

Title: Pooled Analysis of Meningioma Risk Following Treatment for Childhood Cancer

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Background: Childhood cancer survivors who received cranial radiotherapy are at high risk of developing subsequent meningiomas; however, the magnitude of the radiation-related risk, possible effects of chemotherapy, and modifiers of the dose-response relationships are not well characterized.

Material and Methods: We conducted a pooled analysis of four matched case-control studies from Europe and North America with estimates of radiation dose to the subsequent tumor location in cases and comparable locations in controls. The pooled odds ratios (ORs), excess odds ratios (EORs) and associated 95% confidence intervals (CIs) were estimated using multivariable conditional logistic regression.

Results: The pooled data included 273 meningioma cases and 738 controls after a median follow-up of 22 years. Odds of meningioma increased with increasing radiation dose (EOR/Gy: 1.44, 95% Confidence Interval [CI]:0.62-3.61) and there was no evidence of departure from linearity

($p > 0.50$). Participants who received exposures of 24 Gy or more had more than 30-fold higher odds of meningioma compared to unexposed childhood cancer survivors (OR=33.7, 95%CI: 14.1-80.3). The radiation association showed lower risk among patients treated after age 10 years than before age 10 (EOR/Gy= 0.57, 95%CI: 0.18-1.91 vs 2.20, 95%CI: 0.87-6.31, $p=0.03$), but there was no clear trend among patients under age 10 (p -trend=0.41). A non-significantly lower EOR/Gy was observed for survivors of CNS tumors and leukemia than among survivors of other first cancers ($p=0.15$) and results remained unchanged with age at exposure also included in the model as effect modifier ($p=0.23$). There was no evidence for a difference in the EOR/Gy with sex ($p=0.34$), calendar year of follow-up (p -trend=0.46), attained age (p -trend=0.50). There was a non-significant increase in the EOR/Gy with time since exposure ($p=0.11$) and radiation-related risk remained significantly elevated 30 years after exposure (EOR:3.76, 95%CI: 0.77-29.15). We found an increased risk of meningioma after methotrexate (OR: 3.43, 95% CI:1.56-7.57), but no evidence of a dose-response relationship or interaction with radiation dose ($p > 0.11$).

Conclusions: This pooled study shows that the meninges are highly sensitive to radiation, with notably higher risks for children irradiated before age 10. Radiation-related risks remain elevated for decades following exposures underscoring the need for long-term follow-up of childhood cancer survivors who received cranial irradiation.