STUDY TITLE

Predicting cardiovascular disease among childhood cancer survivors: creation and application of a risk score model

WORKING GROUP

Primary: Chronic Disease Working Group
Secondary: Epidemiology & Biostatistics

INVESTIGATORS

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BACKGROUND & RATIONALE

Analyses from the CCSS have shown that among childhood cancer survivors, cardiovascular (CV) disease is an important contributor to late mortality (standardized mortality ratio = 7)[1] and morbidity[2]. Specific outcomes shown to be increased among survivors compared with siblings include myocardial infarction, congestive heart failure, pericardial disease, and valvular disease (hazard ratios [HRs] ranging from 5-6)[2]. Although overall CV mortality and serious morbidity remain rare (~1% cumulative mortality at 30 years[1]; 1.5-4% cumulative incidence of selected outcomes[2]) in this relatively young population (median age 27 years[2]), survivors also have been shown to be at increased risk for conditions that predispose towards future more serious CV disease in the general population, such as hypertension, dyslipidemia, and diabetes[3]. Selected survivor subsets also have been shown to be at increased risk of obesity[4,5]. Therefore, with continued follow-up, the prevalence and overall risk of CV disease is expected to increase disproportionately among survivors compared with siblings or age-adjusted population norms, at least for the next 10-20 years.

CCSS analyses devoted to CV outcomes published to date and/or in process (e.g. approved concept by Armstrong/Meacham currently under analysis) have primarily focused on population-level data, e.g. cumulative incidence(s) or the risk associated with single factors in multivariate models[1-3]. Such studies have identified differential risk associated with sex, age at diagnosis, race/ethnicity, physical activity, treatment era, and select treatment exposures such as higher anthracycline and chest radiation doses. However, the available data have never been analyzed with respect to predicting and discriminating risk on an individual level. With the aging of the CCSS cohort and an increased number of CV outcomes expected, we propose to use updated CCSS data (through Follow-up 2007) to estimate individual-level risk for overall and select CV outcomes, and to describe the cumulative effect of multiple potential CV risk factors in combination. Such an analysis may facilitate the creation of an easily applied, clinically relevant risk score designed to discriminate levels of future CV risk based on individual

characteristics, and thereby inform future health surveillance efforts. Given the overlap in risk factors and disease pathways but also realizing that important differences in pathophysiology exist, the proposed analysis also will examine whether a single risk score model would be useful in predicting global CV morbidity/mortality versus separate models for individual CV outcomes among childhood cancer survivors.

This proposal will employ similar methodology as has been used to generate Framingham[6] and other CV disease risk score models[7] that have been developed for the general population and have been found to be clinically applicable. Similar methodology also has been applied to cancer populations to predict other outcomes[8,9]. One difference between these studies and the proposed analysis will be our application of newer prediction methodology that takes better advantage of the prospective longitudinal follow-up data in the CCSS[10]. The other major difference for any CCSS-based effort versus existing CV risk scores will be the lack of physiologic data in CCSS. However, as the primary goal of this proposal is to define risk categories predictive of individual risk based on baseline treatment and demographic covariates, lack of information on subsequent blood pressure and laboratory values may be of less concern. However, our proposed secondary analysis will examine the effect of self-reported co-morbid conditions such as hypertension and dyslipidemia on our risk model(s). Results may provide additional impetus for future efforts to incorporate physiologic data into risk assessment and prediction of CV late effects for childhood cancer survivors.

SPECIFIC AIMS

1. Generate a prediction model based on proportional hazards models and a time-dependent receiver operating characteristic (ROC) curve approach to predict CV morbidity, mortality and selected individual CV outcomes (myocardial infarction, congestive heart failure, pericardial disease, valvular disease, and stroke) following childhood cancer treatment as associated with baseline treatment and demographic factors.
2. Among individuals free of selected CV outcomes at the time of the baseline survey, determine whether inclusion of available behavioral factors (e.g. inactive lifestyle, current tobacco use) and underlying medical conditions associated with increased CV risk (obesity, hypertension, dyslipidemia, diabetes) improve CV outcomes prediction.
3. Validate prediction model(s) created in Aims #1 and #2 by determining the discriminatory power and calibration of risk scores when applied to a subset of the CCSS cohort.

