CCSS Proposal – EpiBiostat Primary Working Group (version 6/5/2015)
Secondary WG: Chronic Disease, Psychology

Tiled study design: using temporal overlap as a method to extend longitudinal follow-up among carefully selected time-limited cohorts

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Study Aim

We propose to use the CCSS dataset to empirically determine the utility and possible analytic constraints related to the use of a "tiled" study design as a time and resource-efficient way to study the association and correlation of biomarkers over time with outcomes of interest.

- Specifically, we propose to use acute lymphoblastic leukemia (ALL) patients free of relapse or SMNs at the time of the baseline survey, stratified (or adjusted) by cranial radiotherapy (CRT) exposures (none, <20 Gy, ≥20 Gy) and sex, in order to examine the following 2 well-established associations:
    1. Relationship of body mass index (BMI; a continuous "biomarker") with the development of selected cardiometabolic conditions (e.g., diabetes, hypertension), which will serve as outcomes of interest.
    2. Relationship of the Brief Symptom Inventory-18 (BSI-18; another continuous "biomarker") with subsequent reports of being on prescription psychoactive medications (outcome of interest).

- Results from this alternative "tiled" study design will be compared against those estimated from a conventional cohort analysis. Specifically, we will examine differences in point estimates and the precision of estimates from the 2 analytic methods, and will explore and describe sources of potential bias.

Background

In contrast to many other epidemiological study settings, cancer therapy exposures such as chemo- and radiotherapy are time-limited (i.e., transient), but may induce important long-term effects on health. There is growing interest in identifying biomarkers measured soon after exposure that may be correlated/predictive of longer term clinical outcomes [1,2]. However, within a standard <5-year grant cycle it is extremely challenging to create a longitudinal cohort study (Figure 1) that can study

biomarkers associated with an acute therapy-related toxicity (e.g., cardiotoxicity) measured during or shortly after cancer therapy and correlate them with longer-term outcomes. Similarly, there are few cohorts with extended follow-up where such data exist for both acute and longer-term changes. Such data could be useful in defining early biomarkers predictive of future late effects, and aid in more accurately defining survivor subsets who may benefit from more intensive late effects surveillance as well as survivor subsets for whom such screening has less benefit.

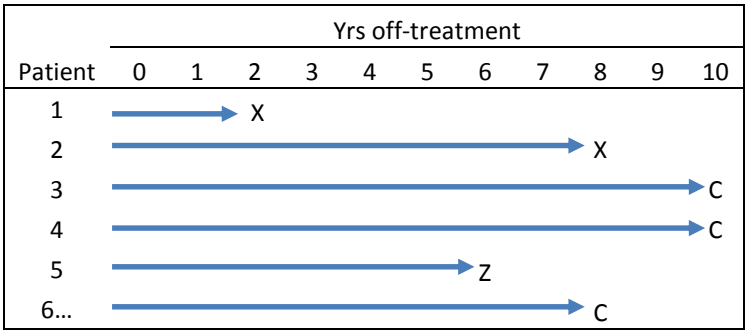

FIGURE 1. *Conventional cohort study design. C = censored (e.g., ended follow-up); X = event occurred; Z = competing risk event (e.g., death from other cause).*

The conventional approach has been to focus on one study period and attempt to select surrogate/intermediate endpoints that might be correlated with prior acute changes, and then assuming some correlation/associations are identified, to try to reassess those same biomarker associations with longer-term changes in a successor study at a different time point either among the original study population (ideally), or if not possible, a similar study population. Given time and funding constraints, study design and modeling methods that allow for the simultaneous study of both acute and long-term changes within multiple concurrent populations selected on the basis of homogeneous cancer treatment exposures, and which are followed for relatively brief periods of time, but which, critically, overlap temporally (in terms of time since cancer diagnosis) would be extremely useful.

Specifically, we propose a study design that incorporates both a cross-sectional component as well as a longitudinal/cohort component (Figure 2) that defines key intervals off-therapy among carefully selected patients who had similar treatment followed longitudinally over ~5 years. This will allow direct assessment of longitudinal changes within each group (hypothetical 6 groups noted by different colors below, assessed in Yrs, 1, 3, 5 of a 5-yr study; e.g., A1-A5, D1-D5, etc.). *Only patients who are free of the outcome of interest at the start of each pre-identified interval would be eligible for longitudinal assessments.*

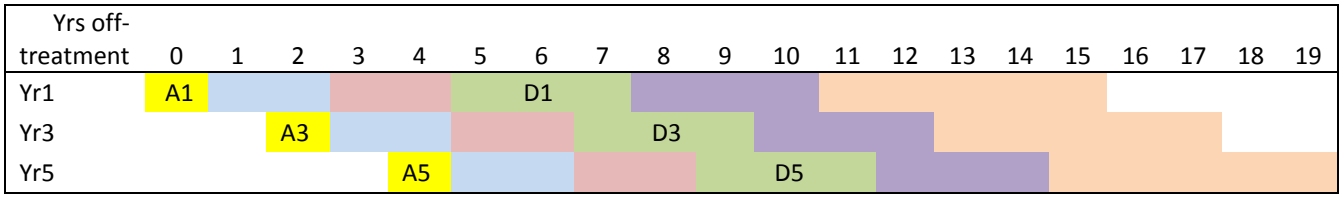

FIGURE 2. *Example of temporally overlapping but time-limited cohorts (each defined by its own color; e.g., A1-3, D1-D5) sampled across 5 years. Longitudinal relationships within each cohort (e.g., A1-A3, D1-D5) can be defined across the study period.*

