

**CHILDHOOD CANCER SURVIVOR STUDY**  
**Analysis Concept Proposal**  
**August 17, 2009**

1. **STUDY TITLE:** Cardiovascular risk factor cluster and cardiovascular outcomes in adult survivors of pediatric cancer
2. **WORKING GROUP AND INVESTIGATORS:** This proposed publication will be within the Chronic Disease Working Group. Proposed Investigators will include:

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3. **BACKGROUND AND RATIONALE**

As the initial cohort of CCSS participants ages, medical outcomes of these survivors may resemble those of middle aged Americans, albeit perhaps at a younger age. Included in these medical problems are increased risks for cardiac disease.<sup>1-9</sup> previously we utilized medication self-report data from the Follow-Up 2 (2003) questionnaire to evaluate the presence of diabetes, hypertension and dyslipidemia in the CCSS cohort (manuscript submitted). Individuals whose data indicated that they had any three of the four conditions (diabetes, hypertension, dyslipidemia or BMI > 30 kg/m<sup>2</sup>) were classified as meeting the criteria for cardiovascular risk factor clustering (CVRFC). This definition accommodates the nature of the CCSS data and mirrors similar definitions in the literature for metabolic syndrome.<sup>10-13</sup>

In our previous analysis (presented at the International late effects meeting, Niagara-on-the-Lake, 2008), survivors when compared to siblings were 2.1 time more likely to be on a medication for hypertension, 1.5 times more likely to be on a medication for dyslipidemia, 1.8 times more likely to be taking a medication for diabetes/hyperinsulinemia. Survivors were not more likely than siblings to be obese. Survivors were more likely than siblings to have 3 of 4 cardiovascular risk factors (CVRFC) OR 1.3 95% CI 0.9-1.9 but this did not reach statistical significance.

In our previous analysis we attempted to correlate the presence of CVRFC with the self report of CV disease and stroke. This analysis was limited because the cardiovascular events (CVE) were reported in the baseline survey (1995) and the CVRFC were determined from follow-up 2003. Despite the disconnect in time, we proceeded with the analysis based on the fact that often silent disease like hypertension, hyperglycemia or insulin resistance and dyslipidemia are present for years preceding diagnosis. With these limitations in mind, survivors with CVRFC were compared to survivors without CVRFC and were found to be

9.2 times more likely to have had a cardiovascular event (95% CI 8.5-23.4) and the OR for those specific events were: hardening of the arteries 4.7 (95% CI 1.1-19.7), myocardial infarction 18.3 (95% CI 8.7-38.6) and coronary heart disease 12.1 (95% CI 5.0-29.2). The OR for stroke was 2.0 with a 95% CI of 0.7-5.4.

In this follow-up project we propose to document the prevalence of the CVRFs, obesity, hypertension, dyslipidemia and diabetes/impaired glucose tolerance, at 3 time points: baseline, follow-up 2 (FU2) and follow-up 4 –2007 (FU4) using the same criteria as in our initial study. We also propose to examine the prevalence of CV events (grade 3, 4 and cardiac surgery) and then identify 1) associations between CVRFs and cardiac events, and 2) determine the predictive nature of CVRFs for cardiac event.

Cardiovascular death is a common cause of treatment-related mortality among survivors of childhood cancer, second only to death attributable to subsequent malignant neoplasms.<sup>14</sup> The most recent CCSS search of the National Death Index through December 31<sup>st</sup>, 2002 identified 176 deaths in the cohort where the underlying cause of death was attributed to diseases of the circulatory system including: cardiomyopathy (46), ischemic heart disease (44), cerebrovascular disease (19), heart failure (6) and other cardiac disease (61).<sup>15</sup> While the cumulative incidence of cardiac death at 30 years is low, the rate of cardiac mortality is increasing with time and merits close observation. Previous analyses have already demonstrated associations with anthracycline cumulative dose and chest RT. However, it is unknown whether the additional cardiovascular risk factors such as obesity, hypertension, diabetes and hyperlipidemia that develop in this population as they age will result in high rates of premature cardiac death. We propose to update the cardiac mortality experience of the CCSS cohort based on NDI data through December 31, 2007 and to identify associations between CVRFs, CVRFC and cardiac death.

