Proposal No: 00-06
Topic: Second Thyroid Carcinomas

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00-06

CHILDHOOD CANCER SURVIVOR STUDY
ANALYSIS CONCEPT PROPOSAL

1. Title: Second thyroid carcinomas in the Childhood Cancer Survivor Cohort
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2. Investigators: This proposed publication will be within the Second Malignancies Working Group. Proposed investigators will include:

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3. Background and rationale:

Long-term cancer survivors of childhood malignancy have an increased incidence of second primary thyroid cancer up to several decades after their treatment. Second thyroid cancer has been most commonly observed following radiotherapy for Hodgkin's Disease, neuroblastoma, Wilm's Tumor, and non-Hodgkin's lymphoma. Thyroid cancers that occur in persons with a history of radiation treated childhood malignancy are associated with radiotherapy dose, age at treatment, time since irradiation, and likely female gender (reviewed in Schlumberger et al. 1999; de Vathaire et al. 1999; Ron et al. 1995; Tucker et al. 1991, reviewed in Shore 1992). The largest pooled study published to date reports an excess relative risk per Gray (ERR/Gy) of 7.7 (95% CI 2.1-28.7) (Ron et al. 1995) and was largely based on low to moderate thyroid exposures ranging from 0.09 to 1.36 Gy. Relative risk estimates vary among studies between 5-47 ERR/Gy (reviewed in Schlumberger et al. 1999) with a linear dose-response curve seen at low doses that tends to flatten above 10 Gy (Tucker et al 1991). However, not all studies agree and more studies are needed at high doses to increase confidence in the shape of the dose response curve. For those children treated at younger ages (< 5 years) the relative risk is higher and risk decreases as age at radiotherapy increases. Detectable excess relative and absolute risks for thyroid cancer occur as soon as 3 to 7 years after irradiation and may persist throughout life although this is not known with certainty. Previous studies have been small, with 14 and 23 thyroid cancer cases arising in European and North American cohorts of childhood cancer survivors, respectively (de Vathaire et al. 1999; Tucker et al. 1991). The Childhood Cancer Survivor Cohort has approximately 45 incident thyroid cancers (5 are third malignant neoplasms) yielding the largest numbers for study to date and will provide much needed information about dose response relationships, temporal patterns, and more narrow confidence intervals around the radiation dose estimates. Besides estimating thyroid organ doses, we intend to also include dose to the hypothalamus/pituitary with the idea that such exposure may result in sub-clinical hypothalamus/pituitary disruption that lowers TSH levels thereby decreasing thyroid cancer risk (Williams 1993 & 1995).

While many aspects of thyroid cancer risk in children and young adults treated for a first primary are reasonably well known, the influence of lifestyle or medical interventions that may affect risk (either independently or as an effect modifier) are not well quantified. Among the lifestyle

and/or medical intervention factors that have been found to potentially modify risk of thyroid cancer are age at menarche, parity, hormone replacement therapy, certain prescription pharmaceuticals, family cancer history, diet and obesity (Shore 1992; reviewed in Ron 1996). Most of the previous reports that assessed the risk of thyroid cancer as a second malignancy were limited to medical record review only. Because the CCSS cohort has clinical and follow-up questionnaire information, factors such as age at menarche, pregnancy, body mass index, physical activity, drug prescriptions and hormone replacement can be evaluated. Although chemotherapy has shown little or no association with thyroid cancer in childhood cancer survivors (Tucker et al. 1991; de Vathaire et al., 1999), we will evaluate the potential role of chemotherapy agents in our analyses. Additionally, it has been hypothesized that a first primary tumor of neuroblastoma may confer increased risk of thyroid cancer (de Vathaire et al. 1999) with the thinking that there may be a common predisposition for both tumors (de Vathaire et al. 1992). However, neuroblastoma is usually diagnosed at very young ages when the susceptibility/sensitivity to radiation-induced thyroid cancer is very high and it may be impossible to separate risk from neuroblastoma as a first primary from an age at radiation treatment effect.

4. Study objectives and hypotheses

The first objective is to quantify risk of second thyroid cancers with respect to radiation dose to the thyroid, age at radiation treatment, temporal patterns and type of initial cancer. We will describe the shape of the dose-response curve, with particular attention to whether or not there is evidence of a flattening of the risk at high doses. We will also similarly analyze the effect of radiation dose to the hypothalamus/pituitary. Second, we will evaluate the effect on risk estimates for other variables of interest using questionnaire and clinical information (such as age at menarche, parity, obesity indices, physical activity, prescription of growth hormone, type of chemotherapy). We are interested in describing the main and joint effects of these variables. Thirdly we will characterize the radiation dose-response for second thyroid cancer by initial primary diagnosis (as numbers permit). Our intent is to assess thyroid cancer risk among those with a diagnosis of neuroblastoma, if such a risk can be convincingly disentangled from age of radiation treatment.