HYPOTHESES

1. Hazards will be increased for those who are: younger at time of initial cancer treatment, female, and exposed to greater cumulative doses of anthracyclines and/or chest radiotherapy.
2. A risk score model(s) can be devised that will discriminate between low, average, and high risk of CV outcomes in this population.
3. Inclusion of behavioral and co-morbid medical conditions, adjusted for current age, will improve discrimination as measured by AUC.

ANALYSIS FRAMEWORK

Outcomes of interest

Outcomes of interest will be abstracted from the baseline survey and subsequent surveys (through 2007). As the CCSS cohort is defined by 5-year survivorship, only outcomes reported ≥5 years from diagnosis will be analyzed. The following outcomes are of interest:

Outcome	Previously reported prevalence, n (%)[a]	Update status
CV morbidity, overall	*Unknown - Oeffinger's 2006 NEJM analysis supplemental file only reports individual outcomes, and not collective outcome.*	
Mortality	176 (0.9%)[b]	Updated NDI search planned
Myocardial infarction	101 (0.7%)[c] / 46 (0.5%)[d]	Follow-up 2007
Congestive heart failure	248 (1.7%)[c]	Follow-up 2007
Pericardial disease	181 (1.3%)[c]	Follow-up 2007
Valvular disease	238 (1.6%)[c]	Follow-up 2007
Stroke	151 (1.8%)[d] / 162 (1.6%)[e]	Follow-up 2007

[a] Individuals from each category may overlap.
[b] Mertens, J Natl Cancer Inst 2008. Based on 20,483 survivors and NDI records through 2002.
[c] Mulrooney, BMJ 2009. Based on 14,348 survivors who responded to the baseline survey and any information from follow-up 2000 survey.
[d] Meacham, Cancer Epidemiol Biomarkers Prev 2010. Based on 8,599 survivors who responded to Follow-up 2003.
[e] Oeffinger, N Eng J Med 2006. Based on 10,397 survivors who responded to the baseline survey.

As a time-to-event analysis is proposed for Aim #1, we will impute the age at occurrence for those individuals who report outcome(s) of interest but without accompanying age of onset information, as done previously (9% of outcomes[2]). This will allow us to better preserve our limited sample size.

Subject population

- Entire CCSS survivor cohort (treated 1970-1986) would be eligible for Aims #1. As our CV outcomes of interest are all potentially life-threatening, individuals who report development of these conditions within 5 years of diagnosis will be excluded from analysis. Competing risks and censoring is described further below (see Statistical Methods, Aim #1).
- Aim #2 would be restricted to survivors who were free of our outcome(s) of interest at the time of the baseline survey.
- Aim #3 would feature all survivors from a validation set (randomly selected 1/3 portion of the CCSS cohort), who developed the same outcome(s) of interest ≥5 years from diagnosis and prior to the diagnosis of any recurrence or secondary malignancy.
- *As the intent of this analysis is to determine CV risk factors relevant to survivors, siblings will not be examined in this analysis. The anticipated very low numbers of adverse CV outcomes among siblings also will likely preclude meaningful analysis of the sibling cohort.*

Exploratory variables

The following exploratory variables will be considered given their potential role in influencing our CV outcomes of interest.

- Diagnostic variables
  - Cancer type (histology)
  - Age at diagnosis
  - Year of diagnosis
- Treatment variables
  - Anthracycline dose
    - Other chemotherapy types have not consistently been associated with adverse CV outcomes in CCSS analyses and therefore will not be included in our risk prediction models
  - Radiotherapy
    - Radiation dose to the heart
    - *In secondary analysis, we will also examine these exposures given their association with adverse cardiometabolic traits*
      - Cranial/craniospinal radiotherapy
      - Neck radiotherapy
      - Abdominal radiotherapy
      - Total body irradiation (expected to be almost always co-linear with hematopoietic cell transplantation)
  - Hematopoietic cell transplantation (disease relapse and secondary cancer will be denoted as separate covariates)
- Demographic variables
  - Sex
  - Race/ethnicity
  - Current age (will be examined in Aim #2)
  - *Household income will only be analyzed in secondary analysis. While socioeconomic status has been associated with CV outcomes in some analyses in the general population, it is not typically included in existing CV risk score models.*
- Behavioral factors
  - Tobacco use
    - Current (within 2 years of survey) vs. others
      - Data from the general population would suggest that >2 years cessation of smoking / tobacco use reduces risk to that of never users.
    - Current (within 2 years of survey) vs. prior use vs. never
      - This categorization will be explored in secondary analysis
  - *Although the following factors have been associated with increased CV risk in the general population, they typically have not been included as parts of existing risk scores. Therefore, they will be analyzed in secondary analysis:*
    - Inactive/sedentary lifestyle
    - Alcohol consumption

