

**Title of the Highlight:**
Breast cancer risk among Swedish hemangioma patients and possible consequences of radiation-induced genomic instability

**Keywords:**
Radiation effects, Breast cancer risk, Genomic instability

**Central statement of the Highlight in one sentence:**
A significant increase of female breast cancer risk after medical treatment with ionizing radiation was observed, which can be well explained by a model of carcinogenesis including potential effects of radiation-induced genomic instability at an early stage of carcinogenesis.

**Text of the Highlight:**
Starting from the 1920s, in Sweden a large number of individuals were treated for skin hemangioma mainly by external application of radium-226. Since skin hemangioma appear at early infancy, the treatment started before the age of two years. Now, about 50 years after the end of treatment, an increase in cancer risk has been observed. In this work the combined skin hemangioma cohorts from Stockholm and Gothenburg of about 17000 women were analyzed for female breast cancer incidence since.

The radiation risks were determined by means of empirical ‘excess relative risk’ (ERR) models, and by the two-stage model of carcinogenesis with clonal expansion (TSCE model). The TSCE model is very well suited to explore possible consequences of radiobiological effects on cancer risk. Due to the very young age at exposure, the Swedish hemangioma cohort data are particularly well suited to test for radiation effects on the initiation rate of carcinogenesis, e.g. to test for possible effects of radiation-induced genomic instability. A model version
including radiation-induced genomic instability with a lifelong enhancement of the initiation rate described the data significantly better than models without such an effect.

For the ERR models, both a constant model and a model with a linear dependence on age gave similar good fits. The results of the best TSCE and ERR models agreed very well for the risk estimates with an excess relative risk at the age of 50, the mean age of breast cancer incidence, of ERR(50)=0.25 Gy⁻¹ (95%CI: 0.14; 0.37). The inclusion of radiation-induced genomic instability in the TSCE model had a significant effect on the age dependence of the excess breast cancer risk: it decreased with from age 40 to age 60 by 50%.

**Publication:**

**Taking account of the HMGU mission and vision:**
The present work analyzes breast cancer risk of women after medical treatment with ionizing radiation at young ages. The cancer risk would be consistent with the radiobiological effect of radiation-induced genomic instability.

**The internal HMGU co-operation partners with whom the Highlight was compiled, if appropriate:**
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The two-stage clonal expansion model (TSCE model)
Possible impact of radiation-induced genomic instability on the initiation rate

Change of the initiation rate for the TSCE models with only an immediate radiation effect and with both an immediate effect and genomic instability after radiation exposure in the age period of 12-18 months. Without genomic instability, the initiation rate returns to its spontaneous value directly after exposure, whereas genomic instability leads to a long-term enhancement of the initiation rate.
Breast cancer risk in the Swedish hemangioma cohort

Comparison of the observed hazard with one standard deviation to the TSCE model with genomic instability and the constant excess relative risk model.
Radiation-induced breast cancer risk

Excess relative risk per dose as a function of age with the 68% and 95% confidence interval for different models. The agreement of the best ERR and TSCE models for the radiation risk is very good.