Title: Clinical Outcomes and Cost-Effectiveness of Early Breast Cancer Prevention for Childhood Lymphoma Survivors Previously Treated with Chest Radiotherapy

Authors: Jenna R. Rogers, BS[1,2]; Sarah Stein, PhD[3]; Clyde B. Schechter, MD, MA[4]; Kayla L. Stratton, MS[5]; Wendy M. Leisenring, ScD[5]; Chelsea Taylor, BA[2]; Oguzhan Alagoz, PhD, MS[6]; Gregory T. Armstrong, MD, MSCE[7]; Melissa M. Hudson, MD[7,8]; Allison W. Kurian, MD, MSc[9]; Kathryn P. Lowry, MD[5,10]; Jeanne S. Mandelblatt, MD, MPH[11]; Lindsay M. Morton, PhD[12]; Chaya S. Moskowitz, PhD[13]; Kevin C. Oeffinger, MD[14]; Lisa Diller, MD[15,16]; Jennifer M. Yeh, PhD[2,15]

[1]Interfaculty Initiative in Health Policy, Harvard University, Cambridge, MA; [2]Department of General Pediatrics, Boston Children's Hospital, Boston, MA; [3]Harvard Pilgrim Health Care Institute, Boston, MA; [4]Albert Einstein College of Medicine, Bronx, NY; [5]Fred Hutchinson Cancer Center, Seattle, WA; [6]Department of Industrial and Systems Engineering and Carbone Cancer Center, University of Wisconsin-Madison, Madison, WI; [7]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN; [8]Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN; [9]Departments of Medicine and Epidemiology and Population Health, Stanford University, Stanford, CA; [10]Department of Radiology, University of Washington School of Medicine, Seattle, WA; [11]Departments of Oncology and Medicine, Georgetown University Medical Center, and Georgetown Lombardi Comprehensive Institute for Cancer and Aging Research at Georgetown University Comprehensive Cancer Center, Washington, DC; [12]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD; [13]Department of Epidemiology and Biostatistics, Memorial Sloane Kettering Cancer Center, New York, NY; [14]Department of Medicine, Duke University School of Medicine, and Duke Cancer Institute, Durham, NC; [15]Department of Pediatrics, Harvard Medical School, Boston, MA; [16]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA.

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Purpose: Survivors of pediatric lymphoma treated with mediastinal chest radiotherapy are at high secondary breast cancer risk. Guidelines recommend mammography and MRI screening starting at age 25, but uptake is low and MRI access is limited. Risk-reducing medications could improve breast cancer control but remain infrequently discussed, in part due to unclear trade-offs relative to screening. We addressed this gap by estimating clinical outcomes and cost-effectiveness across combinations of these strategies.

Methods: We adapted two Cancer Intervention and Surveillance Modeling Network (CISNET) models using data from the Childhood Cancer Survivor Study to reflect breast cancer risk and competing mortality for 5-year survivors previously treated with chest radiotherapy. We compared strategies including mammography (mammo), MRI, and multimodal screening (mammo/MRI) starting annually at age 25 with and without 5-years

of tamoxifen (TAM) beginning at age 30, and no screening or TAM use. Outcomes included breast cancer cases, deaths, and incremental cost-effectiveness ratios calculated using discounted lifetime costs and quality-adjusted life years (QALYs) (3% rate). Optimal strategies were selected using a $150,000/QALY willingness-to-pay threshold. Near-efficiency was defined by whether a strategy fell within 3 days of life lost per person from the efficiency frontier. Results are presented as a range across models.

Results: Among a simulated cohort of 20-year-old lymphoma survivors treated with mediastinal radiotherapy, 77-114 breast cancer deaths were estimated per 1000 women treated without screening or TAM. The numbers of breast cancer deaths averted per 1000 women were 31-50 with mammo, 40-71 with MRI, and 46-79 with mammo/MRI screening. The addition of TAM decreased the number of deaths per 1000 by an additional 3-7 deaths. When both costs and quality of life were considered, each model found MRI only to be cost-effective ($64k-87k/QALYG); additionally, MRI only with TAM and mammo only (with or without TAM) were either efficient or near-efficient in both models. However, multimodal screening (mammo/MRI) was dominated or exceeded the willingness-to-pay ($749k/QALYG for Mammo/MRI only in one model), regardless of TAM use.

Conclusions: Findings suggest that MRI screening starting at age 25 is cost-effective; mammography screening remains an efficient option. Mammography or MRI with TAM are also efficient or near-efficient options, suggesting the importance of survivor preferences. Shared decision-making could improve breast cancer control efforts for survivors.

Figure. Efficient frontier and near-efficient region for all screening strategies in models W (1) and GE (2). Shaded region indicates near-efficiency (defined as 2.92 QALYs per 1000 individuals based on discounted, quality-adjusted life years).