5. Analysis Framework and Matching Rationale

We propose a nested case-control design using a matched (conditional logistic) analysis. The case control study within the cohort is an efficient use of resources since dosimetry calculations will need to be performed (by Marilyn Stovall) and will be incorporated into this analysis. We have chosen a 4 to 1 matching ratio since there is usually little, if any, improvement in statistical efficiency for matching ratios exceeding this when cases are few. The plan for deciding the matching criteria for controls will be in two phases. The first phase will be an assessment of cases by institution and calendar year of thyroid diagnosis. If we find an institution has more thyroid cancer cases than expected, this could be due to heightened detection by clinicians, which would necessitate matching by institution. Similarly, if we find that cases are clustered temporally by year of thyroid cancer diagnosis, then we will also match on calendar year of the first primary diagnosis. Because gender and age at ionizing radiation exposure are known risk factors for thyroid cancer, we will remove their confounding effect by matching. We will match on first primary cancer so that our comparisons will be within diagnosis groups, but radiation treatment will be sufficiently variable to be informative (Tucker et al. 1991). For a valid comparison group, the controls must be at risk for a second thyroid cancer over an equal period of time up to the case's diagnosis. Thus the follow-up interval will be at least as long (it could be longer) for the controls as it was for the case.

(a) *Outcome of interest*: Thyroid cancer

(b) *Study Subjects*: Cases are all persons with second primary thyroid cancers. Controls will be persons selected by stratified random sampling with a 4:1 matching ratio on: gender, diagnosis age ($\pm$ 6 mos), and follow-up interval (controls must survive and be at risk of thyroid cancer at least to the age of case diagnosis). Controls may or may not be matched on institution or calendar year of the first primary cancer diagnosis. Controls must have a thyroid gland (Q I.15). We will not match on first primary cancer.

(c) *Explanatory variables*: radiation dose to the thyroid gland and hypothalamus, type of first primary cancer, type of treatment (including types and doses of chemotherapy), hormone replacement (men and women), use of drugs that increase TSH (eg: phenobarbitol), family cancer history, hereditary conditions, age at menarche and parity (women), physical activity, obesity, alcohol and cigarette use.

(d) *Examples of specific tables and figures*:

Table 1: Descriptive characteristics of thyroid cancer cases and controls

-Total (Males, Females)
-Ethnicity (Non-Hispanic white, African American, Hispanic, Asian, other)
-Age at first cancer (0-4, 5-9, 10-14, 15 –20)
-Calendar year of first cancer (1970-73, 1974-77, 1978-81, 1982-86)
-Years since first cancer (5-9, 10-14, 15-19, 20+)
-Initial Cancer (examples) Hodgkin's Disease, Neuroblastoma, Leukemia, Non-Hodgkin's Lymphoma, CNS Tumor, Soft-tissue Sarcoma, Wilm's Tumor
-Dose of radiation to thyroid (As an example, see Table 2)
-Dose of radiation to the hypothalamus/pituitary
-Type of treatment for first cancer (as numbers allow, such as radiation+surgery or chemo+surgery)
-Type of chemotherapy drug(s) used for first cancer (no, yes)
-History of thyroid cancer in a first degree relative (no, yes)
-History of any cancer in a first degree relative diagnosed before age 45 (no, yes)
-Parity (among female matched sets: zero, one, two or more)
-Prescription Medications (List to be determined from B.8: no, yes)*
-Hormone Replacement (List to be determined from section B.8 & E.8-9, 11: no, yes)*
-Over and underactive thyroid gland, nodules and enlargements (from E.1-4)
-Body Mass Index (from A.10 & A.11: $<$ 18.5, 18.5-24.9, 25.0-29.9, $\geq$ 30).
-Physical Activity (0 days, 1-2 days, 3-4 days, 5 or more days per week from N.9)
-Alcohol (Never or rare [less than once/month], light [less than one per day], moderate [one per day], heavy [2 or 3 per day], very heavy [4 or more drinks per day]
-Cigarette smoking (Never, past, current; pack-years for current and past smokers)

(*Temporal aspects of medications and thyroid cancer diagnosis will be ascertained. Also, we realize these medications are reported for the two years prior to the questionnaire and are intended to assess more chronic medication usage.)

