revised 06-03

Childhood Cancer Survivor Study
Analysis Concept Proposal

1. **Title:** Radiation and thyroid cancer in the Childhood Cancer Survivor Study: Cohort analysis and alternative methods for dosimetry.

2. **Investigators:** These proposed publications will be within the Second Malignancies Working Group. Proposed investigators will include:

Cécile Ronckers (co-lead)	ronckers@nih.gov	NCI / AMC
Parveen Bhatti (co-lead)	bhattip@mail.nih.gov	NCI
Alice Sigurdson	sigurdsa@mail.nih.gov	NCI
Marilyn Stovall	mstovall@mdanderson.org	MDACC
Susan Smith	samsmith@mdanderson.org	MDACC
Rita Weathers	rweather@mdanderson.org	MDACC
Wendy Leisenring	wleisenr@fhcrc.org	FHCRC
Chuck Sklar	sklarc@mskcc.org	MSKCC
Debra L. Friedman	dfriedma@fhcrc.org	FHCRC
Sarah Donaldson	sarah@reyes.stanford.edu	Stanford
Sue Hammond	hammond@chi.osu.edu	Ohio
Ann Mertens	mertens@epi.umn.edu	U Minn
Joe Neglia	jneglia@umn.edu	U Minn
Anna Meadows	meadows@email.chop.edu	Philadelphia
Peter Inskip	inskippe@mail.nih.gov	NCI
Leslie Robison	Les.Robison@st.jude.org	St Jude's

3. Background and Rationale

Cancer of the thyroid gland is relatively uncommon, although it has become the 8th most common malignancy among U.S. women in recent years (Jemal2005). Incidence patterns by age and gender are very different from those for most other solid cancers in that thyroid cancer is most common in females and the average age at diagnosis is in the forties rather than the sixties for most other solid cancers in adults. The etiology of thyroid cancer is not well understood (Ron1996). The only well characterized risk factor is exposure to ionizing radiation in the head and neck at a young age, which was recognized as early as 1950 (Duffy&Fitzgerald1950; Shore1992). A clear dose-response relationship has been shown in many different populations exposed to ionizing radiation from medical or environmental sources (Tronko 2006; Likhtarov 2006; Ron 1995; Thompson 1994; Davis 2004; Kerber 1993, Hamilton 1987). The dose-response pattern at relatively low doses appears to be linear and risk is significantly affected by age at exposure, with those exposed as infants or young children being at the highest risk of radiation-related thyroid cancer later in life. A minimum latency period of 5 years is generally accepted (Ron1995). Two recent studies describe thyroid cancer risk among children exposed to low to medium doses of radiation (all < 11 Gy, most < 1 Gy), mainly from ^{131}I, due to fall-out of the 1986 Chernobyl accident in Belarus and the Russian Federation (Davis2004 ; Cardis2005). The dose-response curves in both studies were essentially linear, although Cardis et al found some evidence for non-linearity (Cardis, 1994). Cautionary notes were made with regard to imprecision in the dose-estimates and lack of biologic plausibility for non-linearity at doses in the 1-10 Gy range (Cardis 2005; Boice 2005). Iodine-deficiency appeared to enhance the effects of ^{131}I on thyroid cancer risk (Cardis 2005).