        - Never vs. 1-2 per day vs. >2 per day. There is some epidemiological data that suggest 1-2 drinks (of any type) per day is associated with an improved CV risk profile.
- Co-morbid cardiovascular conditions
    - Obesity (BMI $\geq$30 kg/m^2)
    - Hypertension
    - Dyslipidemia
    - Diabetes
    - *Secondary analysis will restrict analysis to only those who report being on medications for hypertension, dyslipidemia, and/or diabetes. The reclassification of medications for these diagnoses has previously been accomplished [Meacham, Cancer Epidemiol Biomarkers Prev 2010]*.
- Other co-morbid conditions that may influence cardiovascular risk.
    - Relapse of primary cancer
    - Any secondary malignancy
    - *We recognize that CCSS imperfectly captures treatment exposures associated with relapse and secondary malignancies. However, as patients with these outcomes may be at greatest risk of subsequent cardiovascular disease, we feel it is important to include them in our analyses (albeit adjusting for these outcomes as time-dependent covariates).*

Statistical methods

- Aim #1
    - Cox proportional hazards models will be used to generate hazard functions for overall CV morbidity, mortality, and individual CV outcomes of interest (myocardial infarction, congestive heart failure, pericardial disease, valvular disease, and stroke) associated with baseline treatment and demographic variables of interest.
        - For any baseline covariate found to be associated with CV disease, we will *a priori* explore first order interactions with gender and age at cancer diagnosis.
        - Death will be classified as a competing risk in this analysis.
        - Relapse or original disease and secondary malignancy will NOT be considered competing risks but will be adjusted in the model as covariates.
        - In contrast to some CV prediction analyses performed in adult patients, the time scale used will be 5 years since cancer diagnosis (i.e. entry into the CCSS cohort), adjusted for age at time of diagnosis.
        - In order to examine changes in hazard over time, the hazard function for overall CV morbidity, mortality, and individual CV outcomes will be plotted over time. *However, given the likely imprecision of estimates approaching 30 years post-cancer diagnosis, any final model may be restricted to predicting risk over a shorter time frame.*
    - Separate ROC curves incorporating those covariates identified as being significantly associated with each respective CV outcome will be used to estimate the corresponding area under the curves (AUCs) using a time-dependent approach based on incident sensitivity and dynamic specificity[10] (Figure 1).

        - As AUCs associated with covariates may vary over time, we will first calculate and compare global AUCs (limited to 30 yrs post-cancer diagnosis) and then examine AUCs associated with different time intervals (e.g. 5-10 years, 5-20 years, and 5-30 years from diagnosis; Figure 2)
        - The most parsimonious combination of covariates associated with greater AUC will be selected for each outcome of interest. *A priori*, we will be most interested in knowing which covariates are associated with the largest global AUC.
    - For these selected covariates, a risk score then will be devised by assigning integer points based on the beta-coefficients from their respective proportional hazards model(s) (Table 1).
        - Points are then summed to compute an overall risk score with the corresponding risk of CV outcomes associated with each score. ROC curves with corresponding AUCs also will be generated for risk score sums and compared with the prior ROC/AUCs to ensure that no significant loss in discriminatory power has occurred (Figure 1).
        - Assuming no significant loss in discriminatory power, the summed risk scores will then be categorized into 3 clinically relevant risk categories: low, average, and high (if actual range of CV risk appears narrower, then low vs. high risk categories will be used instead). The true-positive and true-negative rates will then be calculated for each risk category (Table 2).
- Aim #2
    - Starting with the proportional hazards models created in Aim #1, determine behavioral factors and co-morbidities of interest are associated with our CV outcomes when added to the existing models.
    - Following methodology used in Aim #1, generate ROC curves and corresponding AUCs for those behavioral factors and co-morbidities previously found to be significantly associated with CV outcomes. Only those factors/co-morbidities that improve prior AUCs will be kept (Figure 3).
    - Revise the prior risk score from Aim #1 incorporating those behavioral factors / co-morbidities identified above.
    - Re-calculate AUCs associated with the revised risk score model to ensure no significant loss in discriminatory power and re-categorize risk categories (Figure 3).
- Aim #3
    - To minimize any model over-fitting in Aims #1 and #2, we will perform cross-validation within the training set first.
    - Following cross-validation, we will then apply our cross-validated prediction models and risk scores to the formal validation population and generate corresponding AUCs for each CV outcome. Compare the AUCs generated from the validation population to those generated in Aims #1 and #2 with the original training population in order to determine the discriminatory power of risk scores when applied to the validation population.
    - Examine the predicted and actual risks associated with risk scores in the validation population for each CV outcome and assess the differences using the Hosmer-Lemeshow chi-square test (Figure 4).

