

XRCC1 and Glutathione S-Transferase Polymorphism and Susceptibility to Therapy-Related Cancer in Hodgkin's Disease Survivors: A Report from the Childhood Cancer Survivor Study.

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One of the most serious late effects of treatment for childhood cancer is the occurrence of subsequent malignancy. Survivors of Hodgkin's disease have been shown to be at higher risk of subsequent malignancy, particularly leukemias, thyroid cancer and breast cancer. Moreover, the risk of breast cancer has been strongly associated with exposure to radiation therapy. The Childhood Cancer Survivor Study (CCSS) is a 26 institution study of individuals who survived for five or more years after diagnosis of a cancer before the age of 21. Within this cohort, we investigated the association between polymorphisms in *XRCC1*, *GSTM1*, and *GSTT1* and the risk of subsequent malignancy in Hodgkin's disease survivors. Information regarding the development of a subsequent cancer was reported using a mailed questionnaire, and confirmed through pathology report. DNA was extracted from buccal cell samples provided by study participants. Buccal cell samples were collected using a bottle of mouthwash that was returned by mail to our laboratory. Of the 1308 CCSS participants diagnosed with Hodgkin's disease and alive at the time of contact, 647 (49%) had returned a buccal sample as of 1/15/02. Of these subjects, 48 (7%) had a confirmed subsequent malignancy. When comparing those with and without subsequent malignancies, no differences in *GSTT1* and *GSTM1* genotype frequencies were seen (Odds Ratio (OR)= 1.0, 95%CI=0.5-2.0 and OR=0.7, 95%CI=0.4-1.2, respectively). For *XRCC1*, no association was seen between the genotype frequency and a subsequent cancer (OR=1.6, 95%CI=0.9-2.9). The frequency of a genotype containing at least one glutamine allele was increased in Hodgkin's survivors with breast cancer (n=28) compared to those without (OR=2.7, 95%CI=1.1-6.9). The data indicate that the arginine/glutamine polymorphism at codon 399 in the *XRCC1* gene (R399Q) may influence risk of breast cancer. These data support a possible role for *XRCC1* polymorphism in susceptibility of Hodgkin's disease survivors to radiation-associated breast cancer.