Until recently, only 2 studies had included children whose thyroid gland was exposed to high radiation doses (>10 Gy), an American and a European cohort study of childhood cancer survivors, which both reported increased risk of thyroid cancer (Tucker1984; deVathaire1999). Both studies, however, were small, including 23 and 14 patients who developed thyroid cancer, respectively (Tucker1991, de Vathaire1999). We recently completed a nested case-control study of second thyroid cancer in the Childhood Cancer Survivor Study (CCSS) of 72 cases and 287 matched controls (Sigurdson2000; Sigurdson2005). The aims were (1) to more precisely estimate the risk of thyroid cancer among childhood cancer survivors, (2) to evaluate the shape of the dose-response curve, and (3) to assess other characteristics that might influence the dose-response (i.e., effect modification). In brief, the findings indicate that the dose response is linear up to doses around 17 Gy, but that risk declines at higher doses. This is in line with experimental observations of cell killing at high radiation doses (Clifton1986) and speculation about such an effect in radiation-exposed patients (Shore1992). Patient characteristics such as age and gender as well as treatment with chemotherapy did not significantly alter these results; although not statistically significant, risk estimates declined with increasing age at radiation exposure, as was seen in previous studies (Sigurdson2005). Moreover, we found that a diagnosis of Hodgkin lymphoma or neuroblastoma was an independent risk factor for second primary thyroid cancer after the radiation effect had been taken into account. HL patients had smaller tumors than other survivors, and so we postulated that they may have been screened more diligently for thyroid disorders than other survivors, which may partly account for the higher risk. For neuroblastoma, the results were based on small numbers, and the strong effect of age at radiation exposure coupled with the generally very young age at diagnosis of neuroblastoma may have resulted in spurious association (Sigurdson2005).

Although the results of the thyroid case control study have been reported (Sigurdson2005), several questions of clinical and scientific interest remain to be addressed. Therefore, we would like to propose extended analysis and publication on second primary thyroid cancer in CCSS.

The co-authors and reviewers of our initial report clearly indicated a need to be able to translate these findings to clinical practice, which would include calculations of absolute risks overall and for several subgroups of the cohort. This would be computationally complicated in a case-control study and can be done much better with a cohort design. Therefore, we propose a cohort analysis of second primary thyroid cancer using updated cohort data to present several additional measures of risk that were not explored at this level of detail by the original cancer incidence report from CCSS (Neglia 2001) and that will not be addressed in the planned follow-up SMN paper (Deb Friedman, personal communication, December 2005). The general philosophy would partly follow that of the recently published paper on second primary breast cancer in CCSS by Kenney and colleagues (Kenney2004). We propose to compare the cohort to the general population and intend to provide results that can have value beyond the setting of childhood cancer survivors, with respect to other radiation-exposed populations.

The highly detailed and precise dose estimates that were available in the case control study (henceforth referred to as "case-control" dosimetry) cannot be estimated for the entire cohort, due to financial and time constraints. Recently, however, Marilyn Stovall has nearly completed an intermediate level of coding for the radiotherapy data for the entire CCSS cohort that will provide an individual thyroid dose estimate for each person in the cohort. This so-called "detail coding" method will open a new array of opportunities to estimate relative and absolute risks by categories of radiation dose and per Gy of radiation dose. Although these doses will be less precise than the "case-control" doses, the nearly 14,000 survivors who did not develop thyroid cancer will form a strong base to estimate radiation-related risks with a high degree of confidence. The appendix provides a description of the dosimetry methods.

In addition, we propose to provide a so-called 'yard-stick' (Anna Meadows©) on example patients representative of larger groups in CCSS that would allow a general physician that cares for long-term survivors, but is not aware of all the details of treatments, to translate information on a few basic parameters (e.g., age, type of first cancer, tumor dose, area of treatment, etc) into an estimated thyroid exposure level. This information will increase the clinical application of risk estimates that we have provided in the Lancet report. This part of the proposal will include only the most common scenarios in the cohort.

This paper will be targeted to clinicians. We would prefer a general medical journal over an oncology specialty journal to be able to not only reach the pediatric oncologists who initially treat the childhood cancer patients, but also clinicians who are involved in medical care of long-term survivors. Possible journals, in order of preference include JAMA, Ann Internal Med, JCO and Cancer.

4. Study objectives and hypotheses

1. Cohort-based estimates of relative risk and absolute risk overall and for subgroups of the cohort of childhood cancer survivors
2. Estimates of ERR and EAR by radiation dose, based on new, "detail coding" based dosimetry
3. A table with "example patients" to provide clinicians with information to link available basic patient characteristics and treatment information to an estimate of thyroid dose (in categories) to make our study results more accessible and useful to clinicians in daily practice.