Table 2: Thyroid cancer risk by thyroid radiation dose, stratified on age at diagnosis.

	Radiation Dose (cGy)				
	None	1-999	1000-2499	2500-4000	4000+
Less than age 5					
Number of cases					
Number of controls					
Conditional OR	Referent				
95% Confidence Interval					
Age 5 or older (if numbers permit we intend to further characterize this age group)					
Number of cases					
Number of controls					
Conditional OR					
95% Confidence Interval					
Total					
Number of cases					
Number of controls					
Conditional OR					
95% Confidence Interval					

Table 3: Univariate and multivariable odds ratios and 95% confidence intervals for thyroid cancer risk among survivors of childhood cancer

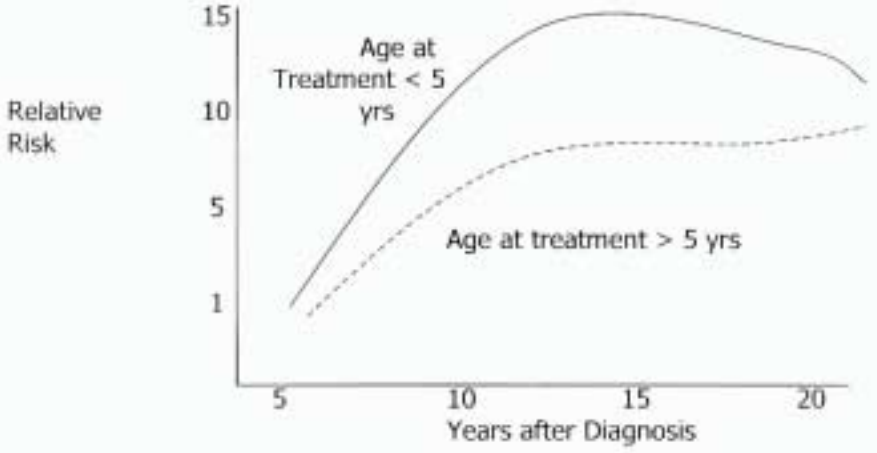
-First cancer (Hodgkin's Disease, Neuroblastoma, Leukemia, Non-Hodgkin's Lymphoma, CNS Tumor, Soft-tissue Sarcoma, Wilm's Tumor)
-Type of treatment (as numbers allow, such as radiation+surgery or chemo+surgery)
-Dose of radiation to thyroid gland and hypothalamus
-Type of chemotherapy drug (no, yes)
-Over and underactive thyroid gland, nodules and enlargements (from E.1-4)
-Hormone Replacement (determined from questionnaire section B.8.)
-History of thyroid cancer in a first degree relative (no, yes)
-History of any cancer in a first degree relative diagnosed before age 45 (no, yes)
-Parity (among female matched sets: zero, one, two or more)
-Prescription Medications (List to be determined: no, yes)
-Body Mass Index (less than 18.5, 18.5-24.9, 25.0-29.9, 30.0 or greater).
-Physical Activity (0 days, 1-2 days, 3-4 days, 5 or more days)
-Alcohol (Never or rare [less than once/month], light [less than one per day], moderate [one per day], heavy [2 or 3 per day], very heavy [4 or more drinks per day]
-Cigarette smoking (Never, past, current; pack-years for current and past smokers)

(Age at first cancer treatment, first cancer, gender and ethnicity were matching variables. Preliminarily multivariable models may include terms for first cancer, radiation dose to the thyroid and chemotherapy. Some variables are likely highly correlated and may not be retained. Variable selection and other model fitting will be determined with the intent to describe the independent effects of lifestyle/medical interventions including, at the least, thyroid radiation dose in the model and after assessment for interaction.)

Table 4+: These tables will be used to describe effect modification. This example is for the effect of parity in females of child-bearing age. (Other tables will be added depending upon results of analyses of potential effect modifiers.)

	Parity	
Radiation Dose (cGy)	None	One or more children
None		
Number of cases		
Number of controls		
Conditional OR		
95% Confidence Interval	Referent	
1-2000 cGy		
Number of cases		
Number of controls		
Conditional OR		
95% Confidence Interval		
2000+ cGy		
Number of cases		
Number of controls		
Conditional OR		
95% Confidence Interval		

Figure 1. Relative risks for thyroid cancer by time after diagnosis and age at treatment.



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