Editorial

Genetic determinants of breast cancer risk in childhood cancer survivors

Magda Meier, MSci and Nick Orr, PhD

Affiliation of authors: The Breast Cancer Now Toby Robins Breast Cancer Research Centre, The Institute of Cancer Research, London SW3 6JB, UK

Correspondence to: Nick Orr, PhD, Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London SW3 6JB, UK (e-mail: nicholas.orr@icr.ac.uk).

In recent decades, survival from childhood cancer has increased dramatically (1) because of improving treatments. In Europe, the five-year relative survival rate presently exceeds 75%, with comparable rates reported in the United States (2,3). These successes come at the cost of a well-documented increased risk of treatment-related second cancers in later life. The US Childhood Cancer Survivor Study (CCSS) reports a 30-year cumulative incidence of second cancers that exceeds 20% in this group of patients (4). Hodgkin's lymphoma and Ewing sarcoma survivors have the greatest risk of developing a second cancer of which breast, brain, bone, thyroid, soft tissue, melanoma, and acute myeloid leukemia are most frequently observed (5).

Despite occurring almost exclusively in females, breast cancer is one of the most common subsequent neoplasms in survivors of childhood or adolescent cancer. It is particularly prevalent in patients with a primary diagnosis of Hodgkin's lymphoma who received supradiaphragmatic radiotherapy as part of their treatment. In a recent UK study of more than 5,000 such women, Swerdlow *et al* reported a six-fold increased relative risk of subsequent breast cancer when radiotherapy was the sole treatment (6). More dramatic increases were observed when breast cancer risks were estimated by age at first radiotherapy treatment; the relative risk of breast cancer increased more than 20-fold when radiotherapy was first administered at ages 10-14 years, with a peak of almost 50-fold at age 14 years that presumably is coincident with breast development (6). Critically, elevated breast cancer risks may persist for up to 30 years post-radiotherapy treatment before diminishing (6) and consequently, intensive long-term surveillance is warranted for this group of patients.

At present, besides variables pertaining to treatment, little is known about the effects of either genetic or environmental exposures in modifying risk of radiation-

induced second malignancies in childhood cancer survivors. Predicated on the hypothesis that common or rare germline variants influence risk of radiation-induced breast cancer in this group of individuals, Morton and colleagues (7) performed a genome-wide association study (GWAS), which they report in this issue of the Journal. They analysed 178 cases and 2,200 controls from the CCSS and 29 cases and 574 controls from the St. Jude Lifetime Cohort (SJLIFE), amongst whom a total of 131 cases (63%) and 493 controls (18%) received at least 10 Gy radiation exposure to the breast during treatment for their first malignancy. Genome-wide genotyping and imputation of unobserved genotypes was used to generate a dataset of almost 17 million single nucleotide polymorphisms (SNPs) that were represented in both cohorts and that were of sufficient quality for statistical analysis.

SNP rs4342822, localising to 1q41, was statistically significantly associated with an almost two-fold raised risk of breast cancer in patients who received at least 10 Gy radiation to the breast in both CCSS and SJLIFE and surpassed the widely applied threshold for genome-wide statistical significance ($P \leq 5x10^{-08}$) upon joint analysis. The same locus showed no evidence for an association with breast cancer risk in individuals who had received lower doses of radiotherapy. Despite the relatively small sample size, Morton and colleagues also explored the contributions of rare variants upon radiation-induced breast cancer risk and detected independent associations of two SNPs, rs74949440 and rs17020562, mapping respectively to 11q23 and 1q32.3. The associations attributable to these SNPs differed with respect to the magnitude of radiation exposure; the former was associated with risk in women receiving at least 10 Gy, while the latter was associated with risk only in women who received less than 10 Gy.