5. Analysis frame work

A. Risk of thyroid cancer by radiation dose for entire cohort
We will use a classic a person-year approach to calculate the ratio of observed (O) and expected (E) numbers of cases for thyroid cancer in the CCSS cohort relative to an age, sex, and calendar year matched segment of the U.S. general population (from the SEER cancer registries). Furthermore, we will use O and E to calculate overall and stratum-specific estimates of the excess absolute risk (EAR) for thyroid cancer. All these analyses will be done for the total cohort and for several subgroups based on relevant personal, diagnostic, and treatment characteristics. Internal analyses will be based on Poisson regression analyses. We will also present the cumulative risk of thyroid cancer in the cohort relative to the general population, for men and women separately. These analyses will be done in the statistical center in Seattle.

B. 'Yard stick' table with example patients (Anna Meadows©)
This part of the protocol requires a two-step approach. First, collaborators at MD Anderson, together with the epidemiologists (Bhatti/Ronckers) and radiation oncologist (Donaldson) will create subgroups to classify patients in the entire CCSS cohort by the most obvious variables that will have affected their radiation dose to the thyroid gland, which are (1) the type of childhood cancer, (2) age at treatment (in 5-yr categories or otherwise meaningful, depending on type of first cancer, e.g., for neuroblastoma, Wilms and ALL 0-1, 2-4, 5-9 yrs , may be more meaningful), and (3) body part at which RT was directed.

Then we will determine the level of homogeneity within the groups that were created with respect to thyroid dose and other characteristics (e.g. treatment dose, blocking) that determine thyroid dose. The goal of this exercise is to find homogenous groups in the cohort based on as few variables as possible that can be represented by one example patient in the 'yard stick' table. The proposed selection and the required variables will then be discussed with our collaborators who provide long-term care (Meadows, Sklar) and possible others (e.g., Kevin Oeffinger, Elizabeth Bluhm).

Three requirements guide this process: (1) the yard-stick table will only be useful to general practitioners/internal medicine practitioners if we do not assume detailed knowledge on treatment characteristics on their part; (2) the result of this effort will, by necessity, not cover all the patients and thus all the diversity present in the cohort; however, we will try to cover as many scenarios as we can with as few variables as possible; and (3) for types of childhood cancer that do not appear to be associated with strongly increased risk (as compared to the general population) we may not need to get more detail, but, represent most of that subgroup by one patient to show that no increased risk is to be expected.

When we have made a final selection of meaningful subgroups that lend themselves to be represented each by one example patient, we will determine the level of thyroid exposure for the patients in that subgroup. As an example, Table 4 provides a cross tabulation of the study population by categories that would be expected, *a priori*, to yield homogenous thyroid doses (Marilyn Stovall and Rita Weathers).

C. Comparison of three dosimetry methods

Finally, we will use the "detail coding" dosimetry data to estimate the low-dose ERR and the EAR per unit of radiation dose, gray (Gy). These analyses will be based on Poisson regression analyses from the Amfit module of the statistical program Epicure. These analyses will be performed at the NCI, as we have extensive in-house expertise with such dose-response evaluations.

Comparison of the dosimetry methods is not an explicit goal of this paper. We will, however, compare the ERR/Gy that was obtained for the case-control sample using the most comprehensive dosimetry to that obtained for the same sample using "detail coding" dosimetry, to provide a framework for a brief discussion of differences and similarities.

(i) *Outcome of interest:* thyroid cancer;

(ii) *Study subjects:* the latest "fixed" CCSS cohort of 14,363 subjects will be used as basis for these analyses. The study will include 121 thyroid cancer cases that occurred in the cohort until 2006.

(iii) *Explanatory variables:* the exposure of main interest is radiation dose to the thyroid gland, which will be available in the form of "detail coding" dosimetry to be provided by Marilyn Stovall and her team; Furthermore, we will assess EAR/Gy and ERR/Gy separately for subgroups defined by gender, age at first cancer diagnosis, age at thyroid cancer diagnosis, time between the two cancer diagnoses, any chemotherapy, any anthracyclines, any alkylating agents, and any epipodophyllotoxins, as they were used in the earlier report (Sigurdson2005).