#### 4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

**Aim 1** Identify changes in the prevalence of obesity, diabetes, hypertension, or dyslipidemia requiring medications for management and CVRFC in cancer survivors over time (baseline, follow-up 2, follow-up 4) compared to siblings at the same time points.

Hypothesis 1: Compared to siblings, survivors, at all time points, will have greater prevalence of:

- Obesity
- Hypertension on medication therapy
- Dyslipidemia on medication therapy
- Diabetes mellitus on medication therapy

Hypothesis 2: Adult survivors compared to siblings will have a higher prevalence of CVRFC.

Hypothesis 3: The increase in prevalence of CVRF and CVRFC over time will be greater in survivors than in sibling.

**Aim 2** Identify correlates of risk for CVRF and CVRFC in follow up 4.

Hypothesis 1: Previously demonstrated demographic variables (race/ethnicity, age at questionnaire, sedentary lifestyle) will become even more strongly associated with CVRF and CVRFC with time.

Hypotheses 2: Previously demonstrated cancer diagnostic categories will be even more strongly associated with CVRF and CVRFC with time and new associations will be found as more survivors are diagnosed with CVRF and CVRFC.

Hypothesis 3: Previously demonstrated treatment variables (anthracycline exposure, RT exposure including: chest, abdomen, cranial, total body irradiation) will be even more strongly associated with CVRF and CVRFC with time and new associations will be found as more survivors are diagnosed with CVRF and CVRFC.

**Aim 3** Identify associations between CVRFs/CVRFC and long-term cardiac morbidity, defined as a grade 3-5 cardiovascular event or cardiac surgery.

Hypothesis 1: All four CVRFs and CVRFC will be associated with an increased risk for a grade 3/4 cardiac event.

Hypothesis 2: Prevalence of a CVRF or of CVRFC will be predictive of a future cardiac event.

**Aim 4** Describe cardiac mortality (mortality rate, cumulative incidence, standardized mortality ratios) in the CCSS cohort through Dec. 31, 2007 and identify cardiovascular risk factors associated with cardiac death.

Hypothesis 1: Survivors, now at a median age of 34 years, will have increasing rates of cardiac mortality with age.

Hypothesis 2: CVRFs and CVRFC will be associated with increased risk of cardiac death.

## **5. ANALYSIS FRAMEWORK:**

a. Subject population:

**Aim 1 & 2:** Childhood cancer survivors who are enrolled in CCSS who have completed any combination of surveys (baseline, follow-up #2, follow-up #4). Survivors with a second malignant neoplasm and recurrence after completion of the MRAF should be excluded after they develop the SMN or recurrence.

**Aim 3 & 4:** Childhood cancer survivors who completed the baseline survey and at least one additional follow-up survey (either Follow-up #2 or Follow-up #4). Survivors with a second malignant neoplasm and recurrence after completion of the MRAF should be excluded after they develop the SMN or recurrence.

b. Comparison group: Siblings who have completed any combination of surveys (baseline, follow-up #2, follow-up #4) and have not been diagnosed with cancer. Mortality data will be compared with age and gender matched data from the National Center for Health Statistics.

c. Outcomes of interest:

**Aims 1 & 2:** Cardiovascular Risk Factors (Baseline, FU2 and FU4)

- Body mass Index  $\geq 30$  kg/m<sup>2</sup>
- Dyslipidemia defined as treatment with medications to lower cholesterol or triglycerides. (using the list established for the Meacham, CVRF project)
- Hypertension defined as treatment with medications for high blood pressure for hypertension . (using the list established for the Meacham, CVRF project)
- Impaired glucose tolerance / DM defined as treatment with oral medication or insulin for diabetes. (using the list established for the Meacham, CVRF project)

**Aim 3:** Cardiovascular events

Grade 3: coronary artery disease (on medication), CHF (on medication), atrial fibrillation or flutter, supraventricular dysrhythmia.

