do not recognize this as the general risk with a non-random selection strategy.

We appreciate Kinlen and Peto's illumination on the origins of the population mixing hypothesis and agree that some readers may have been interested in the role of the Sellafield nuclear complex in the "striking local influxes" in the "isolated village of Seascale in NW England". We are however concerned about the scientific value of discussing the specific details of any study that suffers the selection biases we describe and fear it may only reinforce the confusion about what is genuinely extreme versus what is statistically unsurprising. For this reason, we trust it is obvious why we would not seek to draw attention to the "world's most sharply defined localized excess of childhood leukemia in the small Nevada desert town of Fallon." [4]

References

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4. Kinlen L, Doll R. Population mixing and childhood leukaemia: Fallon and other US clusters. Br J Cancer. 2004;91:1-3.