Germline Mutations in *BRCA2* and Pediatric/Adolescent non-Hodgkin's Lymphoma: A Report from the St. Jude Lifetime (SJLIFE) and Childhood Cancer Survivor Study (CCSS) Cohorts

Short title: *BRCA2* and non-Hodgkin's Lymphoma

Zhaoming Wang, Ti-Cheng Chang, Carmen L. Wilson, Chimene A. Kesserwan, Todd M. Gibson, Nan Li, John Easton, Heather Mulder, Gang Wu, Michael N. Edmonson, Michael C. Rusch, James R. Downing, Kim E. Nichols, Smita Bhatia, Gregory T. Armstrong, Melissa M. Hudson, Jinghui Zhang, Yutaka Yasui, Leslie L. Robison

Pathogenic or likely pathogenic (P/LP) monoallelic germline mutations in *BRCA2* increase risk of developing breast, ovarian, prostate, and pancreatic cancers. In a prior report from the SJLIFE study, *BRCA2* was the third most frequently mutated gene (14 occurrences) among 3006 survivors of childhood cancer with the highest number observed among lymphoma survivors (7/586). To further investigate *BRCA2* as a potential predisposition gene for pediatric/adolescent lymphoma, we analyzed 781 additional lymphoma survivors in the SJLIFE and CCSS cohorts with whole-genome sequencing (30X coverage). In the combined set of 1367 survivors (808 Hodgkin lymphoma's [HL], 559 non-Hodgkin's lymphoma [NHL]; 54% male; median age at diagnosis 12.6 [range 1.1-22.7] years), 13 P/LP mutations in *BRCA2* were identified, with 7 mapped to the breast or ovarian cancer cluster regions defined by the Consortium of Investigators of Modifiers of *BRCA1/2*. Compared to reference controls in the Genome Aggregation Database (gnomAD) (Table 1), a significant association was observed between lymphoma and mutations in *BRCA2* (odds ratio [OR], 3.1; 95% CI, 1.7-5.5) but not *BRCA1*. When stratified by diagnosis, the association was significant for NHL (OR, 4.8; 95% CI, 2.0-9.6) but not for HL. *BRCA2* mutation carriers included a broad spectrum of NHL histological subtypes. Our findings support inclusion of pediatric/adolescent NHL in the spectrum of cancers associated with germline *BRCA2* mutations. Approximately 1.4% of survivors of pediatric/adolescent NHL are carriers of a P/LP mutation in *BRCA2*, which may be the underlying etiology of their primary diagnosis. Clinically, counselling regarding *BRCA2* mutation status should be considered for pediatric/adolescent NHL patients. Large scale genetic studies of newly diagnosed pediatric/adolescent lymphoma patients are warranted to replicate and refine diagnosis-specific risk estimates.

Table 1. Comparisons of Mutation Carriers for *BRCA1/2* Genes Between Lymphoma Survivors and gnomAD Controls

		Lymphoma Survivors		gnomAD Controls (Hu et al. JAMA 2018)		Cancer Risk (Fisher's Exact Test)	
Gene	Cancer Diagnosis	Carriers	Non-Carriers	Carriers	Non-Carriers	Odds Ratio (95% CI)	P Value
BRCA2	HL+NHL	13	1354	313	102426	3.1 (1.7-5.5)	0.00045
	HL	5	803	313	102426	2.0 (0.7-4.8)	0.11
	NHL	8	551	313	102426	4.8 (2.0-9.6)	0.00041
BRCA1	HL+NHL	3	1364	208	103914	1.1 (0.2-3.3)	0.76
	HL	1	807	208	103914	0.6 (0.02-3.5)	1.0
	NHL	2	557	208	103914	1.8 (0.2-6.6)	0.31