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“Bioavailable serum estradiol may alter radiation risk of postmenopausal breast cancer: a nested case-control study”

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Study Findings

Results showed modest evidence that radiation exposure increased the risk of breast cancer through a biological system not typically considered: an indirect pathway in which circulating estradiol levels were raised after radiation exposure. Higher levels of estradiol (an estrogen) have long been known to be associated with higher breast cancer rates. A unique feature of this study was the ability to investigate serum estrogen levels that had been collected prior to breast cancer diagnosis. Biological measurements made before disease onset are more reliable for research purposes, providing justification for our conclusions despite the small size of the study. Nevertheless, further work is needed to clarify and increase confidence in the findings.

Explanation

Ionizing radiation exposure and estradiol (the predominant estrogen in women) are both known breast carcinogens. It has been understood for some time that radiation exposure can lead to breast cancer through direct mutations induced in breast tissue, but little is known about the role of radiation in relation to endogenous sex hormones. In a recent study, we observed that radiation exposure was associated with higher levels of estradiol in women who did not suffer breast cancer. We therefore wondered if radiation exposure might have increased the risk of breast cancer by increasing estradiol levels. This is called a *mediated path* and is shown as the dotted line in the Figure below. We evaluated the level of mediation and determined that a small but statistically significant fraction of the overall radiation risk was through this pathway.

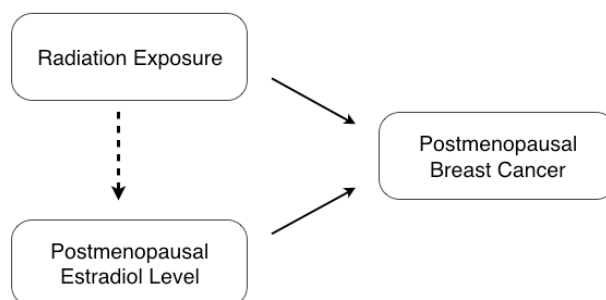


Figure. Radiation exposure increases the risk of breast cancer. Higher serum estradiol concentration is also a known breast carcinogen. In a previous study, we observed that radiation exposure caused an increase in estradiol level (dotted line). We can test how much of the radiation risk of breast cancer is by the direct path versus an indirect path (i.e. through raising estradiol levels which, in turn, raises breast cancer risks) through a statistical test for “mediation.”

1. Study purpose

A previous, interview-based study of female atomic bomb survivors in the RERF Life Span Study produced evidence of interaction between radiation and reproductive behaviors. Generally, protective factors (such as earlier age at first pregnancy and more children) also lowered the risks of cancer after radiation exposure. However, the mechanism for such an interaction was not clear, although there was reason to speculate that it might involve cumulative exposure to endogenous sex hormones such as estradiol. We therefore investigated the risk of breast cancer in relation to the combined effects of whole-body ionizing radiation exposure and prediagnostic levels of

postmenopausal sex hormones, particularly bioavailable estradiol (bE_2), with two aims: one was to assess whether a similar interaction exists between radiation dose and endogenous sex hormone levels, and the other was to assess the potential role of mediation (as explained above). Because the survivors were at older ages at the time the study was conducted, we focused on post-menopausal breast cancer, which comprised the majority of cases.

2. Study methods

We investigated the risks of breast cancer by using a nested case-control study of 57 incident breast cancer cases matched with 110 controls among atomic bomb survivors who attended the RERF clinic as part of the Adult Health Study. Risk factors for breast cancer that were investigated in this study included radiation dose to the breast, levels of various serum hormones, age at menarche, age at menopause, body mass index, and several factors related to parity. Joint effects of breast radiation dose and circulating levels of sex hormones were assessed using binary regression and path analysis.

3. Study results

Findings related to breast cancer in general were as expected, in that breast cancer risk was associated with known risk factors, including higher radiation doses, higher levels of endogenous sex hormones (bE_2 , testosterone, and progesterone), and higher body mass index levels. Also, breast cancer risks were lower in women with later onset of menarche and a greater number of pregnancies, which are factors known to reduce the risk of breast cancer. Analyses of interaction between radiation and serum hormones were inconclusive. A test for mediation of the effect of radiation via bE_2 level suggested a small (14%) but significant mediation ($p=0.002$). The interpretation of this is that about 14% of the total radiation risk, or occurrence of excess cases of cancer among radiation-exposed women, might be the result of higher estradiol levels induced by the radiation exposure as opposed to other mechanisms including direct mutations in breast tissue induced by radiation.

Study Significance

There is accumulating evidence that ionizing radiation not only damages DNA (a primary cause of cancer), but also induces alterations in other organ systems, which can further increase the risk of cancer. The results suggest that some portion of the radiation risk of postmenopausal breast cancer might be mediated through bE_2 levels. If this can be confirmed, it would suggest a previously unknown mechanism of radiation risk that could be used for intervention to reduce risk for radiation exposure.

The Adult Health Study cohort is one of the few resources in the world with which a study of this nature could be performed. Unique features include the existence of stored biological specimens that predate the onset of disease and the collection of data in a controlled clinical setting. Based on such advantages, the effects of radiation can be studied in terms of both its direct effects and its effect on systemic changes that can be measured in the clinic.

The study was quite small with only 57 cases, and therefore, while the results were interesting and raise important questions on the mechanisms of radiation-associated breast cancer, the results should be interpreted cautiously, because small studies can sometimes produce ambiguous or non-repeatable results.

The Radiation Effects Research Foundation has studied A-bomb survivors and their offspring in Hiroshima and Nagasaki for around 70 years. RERF's research achievements are considered the principal scientific basis for radiation risk assessment by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and for recommendations regarding radiation protection standards by the International Commission on Radiological Protection (ICRP). RERF expresses its profound gratitude to the A-bomb survivors and survivors' offspring for their cooperation in our studies.

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