

## Re: Cancer Risk in Adult Residents Near Nuclear Power Plants in Korea - A Cohort Study of 1992-2010

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### To the Editor:

We took a great interest in reading the paper that analyzed cancer risks of residents living near nuclear power plants (NPPs) in South Korea (the KREEC-R Study) (1). This is the first and the only prospective cohort study on this topic in Korea, and even one of the few worldwide.

The KREEC-R group concluded that there was no epidemiological evidence to support an increased cancer risk due to radiation from NPPs, and suggested that “radiological study results or surveillance data of radiation doses around NPPs could be well documented for risk estimation of radio-inducible cancers, instead of long-term epidemiological study results.”

However, before reaching such conclusions, we suggest the following limitations of the study should be addressed first.

First, the control groups of the study are not comparable to the exposed group in many ways, especially in socioeconomic status. According to the detailed technical report of this study (2), at least 10% of the male participants in the exposed and control groups did not graduate elementary school, while the national average figure for males older than 19 years is only 3.3% (derived from the 2,000 census). In addition, 28.7% of the exposed, 20.0% of the intermediate control ('control-1'), and 9.4% of the remote control ('control-2') group had a college degree or higher, while 28.1% of male adults in the nation did so. Overall, the cohort members were in lower socioeconomic positions than the national average, and this gap was especially large for the remote control group. It is well known that a lower socioeconomic position is associated with an increased cancer risk (3, 4). If the baseline cancer risk of the control group was higher than that of the general population as well as that of the exposed group, then the relative risk of the exposed group with reference to the control group could have been underestimated.

Second, if the key independent variable of this study was the

time living near NPPs as a proxy for cumulative radiation exposure, the exposure time (time at risk) and eligibility criteria should have been defined differently. Before the enrollment of cohort members, NPPs had already begun operation; for example, the first NPP in Korea (Gori #1 plant) started commercial operation in 1978 (2). As the KREEC-R study had enrolled the members with a series of baseline surveys between 1992 and 2005, some participants could have been exposed for up to 27 years even before their enrollment in the cohort. Consequently, by excluding all cancer cases in the baseline survey, the study had effectively removed those who might have developed NPPs related cancer before the baseline survey. In fact, according to the technical report (2), the KREEC-R group identified 150 and 377 prevalent cases for the exposed and unexposed cohorts, respectively; these numbers are not negligible compared to the newly developed cases of 705 and 1,593 during the follow-up period. The valid way should have been to exclude only those who developed cancer before their exposure, that is, residence near NPPs, or before the midst of the minimum latency period (5, 6).

Third, if one constructs multivariate models by selecting covariates based only on statistical association (or significance), variables of known risks could have been omitted (7, 8). For example, none of smoking or drinking variables was included in the multivariate Cox proportional hazard models for females because the authors relied exclusively on statistical significance for selecting covariates. In addition, it was not appropriate to use the same multivariate model with the same but limited covariates repeatedly for different types of cancer despite the known heterogeneity of the risk factors across various cancers.

Fourth, the gender difference in cancer epidemiology is a well-known fact (9-11). Even if the exact mechanism is not clear, it cannot be disregarded as a “self-contradictory” (1) phenomenon. There are many ways to explain the difference, including differences in exposure, biological response, or access to health care, and the study finding of increased cancer risk in only one gender should be explored and explained more cautiously.

Finally, before we reach any conclusion about health effects from NPPs, we have to examine the most vulnerable group. However, the KREEC-R study had targeted only adults older than 19 years. It is well known that children and adolescents are more sensitive to ionizing radiation. Children should have been the main subjects of studies of the environmental cancer risk (12), and even the U.S. National Research Council recommended a record-linkage based case-control study of cancers in children born near nuclear facilities (6).

Considering these limitations, we believe that further studies are warranted, including re-analysis of the existing data, before

drawing a hasty conclusion that epidemiologic studies are no longer necessary.

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## The Author Response: (Yoon-Ok Ahn et al.)

The correspondent depicted five limitations of the study should be addressed, and argued finally that ‘further studies, including re-analysis of the existing data, are warranted before drawing a hasty conclusion that epidemiologic studies are no longer necessary.

All the points of the 5 limitations commented, however, are

not relevant to our study, its hypothesis (purpose), methods, and conclusion, and believe that there is a lack of understanding of our study. And furthermore, since no logical grounds for the final arguments were presented, the arguments are hollow. For instance, the correspondent argued that re-analysis of the existing data is necessary as a further study warranted. However, specifically what needs to be re-analyzed is not even addressed. And no logical grounds were presented for the ‘drawing hasty conclusion.’ In short, the correspondence to our study was insufficient, and the arguments against our study were not even relevant points to our study.

Point 1, the first limitation depicted is not pertinent to our study. Potential confounders need to be controlled for when studying the association between exposure variable and outcome. In our study, multivariate analysis was done (1). So, the study results, i.e. hazard ratios or relative risks, are least likely biased estimates.

Point 2 is definitely not relevant to our study, a cohort study. The correspondent may have misunderstood the cohort study. Since the first inclusion criterion for the cohort member or recruitment is the eligibility or potential for outcome occurrence (2). The past or prevalent cases at baseline are to be excluded from the cohort recruitment.

Point 3 is also not pertinent to our study, a study on the causal relation between a particular exposure factor and outcome (cancer) occurrence, not examining all the potential risk factors for the outcome. Other well-known risk factors for the outcome are to be included in the multivariate analysis model as co-variables, only when they were estimated as potential confounder.

Point 4 is also not relevant to our study, and a conjecture. The correspondent does not seem to clearly understand the purpose of our study in addition to a solid knowledge of distinctive points between statistical association (or significance) and causal inference. Our study purpose was to examine the causal relation (i.e., inference) between radiations from NPPs and cancer risk, not cancer patterns between study populations. It is a conjecture to argue that the gender difference in cancer pattern does mean or suggest the gender-specific carcinogenicity. The ‘self-contradictory’ denotes that evidences for the causal inference contradict themselves.

Point 5 is also not relevant to our study. Looking at subjects under 19 years of age, although their risk for health effects from NPPs may be greater, was not our study objective, as accounted in the title of our paper.

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