Grade 4: myocardial infarction (MI), heart transplant for cardiomyopathy, cerebrovascular accident, endocarditis, cardiac arrest, arterial embolism.

Cardiac surgery: coronary artery bypass, pericardectomy, heart catheterization, angioplasty, surgery for heart valve replacement, surgery for pacemaker, other heart surgery.

\*Note: We acknowledge the potential for missing data among deceased patients for events that occurred between the time of their last survey completion and the time of their death. Considering the high likelihood that patients who experienced a cardiac cause of death also experienced a cardiac health condition we will include patients who are deceased of cardiac death, who did not report a prior cardiac condition as incident cases of a cardiovascular event for the purposes of Aim 3.

**Aim 4:** Death due to Disease of the Circulatory System (ICD 390-459)

d. Exploratory variables of interest :

Socio-demographics

- Gender
- Race/ethnicity
- Annual household income
- Age at interview
- Sedentary lifestyle
- Tobacco/smoking
- Alcohol consumption
- Current steroid use

Cancer diagnosis  
Cancer treatment  
Radiation  
    TBI  
    Cranial  
    Craniospinal RT  
    Abdominal (no chest)  
    Abdominal (w/ chest)  
    Chest (no abd)  
    Other  
    None  
Chemotherapy  
    Alkylating Agents  
    Anthracyclines  
    Cisplatin  
HSCT  
Cardiovascular Risk Factors

- Body mass Index  $\geq 30$  kg/m<sup>2</sup>
- Dyslipidemia defined as treatment with medications to lower cholesterol or triglycerides.
- Hypertension defined as treatment with medications for high blood pressure for hypertension.
- Impaired glucose tolerance / DM defined as treatment with oral medication or insulin for diabetes.

f. Statistical analysis

**Aim 1:** Give prevalence of CVRFs/CVRFC at baseline, FU2, FU4, for survivors and siblings who participated in each of these surveys with calculated odds ratios adjusted for age, sex and ethnicity and accounting for intra-family correlation (Table 2).

**Aim 2:** Multivariable logistic regression including all variables in Tables 3 and 4 (two models)

**Aim 3:** This aim will consist of an initial analysis to identify associations between CVRFs/CVRFC and cardiac outcomes and then assess the predictive nature of a CVRF or CVRFC for the development of a future cardiac outcome. For the analysis of association, we will explore combinations of timing or frequency of CVRFs reported across three surveys (baseline, FU2, FU4) and their associations with Grade 3/4 cardiac outcomes and cardiac surgery (Table 5), and additionally for specific cardiac outcomes (Table 6). Then, the predictive nature of CVRFs and CVRFC will be determined by excluding cardiac events identified at baseline. CVRFs/CVRFC identified prior to FU4 (or prior to FU2 if a cardiac event occurred at FU2) will be quantified to determine whether they predict a cardiac event at FU2 or FU4.

**Aim 4:** We will report, based on an updated NDI search, the cumulative incidence of cardiac death, SMR and Annual Mortality rate (Table 7) as well as a list of the specific causes of cardiac death (Table 8). Multiple Poisson regression will be used to calculate the relative rate of mortality due to cardiac disease across key independent risk factors including: sex, age at diagnosis, years since diagnosis, CVRFs, RT (including chest, spine and TBI), alkylating score, anthracycline cumulative dose and Cisplatin (yes/no).