Though potentially exciting, a liberal measure of caution is warranted until these associations are replicated in independent cohorts; discoveries from small GWAS, particularly rare variant associations, often suffer from a high rate of attrition as hits that are initially promising subsequently fail to replicate. Indeed, the data from Morton *et al* (7) casts an element of uncertainty upon two previously reported associations detected in this setting, at 6q21 and 10q26.13 (8,9). While genetic epidemiological studies of sporadic cancer predisposition in the general population have identified and robustly validated hundreds of variants that influence of risk of most common types of the disease (10), these successes have depended on global collaborative efforts to pool vast numbers of samples for analysis (11-13). Clearly there are fewer analogous studies with sufficient epidemiological and treatment data that also have genetic material for germline analysis, with which to prosecute susceptibility to breast cancer in childhood cancer survivors. Nonetheless, this field must now move to consolidate available resources in order to expedite validation of promising leads.

Much effort is currently being expended on the development of breast cancer predictive models for population-based risk stratification that incorporate germline predisposition SNPs. A challenge is that since the breast cancer relative risk effects of SNPs are small, they are of little use individually and instead must be combined to identify different levels of risk (14). The data reported by Morton *et al* (7) indicate that larger effects might be conferred by a subset of loci involved in mediating risk of radiation-induced cancer, suggesting that meaningful risk stratification might be attainable with a small number of independent loci. If confirmed, the associations presented by Morton *et al* (7) represent an important step toward delivering upon the promise of second cancer risk prediction in childhood cancer survivors.

Funding

This work was supported by Breast Cancer Now as part of their funding to the Breast Cancer Now Toby Robins Breast Cancer Research Centre.

Notes

The funder had no role in the writing of the editorial or decision to submit it for publication. The authors have no conflicts of interest to disclose.

References

1. Gatta G, Capocaccia R, Stiller C*, et al.* Childhood cancer survival trends in Europe: a EUROCARE Working Group study. J Clin Oncol 2005;23(16):3742-51.

2. Morton LM, Onel K, Curtis RE*, et al.* The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults. Am Soc Clin Oncol Educ Book 2014; 10.14694/EdBook_AM.2014.34.e57:e57-67.

3. Trama A, Botta L, Foschi R*, et al.* Survival of European adolescents and young adults diagnosed with cancer in 2000-07: population-based data from EUROCARE-5. Lancet Oncol 2016;17(7):896-906.

4. Friedman DL, Whitton J, Leisenring W*, et al.* Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2010;102(14):1083-95.

5. Inskip PD, Ries LA, Cohen RJ*, et al.* New malignancies following childhood cancer. In. *New malignancies among cancer survivors: SEER cancer registries, 1973-2000*; 2006, 465-482.

6. Swerdlow AJ, Cooke R, Bates A*, et al.* Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol 2012;30(22):2745-52.

7. Morton LM, Sampson JN, Armstrong GT*, et al.* Genome-wide association study to identify susceptibility loci that modify radiation-related risk for breast cancer after childhood cancer. J Natl Cancer Inst 2017. In press.

8. Best T, Li D, Skol AD*, et al.* Variants at 6q21 implicate PRDM1 in the etiology of therapy-induced second malignancies after Hodgkin's lymphoma. Nat Med 2011;17(8):941-3.

9. Ma YP, van Leeuwen FE, Cooke R*, et al.* FGFR2 genotype and risk of radiation-associated breast cancer in Hodgkin lymphoma. Blood 2012;119(4):1029-31.

10. Welter D, MacArthur J, Morales J*, et al.* The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. Nucleic Acids Res 2014;42(Database issue):D1001-6.

11. Eeles RA, Olama AA, Benlloch S*, et al.* Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nat Genet 2013;45(4):385-91, 391e1-2.

12. Michailidou K, Beesley J, Lindstrom S*, et al.* Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet 2015;47(4):373-80.

13. Michailidou K, Hall P, Gonzalez-Neira A*, et al.* Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 2013;45(4):353-61, 361e1-2.

14. Mavaddat N, Pharoah PD, Michailidou K*, et al.* Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst 2015;107(5).