

A CAUTIONARY NOTE ON THE METHODOLOGY FOR THE ANALYSIS OF SECOND MALIGNANT NEOPLASM (SMN) RISK IN CHILDHOOD CANCER SURVIVORS: BREAST SMN AFTER HODGKIN DISEASE AS AN EXAMPLE.

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Girls treated at age 10-16 for Hodgkin disease (HD), compared to those treated at younger ages, have been shown to be at an increased risk for breast SMN, presumably due to the radiation exposure of breast epithelial cells when their mitotic rates are high (NEJM 334(12):745-51, 1996). Here we show that it is critical to account for the age-associated increase of breast cancer risk seen in the general population when assessing the risk of secondary breast cancers in a cohort of childhood cancer survivors. We illustrate that conclusions from the analysis could be modified, even reversed, by taking into account the rise of breast cancer risk that occurs with age, using the data from the Childhood Cancer Survivor Study (CCSS; 5,840 females) and the Late Effects Study Group (LESG; 472 females). As shown below, both descriptive and regression analyses which do not account for the natural increase of breast cancer risk with age (*in bold italic*) suggest that older ages at the HD (and other childhood cancer) diagnosis are associated with substantially increased risk of breast SMN. Standardized incidence ratios (SIRs) of breast cancer based on the rates from the NCI's Surveillance, Epidemiology, and End Results cancer registry, on the other hand, show no, or at most weak, association with the age at diagnosis of the original cancer. We will discuss the cause of the problem and different analysis methods appropriate for its handling.

Study	Age at diagnosis (dx)	Descriptive analysis				Rate ratio estimate from regression			
		<i>Rate per 10⁴ person years</i>		SIR		<i>Cox model</i>		Poisson SIR model	
		<i>All dx</i>	<i>HD</i>	All dx	HD	<i>All dx</i>	<i>HD</i>	All dx	HD
CCSS	0-4	0.0	0.0	0.0	0.0	0.00	0.00	0.00	0.00
	5-9	3.2	0.0	17.1	0.0	0.09	0.00	1.04	0.00
	10-14	12.5	27.7	16.9	30.7	0.35	0.45	1.03	1.21
	15-21	35.4	60.8	16.5	25.3	1.00	1.00	1.00	1.00
LESG	0-9		11.9		31.9		1.00		1.00
	10-16		50.0		53.8		4.83		1.69