## 6. TABLES/FIGURES:

**Table 1. Demographic and cancer-related demographics of participants**

	Questionnaire	Survivors # and %	Siblings # and %
Gender Male Female	Baseline		
Ethnicity White Black Hispanic other	Baseline		
Age at diagnosis <5 5-9.9 10-14.9 >15	Baseline		
Household income <20K 20-39,999K >40K Not indicated	FU4 A6		
Age at last follow-up <20 20-29 30-39 40-49 >50			
Mean age at last interview			
Smoker Current Former Never	FU 4 N7 FU4 N9		
Physical Activity Physical activity during leisure time during the last month Yes No Did not respond	FU4 N15 Other questions?		
BMI <18.5 kg/m2 18.5-24.99 25-29.99 >30	FU4 A1 and A2		
Cancer Diagnosis All Leukemias ALL AML Other leukemia  CNS Tumors (all) Astrocytoma Medulloblastoma/PNET Other CNS tumor	Baseline		

Hodgkin Disease NHL Wilms' Neuroblastoma Bone Tumors (all) Soft Tissue Sarcoma Ewings Sarcoma Osteosarcoma Other bone malignancy			
Radiation None CRT (w/o spinal) Craniospinal Chest + Abdomen Chest (without abdomen) Abdomen (without chest) TBI Other Radiation			
Alkylator None First Tertile Second Tertile Third Tertile			
Anthracycline None <100 100-299 >300 Any dose plus chest, heart RT, CSRT or TBI			
Carboplatin or Cisplatin			
Steroids			
BMT			
Diabetes*			
Hypertension*			
Hyperlipidemia*			



Cardiovascular events (all grade 3/4)			
Coronary Artery disease			
Congestive Heart Failure			
Atrial Flutter/Fibrillation			
Supraventricular Dysrhythmia			
Myocardial Infarction			
Cardiac Transplant			
Cerebrovascular accident			
Endocarditis			
Cardiac arrest			
Coronary Artery Bypass			
Heart Catheterization			
Angioplasty			
Valve Replacement			
Pacemaker			

\*See analysis framework (section 5c) for specific definition of these outcomes

**Table 2. Frequencies of individual and clustered cardiovascular risk factors with odds ratio for survivors compared with siblings.**

<b>Baseline</b>	<b>BMI ≥ 30 kg/m<sup>2</sup></b>	<b>Hyper- tension*</b>	<b>Dyslipidemia*</b>	<b>Diabetes mellitus*</b>	<b>CVRFC</b>
Baseline % Survivors					
Baseline% Siblings					
<b>Baseline OR (CI)</b>					
FU 2 % Survivors					
FU 2 % Siblings					
<b>FU 2 OR (CI)</b>					
FU 4 % Survivors					
FU 4 % Siblings					
<b>FU 4 OR (CI)</b>					

\* On current medication therapy for condition.

+ Clustered CVRFC: obesity plus at least two of the three CVRFC.

**Table 3. Relative odds and 95% confidence intervals of having individual or combined cardiovascular disease risk factors for adult survivors of childhood cancer by diagnosis, adjusted for sex, race/ethnicity and age at questionnaire completion**

FU 4	Obesity		Hypertension		Dyslipidemia		Diabetes		Any Th
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR
<b>Sex</b>									
Male(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1.0
Female									
<b>Race/Ethnicity</b>									
White(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1.0
Black									
Hispanic									
Other									
<b>Age at questionnaire</b>									
< 30 years(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1.0
30-39 years									
40+ years									
<b>Cancer diagnosis</b>									
Siblings(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1.0
Acute lymphoblastic leukemia									
Acute myeloid leukemia									
Other leukemia									
Astrocytoma									
Medulloblastoma									
Other CNS malignancy									
Hodgkin Lymphoma									
NHL									
Wilm's Tumor									
Neuroblastoma									
Soft tissue sarcoma									
Ewings sarcoma									
Osteosarcoma									
Other bone malignancy									

NE=Not estimable, OR=Odds ratio, CI=Confidence interval

**Table 4. Relative odds and 95% confidence intervals of having individual or combined cardiovascular disease risk factors for adult survivors of childhood cancer by demographic and lifestyle factors, cancer treatment parameters, and current steroid use.**