PLANNED TABLES / FIGURES

[TABLE 1: Multivariate hazard function coefficients (coeff) for covariates associated with each CV outcome of interest and corresponding risk score (if assigned).]

	Overall CV morbidity			CV mortality			Myocardial infarction			Congestive heart failure		
Covariate	Coeff	95% CI	Risk score	Coeff	95% CI	Risk score	Coeff	95% CI	Risk score	Coeff	95% CI	Risk score

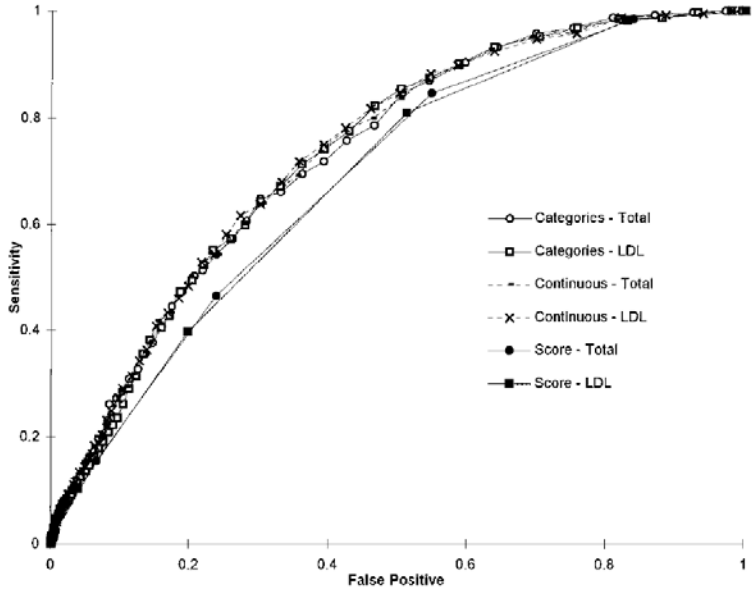
	Pericardial disease			Valvular disease			Stroke		
Covariate	Coeff	95% CI	Risk score	Coeff	95% CI	Risk score	Coeff	95% CI	Risk score

[TABLE 2: XX year cumulative incidence of CV outcomes, true-positive rates, and true-negative rates associated with each risk score category.]

Outcome	Low risk			Average risk			High risk		
	Cum. incid	True-positive rate	True-negative rate	Cum. incid	True-positive rate	True-negative rate	Cum. incid	True-positive rate	True-negative rate
Overall morbidity									
Mortality									
Myocardial infarction									
Congestive heart failure									
Pericardial disease									
Valvular disease									
Stroke									