(iv) Examples of tables and figures

Table 1 General characteristics of study subjects for the CCSS study on radiation and relative and absolute risk of second primary thyroid cancer among childhood cancer survivors

Characteristic	Person-years	Thyroid cancer cases (O)	O/E ratio (95% CI)	EAR/10,000 PY
Gender				
Male				
Female				
Type of first cancer				
<List 8>				
Age at childhood cancer diagnosis, yrs				
<5				
5-9				
10-14				
15-20				
Attained age at end of follow-up, yrs				
<10				
10-19				
20-29				
30-39				
≥40				
Time since childhood cancer diagnosis, yrs				
5-10				
10-19				
20-29				
≥30				

O observed number of cases; E expected number of cases; O/E ratio risk relative to general population. EAR excess absolute risk expressed per 10,000 patients per year

Table 2 O/E and EAR for treatment categories, if of interest, possibly using simultaneous stratification on more than one variable, for example, HL vs other cancers and treatment;

Characteristic	CCSS cohort* (N=)	Thyroid cancer cases (O) (N=121)	O/E ratio (95% CI)	EAR/10,000 PY
Any radiotherapy				
Yes				
No				
No CT, no RT				
RT only				
CT only				
RT+CT				
Radiation dose to thyroid gland, Gy†				
0				
<10				
10-19				
20-29				
30-39				
≥40				

* including patients who developed thyroid cancer
† based on "detail coding" dosimetry
O observed number of cases; E expected number of cases; O/E ratio risk relative to general population. EAR excess absolute risk expressed per 10,000 patients per year

Figure 1: cumulative incidence of thyroid cancer in the CCSS cohort and in the general US population, for males and females.

Table 3: Relative and absolute risks per unit radiation dose overall and for subgroups of the cohort

Characteristic	ERR/Gy (95% CI)	EAR/10,000 PY*Gy (95% CI)
Overall		
Gender		
Male		
Female		
Type of first cancer		
Leukemia		
CNS		
HD		
NHL		
Wilms/Kidney		
Neuroblastoma		
Soft Tissue Sarcoma		
Bone tumors		
Age at childhood cancer diagnosis, yrs		
<10		
≥10		
Attained age at end of follow-up, yrs		
<25		
≥25		
Time since childhood cancer diagnosis, yrs		
<15		
≥15		
Any chemotherapy		
No		
Yes		

Table 4: Selection of representative/typical patients to illustrate effects of various patient and treatment characteristics on estimated thyroid dose

Patients with XRT			Age at Diagnosis Number of patients (% age group)				
CCSS Primary Disease	% of Primary Group	Total number of patients	<5	5 to 9	10 to 14	15 to 20	Thyroid Radiation Exposure
Leukemia		2913					
Spine XRT	15%	439	243(16%)	113(15%)	66(15%)	17(8%)	high
No Spine XRT	84%	2474	1241(84%)	655(85%)	379(85%)	199(92%)	low
CNS		1153					
C-Spine XRT	39%	453	147(39%)	159(45%)	107(37%)	40(31%)	high
No C-Spine XRT	61%	700	234(61%)	194(55%)	183(63%)	89(69%)	medium
HD		1567					
Above the diaphragm	95%	1496	36(84%)	170(89%)	512(96%)	778(97%)	medium-high
No treatment above the diaphragm	5%	71	7(16%)	21(11%)	20(4%)	23(3%)	low
NHL		636					
Above the diaphragm	57%	365	39(42%)	116(58%)	115(58%)	95(65%)	medium-high
No treatment above the diaphragm	43%	271	53(58%)	83(42%)	83(42%)	52(35%)	low
Wilms/Kidney		693					
Chest treated	38%	263	157(33%)	93(51%)	11(41%)	2(29%)	medium
No chest treatment	62%	430	318(67%)	91(50%)	16(59%)	5(71%)	low
Neuroblastoma		412					
Chest or neck	47%	195	165(46%)	21(57%)	8(73%)	1(25%)	medium-high
No chest or neck	53%	217	195(54%)	16(43%)	3(27%)	3(75%)	low
Soft Tissue Sarcoma		686					
Chest or neck or face	58%	396	141(57%)	119(73%)	76(53%)	60(46%)	medium-high
No chest or neck or face	52%	290	105(43%)	45(27%)	68(47%)	72(55%)	low
Bone tumors		382					
Chest or neck or face	48%	197	13(65%)	38(49%)	73(53%)	61(42%)	medium-high
No chest or neck or face	52%	185	7(35%)	40(51%)	65(47%)	85(58%)	low
TOTAL		8442					