FU 4	Obesity		Hypertension		Dyslipidemia		Diabetes		A C
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	
<b>Sex</b>									
Male(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
Female									
<b>Race/Ethnicity</b>									
White(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
Black									
Hispanic									
Other									
<b>Age at questionnaire</b>									
< 30 years(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
30-39 years									
40-49 years									
50+ years									
<b>Age at diagnosis</b>									
< 5 years(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
5-9 years									
10-14 years									
15-20 years									
<b>Annual household income</b>									
\$40,000+ (reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
<\$20,000									
\$20,000-39,000									
Not indicated									
<b>Platinum</b>									
No(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
Yes									
<b>Anthracycline dose</b>									
None(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
< 100 mg/m <sup>2</sup>									
100-299 mg/m <sup>2</sup>									
> 300 mg/m <sup>2</sup>									
<b>Chest Radiation</b>									
No (reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
Yes									
<b>Cranial radiation</b>									
No(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
Yes									
<b>Abdominal radiation</b>									
No(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
Yes									
<b>Total body irradiation</b>									
No(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
Yes									
<b>MD visit past 2 years</b>									
No(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1

Yes									
<b>Sedentary</b>									
No(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
Yes									
<b>Smoking status</b>									
Never(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
Former									
Current									
<b>Current steroid use</b>									
No(reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
Yes									
<b>BMT</b>									
No (reference)	1.0	reference	1.0	reference	1.0	reference	1.0	reference	1
Yes									
<b>Alkylating Score</b>									
None	1.0	reference	1.0	reference	1.0	reference	1.0		
1 <sup>st</sup> tertile									
2 <sup>nd</sup> tertile									
3 <sup>rd</sup> tertile									

Table 5. Cardiovascular Risk Factors (identified at various possible survey times) and Cardiovascular Events occurring after baseline

	Any Grade 3 Event		Any Grade 4 Event		Any Grade 3 or 4 Event		Cardiac Surgery		Grade 3 Surg	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
CVRFC Baseline										
CVRFC FU2										
CVRFC FU4										
CVRFC Baseline + FU2										
CVRFC Baseline + FU4										
CVRFC Baseline + FU2 + FU4										
CVRFC FU2 + FU4										

	Grade 3 Event		Grade 4 Event		Grade 3+4 Event		Cardiac Surgery		Grade 3 Surg	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Obesity Baseline										
Obesity FU2										
Obesity FU4										
Obesity Baseline + FU2										
Obesity Baseline + FU4										
Obesity + FU2 + FU4										
Obesity FU2 + FU4										

	Grade 3 Event		Grade 4 Event		Grade 3+4 Event		Cardiac Surgery		Grade 3 Surg	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
HTN Baseline										
HTN FU2										
HTN FU4										
HTN Baseline + FU2										
HTN Baseline + FU4										
HTN Baseline + FU2 + FU4										
HTN FU2 + FU4										

	Grade 3 Event		Grade 4 Event		Grade 3+4 Event		Cardiac Surgery		Grade 3 Surg	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Dyslipidemia Baseline										
Dyslipidemia FU2										
Dyslipidemia FU4										
Dyslipidemia Baseline + FU2										
Dyslipidemia Baseline + FU4										
Dyslipidemia Baseline + FU2 + FU4										
Dyslipidemia FU2 + FU4										

	Grade 3 Event		Grade 4 Event		Grade 3+4 Event		Cardiac Surgery		Grade 3 Surg	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Diabetes Baseline										
Diabetes FU2										
Diabetes FU4										
Diabetes Baseline + FU2										
Diabetes Baseline + FU4										
Diabetes Baseline + FU2 + FU4										
Diabetes FU2 + FU4										





Table 6. Cardiovascular Risk Factors (identified at various possible survey times) and Specific Cardiovascular Events (occurring after baseline)