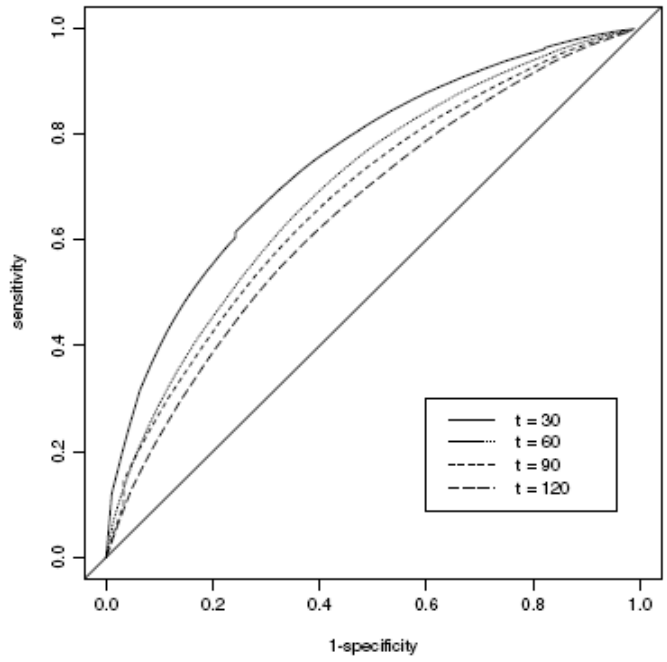
[FIGURE 1: ROC curves for models containing selected baseline treatment and demographic covariates, along with curves associated with the resultant global risk scores. AUC values listed in the legend.]

Example from Wilson PW, D'Agostino RB, Levy D, et al. Circulation 1998;97:1837.



[FIGURE 2: ROC curves for different time intervals associated with most parsimonious model identified in figure 1. AUC values listed in the legend.]

Example from Heagerty PJ, Zheng Y. Biometrics 2005;61:92.

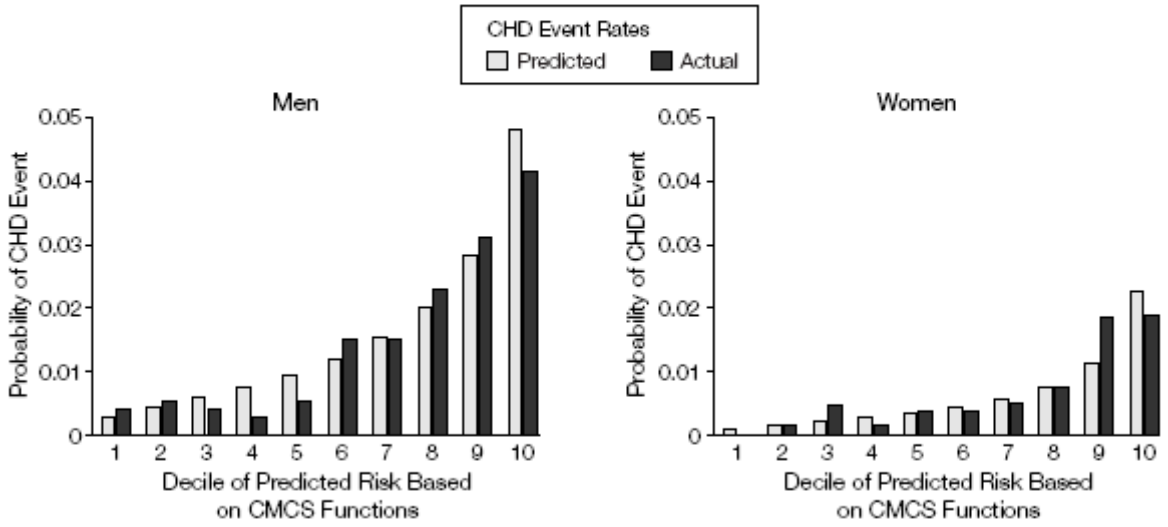


[FIGURE 3: ROC curves for models containing selected baseline treatment, demographic, and behavioral factors and comorbidities, along with curves associated with revised global risk scores. AUC values listed in the legend.]

[FIGURE 4: Bar graphs delineating predicted vs. actual risks based on risk score predictions in the validation population.]

Example from Liu J, Hong Y, D'Agostino RB, et al. JAMA 2004;291:2591.

Figure 1. Ten-Year Prediction of CHD Events in CMCS Men and Women Using the CMCS Functions



CMCS indicates Chinese Multi-provincial Cohort Study. Coronary heart disease (CHD) events included coronary death and myocardial infarction.

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