Table 5 Comparison of 3 dose estimation methods for thyroid radiation dose among children who had radiotherapy for a childhood cancer, Childhood Cancer Survivor Study#

Dose category*	Dosimetry classification method†				
	Case-control§	Detail coding		First Pass	
	N	N	% agreement	N	% agreement
None					
Low					
Medium					
High					
Very High					
Unknown					
Total					

* cut-points based on "case-control" dosimetry: 0, 10, 20, and 30 Gy.
† see Appendix for technical details
§ gold standard for the validation study
Note: we can only do this for the 69 cases that were included in the case-control study and for whom sufficient radiation info was available; the rest of the paper can include N=107 cases (minus those with insufficient Rx info)

References

Clifton KH. Thyroid cancer: reevaluation of an experimental model for radiogenic endocrine carcinogenesis. In: Upton AC, Albert RE, Burns FJ, Shore RE (eds). Radiation Carcinogenesis. Elsevier Science Publishers, Amsterdam, 1986; p. 189.

Davis S, Stepanenko V, Rivkind N, Kopecky KJ, Voilleque P, Shakhtarin V, Parshkov E, Kulikov S, Lushnikov E, Abrosimov A, Troshin V, Romanova G, Doroschenko V, Proshin A, Tsyb A. Risk of thyroid cancer in the Bryansk Oblast of the Russian Federation after the Chernobyl Power Station accident. Radiat Res 2004;162:241-8.

de Vathaire F, Hardiman C, Shamsaldin A, Campbell S, Grimaud E, Hawkins M, Raquin M, Oberlin O, Diallo I, Zucker JM, Panis X, Lagrange JL, Daly-Schveitzer N, Lemerle J, Chavaudra J, Schlumberger M, Bonaiti C. Thyroid carcinomas after irradiation for a first cancer during childhood. Arch Intern Med 1999;159:2713-9.

Hamilton TE, van Belle G, LoGerfo JP. Thyroid neoplasia in Marhall Islanders exposed to nuclear fall-out. JAMA 1987;258:629-36.

Kenney LB, Yasui Y, Inskip PD, Hammond S, Neglia JP, Mertens AC, Meadows AT, Friedman D, Robison LL, Diller L. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Intern Med 2004;141:590-7.

Kerber RA, Till JE, Simon SL, Lyon JL, Thomas DC, Preston-Martin S, Rallison ML, Lloyd RD, Stevens W. A cohort study of thyroid disease in relation to nuclear weapons testing. JAMA 1993;17:2076-82.

Likhtarov I, Kovgan L, Vavilov S, Chepurny M, Ron E, Lubin J, Bouville A, Tronko N, Bogdanova T, Gulak L, Zablotska L, Howe G. Post-Chornobyl thyroid cancer in Ukraine. Report 2: risk analysis. Radiat Res 2006;166(2):375-386.

Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study. J Natl Cancer Inst. 2001;93:618-629.

Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA, Boice JD Jr. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995; 141:259-77.

Ron E. Thyroid cancer. In: Schottenfeld D & Fraumeni JF Jr. (eds). Cancer epidemiology and prevention. 1996 Oxford Press, 2nd edition.

Shore RE. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. Radiat Res 1992;131:98-111.

Sigurdson AJ, et al. Second thyroid carcinomas in the childhood cancer survivor cohort. CCSS Concept Proposal 00-06. 2000.

Sigurdson AJ, Ronckers CM, Mertens AC, Stovall M, Smith SA, Liu Y, Berkow R, Sklar CA, Hammond S, Neglia JP, Meadows AT, Robison LL, Inskip PD. Second primary thyroid cancer after a first childhood malignancy: A report from the Childhood Cancer Survivor Study. Lancet 2005;365:1014-23.

Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, Sugimoto S, Ikeda T, Terasaki M, Izumi S, et al.Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958-1987. Radiat Res 1994;137(2 Suppl):S17-67.

Tronko MD, Howe GR, Bogdanova TI, Bouville AC, Epstein OV, Brill AB, Likhtarev IA, Fink DJ, Markov VV, Greenebaum E, Olijnyk VA, Masnyk IJ, Shpak VM, McConnell RJ, Terenshchenko VP, Robbins J, Zvinchuk OV, Zablotska LB, Hatch M, Luckyanov NK, Ron E,

Thomas TL, Voilleque PG, Beebe GW. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: thyroid cancer in Ukraine detected during first screening. J Natl Cancer Inst 2006;98(13):897-903.

Tucker MA, Jones PH, Boice JD Jr, Robison LL, Stone BJ, Stovall M, Jenkin RD, Lubin JH, Baum ES, Siegel SE, et al. Therapeutic radiation at a young age is linked to secondary thyroid cancer. The Late Effects Study Group. Cancer Res 1991;51:2885-8.

Appendix

Dosimetric methods

(1) First pass coding
1st pass coding allowed abstractors to check regions of the body treated including:
brain, head (not brain), neck, chest, abdomen, pelvis, spine, total body, limb or unknown.
Regions treated were grouped if the dates of treatment were the same (within a few days) and the tumor doses were in the same dose category.

Dose to thyroid from 1st pass coding was calculated as follows:
Generic doses were run for a 1, 3, 10, and 15 year old for central 10x10 fields to 1000 tumor dose (TD) in the head, chest, abdomen, pelvis and leg. The chest field was reduced for 1 and 3 year old to place the thyroid out of beam. The head treatment was L and R lateral (brain), all others were run as ap/pa. Doses were calculated for Co-60 and 6 MV. The doses at the ages selected were averaged to get doses for 3 broad age categories: 0-3, 3-10 and 10-adult.

Thyroid dose was assumed to be in beam for all neck, TBI and spine fields unless coded otherwise. If "thyroid" was coded "blocked" or "maybe" thyroid dose was reduced to 10% and 50% of reported TD range respectively. For all other body regions, the thyroid was considered out of beam and the doses were calculated as a percentage of the coded TD range using the "nearest" region treated and the tables below.

6MV data: dose per cGy TD

Region	0 to 3 yr old	3 to 10 yrold	> 10 yrs	Electron	Brachy
Head	0.0170	0.0100	0.0060	0.0000	0.0000
Neck	1.0000	1.0000	1.0000	1.0000	1.0000
Chest	0.0360	0.0530	0.0330	0.0000	0.0000
Abdomen	0.0120	0.0060	0.0020	0.0000	0.0000
Pelvis	0.0030	0.0010	0.0007	0.0000	0.0000
Lower Limb	0.0010	0.0005	0.0002	0.0000	0.0000

Co-60 data: dose per cGy TD

Region	0to3yrold	3to10yrold	>10yr	Electron	Brachy
Head	0.044	0.030	0.021	0.000	0.000
Neck	1.000	1.000	1.000	1.000	1.000
Chest	0.080	0.095	0.063	0.000	0.000
Abdomen	0.035	0.025	0.010	0.000	0.000
Pelvis	0.014	0.010	0.004	0.000	0.000
Lower Limb	0.005	0.003	0.001	0.000	0.000

The data was applied by region selected in 1st pass coding and age category was based on age at beginning of therapy. The coded TD range was used to calculated an upper bound, lower bound and midpoint of the dose category coded for the body region "nearest" the thyroid. The upper limit of the highest dose category was set to 7500 cGy. No doses were estimated for dose category "incident dose", "unknown dose" or "unknown site of treatment".