Grade 3	Coronary Artery Disease		Congestive Heart Failure		Atrial Fibrillation/Flutter		Supraventricular Dysrhythmia			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
CVRFC Baseline										
CVRFC FU2										
CVRFC FU4										
CVRFC Baseline + FU2										
CVRFC Baseline + FU4										
CVRFC Baseline + FU2 + FU4										
CVRFC FU2 + FU4										

Grade 4	Myocardial Infarction		Transplant for Cardiomyopathy		Cerebrovascular Accident		Endocarditis		Cardiac Arrest	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
CVRFC Baseline										
CVRFC FU2										
CVRFC FU4										
CVRFC Baseline + FU2										
CVRFC Baseline + FU4										
CVRFC Baseline + FU2 + FU4										
CVRFC FU2 + FU4										

Surgery	Coronary Artery Bypass		Heart Catheterization		Angioplasty		Valve Replacement		Pacemaker	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
CVRFC Baseline										
CVRFC FU2										
CVRFC FU4										
CVRFC Baseline + FU2										
CVRFC Baseline + FU4										
CVRFC Baseline + FU2 + FU4										
CVRFC FU2 + FU4										



Table 7 Life status and standardized mortality ratios in 5-year survivors for cardiac death

	Eligible cohort No. of patients	Cardiac death No. of patients	SMR (95% CI)	P value	Annual Mortality Rate	P value
All patients						
<b>Sex</b>						
Male						
Female						
<b>Treatment Era</b>						
1974-1980						
1981-1987						
1988-1994						
1995-2000						
<b>Age at diagnosis</b>						
0-4						
5-9						
10-14						
15-19						
>19						
<b>Survival after diagnosis (years)</b>						
5-9	-	-				
10-14	-	-				
15-19	-	-				
20-24	-	-				
25-29	-	-				
30-34	-	-				
<b>Diagnosis</b>						
ALL						
AML						
Hodgkin Disease						
Non-Hodgkin						
Astrocytoma						
Medulloblastoma						
Ependymoma						
Osteosarcoma						
Ewing's Sarcoma						
Rhabdomyosarcoma						
Neuroblastoma						
Hepatic Tumor						
Renal Tumor						
Retinoblastoma						

Table 8. Specific Causes of cardiac death

<b>Specific Cause of death (ICD codes)</b>	<b>Total</b>	<b>Male</b>	<b>Female</b>
Diseases of the Circulatory system (390-459)			
Ischemic Heart Disease (410-414)			
Cardiomyopathy (425)			
Heart Failure (428)			
Cerebrovascular disease (430-438)			
Other (list)			

**Table 9. Risk factors for mortality due to cardiac disease**

<b>Risk factor</b>	<b>RR (95% CI)</b>	<b>P value</b>
<b>Sex</b>		
<b>Male (referent)</b>		
<b>Female</b>		
<b>Age at diagnosis</b>		
<b>0-4</b>		
<b>5-9</b>		
<b>10-14</b>		
<b>15-19</b>		
<b>&gt;=20 (referent)</b>		
<b>Years since diagnosis</b>		
<b>5-9 (referent)</b>		
<b>10-14</b>		
<b>15-19</b>		
<b>20-24</b>		
<b>&gt;=25</b>		
<b>CVRF</b>		
<b>Obesity</b>		
<b>Hypertension</b>		
<b>Dyslipidemia</b>		
<b>Diabetes</b>		
<b>CVRF cluster</b>		
<b>None (referent)</b>		
<b>Radiation*</b>		
<b>Chest RT</b>		
<b>non- Chest RT</b>		
<b>no (referent)</b>		
<b>Alkylating agent score</b>		
<b>none (referent)</b>		
<b>1-2</b>		
<b>3-4</b>		
<b>&gt;=5</b>		
<b>Anthracycline</b>		
<b>none (referent)</b>		
<b>1-100mg/m2</b>		
<b>101-250 mg/m2</b>		
<b>251-400 mg/m2</b>		
<b>&gt;400 mg/m2</b>		

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