I calculated doses using the coded categories from 1st pass as "treatment doses" and calculate doses using the highest, lowest and midpoint for the categories. I added the thyroid dose calculated from each of the "body regions" treated to get a "range of dose". I added the highest to all other highest and lowest to all other lowest and midpoints to all other midpoints for each patient and ended up with 3 "thyroid doses" for each subject "high, mid, low". I have all three doses, so I actually have a range of dose for each patient
[source: Emails Rita Weathers, dd. May 5 and May 10, 2005]

(2) Detail coding
Detail coding provides descriptions of each radiation treatment field or set of fields used in a patient's therapy. Information recorded includes total dose to each field or total tumor dose from the combination of fields, the size of the fields as measured at the surface of the patient, direction of entry of the beam (lateral, anterior, posterior), energy of beam used and location of the fields on the body. The fields are located either by the center of the targeted site on the body or by specifying the area covered using anatomical locations for top and bottom of the field (such as suprasternal notch to diphragm, umbilicus to pelvic floor, or specific vertebra such as C6 to T9). Information about shaping blocks, wedges or other beam modifiers is not included in detail coding.

Dose to thyroid from detail coding was calculated as follows: The list of eligible patients was used to pull the coded data from the CCSS detail coding. Missing information about beam energy, field extent and dose definition was determined by reviewing known treatment details for similar treatments. Additional assumptions were added that related to the thyroid in particular. These included:

- CNS treatment for leukemia that included the spine also included treatment to the cervical spine either through the spinal field or an extended lateral brain field. In either case the thyroid was assumed to be in beam;
- Mantle fields for Hodgkin disease extend to least the midneck and most extend to the jaw, therefore, the thyroid will fall in the primary beam for mantle fields;
- The thyroid is on the edge or in a lateral neck field depending on size of the field, and size of the patient – location and size are used as coded from the record;
- Anterior neck+supraclav fields extend to midline, so one lobe of the thyroid is in beam and the other is just outside the beam. Not all fields were reviewed, but defaults were set for this configuration to extend to midline;
- Blocking of the thyroid is not assumed for any treatment, although we know the thyroid was blocked for all or part of some treatments. We elected to ignore information from 1st pass coding about thyroid blocking because linking the fields to the 1st pass coding would require additional review.
- Fields should not overlap unless there was extensive treatment directed to the neck (patient 09035693 – melanoma of neck at age 37)
- No treatment was eliminated assuming we would not have individual cutoff dates for a cohort study, therefore some doses include treatment after the case/control cutoff dates.

The MDA generic dose program with the mathematical phantom was used to calculate doses to 9 points in the left thyroid lobe and 10 in the right lobe. The generic program adjusts distances and depth from fields to regions of interest (thyroid in this case) to be appropriate for the age of the patient at the time of treatment. The dose to each point in each lobe is calculated and averaged to provide an single average dose to each thyroid lobe. The same points were used for the case control calculations. For treatments far from the thyroid, the same detail coding and generic program was used to calculate dose contribution to the thyroid so there should be perfect

agreement for most of the patients not treated to the chest, head or neck unless treatment was after the case control cutoff dates or additional information was received after the case control doses were submitted.
[source: Email & attachment from Rita Weathers, dd. June 3, 2005]

(3) Case-control
Dose to the left and right lobes of the thyroid gland and the pituitary gland were calculated separately. Absorbed organ doses, including doses from radiation scatter, were estimated by one of three methods, depending on the proximity of the organs to treatment beams. If the organ was outside the nearest treatment field, doses were based on out-of-beam measurements in a water phantom.[1] Dose to organs in the beam was derived using standard radiotherapy techniques.[2] Treatment planning system calculations were used when the organ was under blocking.[3]
[source: Sigurdson, 2005]

References
(1) Stovall M, Weathers R, Kasper C, Smith SA, Travis L, Ron E, Kleinerman R. Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiologic studies. Radiat Res. 2006;166:141-57.
(2) Anonymous. Central axis depth dose data for use in radiotherapy: a survey of depth doses and related data measured in water or equivalent media. Br J Radiol Suppl. 1983;17:1–147.
(3) Philips Medical Systems. Radiation Oncology Systems: Pinnacle3. Available at: http://www.medical.philips.com/main/products/ros/products/pinnacle3/ Accessibility verified June 14, 2004.