However, because of the overlapping time periods among groups, the pattern of biomarker values across groups defined by similar time off-therapy at the time of assessment can also be

compared (Figure 3; e.g., B1 vs. A3, or C1 vs. B3 vs. A5, or D1 vs. C3 vs. B5, etc.). Although these "cross-sectional" comparisons are not based on same-subject data (i.e., not repeated observations of the same person over time), because each group (A1, B1, or C1) will be defined by similar cancer therapy exposures initially and will be compared at a similar time off-therapy, one may have greater confidence in assuming that any change in biomarker distributions seen consistently across groups could reflect longitudinal changes among the overall population treated in this fashion. This assumption could also be directly tested by seeing if the distribution/correlation of biomarker profiles across groups assessed at the same time off-therapy are similar (e.g., correlation between Biomarkers X and Y are similar for B1 vs. A3, C1 vs. B3 vs. A5, etc.).

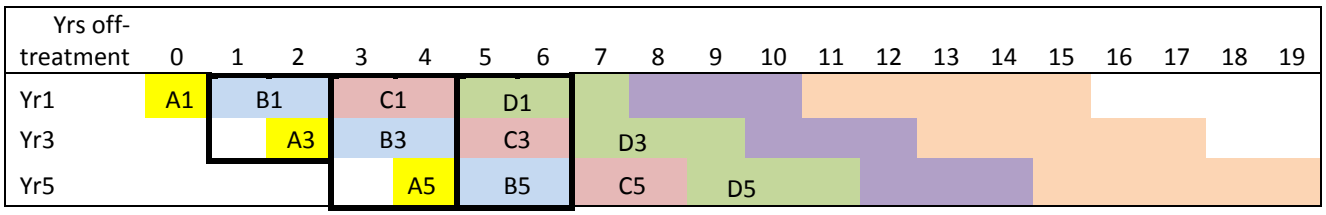

FIGURE 3. *Relationships also can be defined between cohorts based on similar time interval since treatment (e.g. B1 to A3, C1 to B3 to A5, etc.).*

If the distribution and pattern of biomarkers across groups can be assessed, because of the temporal overlap of observations, one may be able to then more directly estimate biomarker change across the entire time spectrum assessed (Figure 4). Assuming a true association between the biomarker and outcome of interest, the robustness of any conclusions drawn from this type of study design will likely depend on at least several conditions:

1. Cancer treatment exposures experienced by all the selected cohorts need to be homogeneous (and ideally, identical).
2. Either the biomarker is independent of any other secular effect (i.e., related to birth year), or if a secular effect exists, its influence on the biomarker is greatly outweighed by the influence from cancer treatment exposures.
3. Either the biomarker is independent of the normal aging process, or if an aging effect exists, the influence from cancer treatment exposures is strong enough to be detectable even after adjusting for chronologic age.

Less relevant in this type of study design, compared with a conventional longitudinal study, is the stability of biomarker assessment and clinical outcome definitions and assessments because the assessments take place within a compressed period of time.

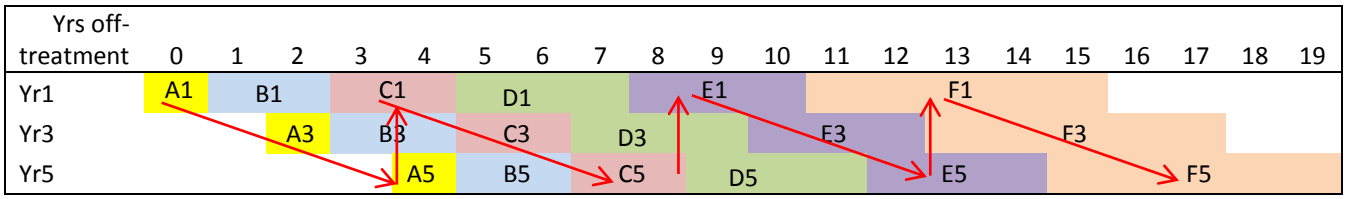

FIGURE 4. *Relationships can thus be defined both within and between cohorts, allowing one to extrapolate relationships established during/soon off-therapy to those many years later.*

Related ideas that attempt to use cross-sectional data to infer longitudinal changes have been previously published. One common example of this is the comparison of estimates derived from one-

time surveys repeated over time, but in different individuals representing the same population (e.g., NHANES) [3]. Incorporation of a formal longitudinal component to a cross-sectional study has been added by others as well, mainly in the psychology and developmental/aging literature, and has been termed a "cross-sequential" study [4,5]. Such designs and analysis methods have been applied to the study of acute exposures such as spinal cord injury, whose timing has greater similarity to acute time-limited cancer treatment exposures [6]. It is important to note that specific biases in statistical interpretation may occur in situations where the number of cohorts being analyzed greatly out-numbers the number of times an individual within each cohort is assessed [7,8] and that some of the conditions proposed in the original cross-sequential study design may not be tenable [9].

To our knowledge, the potentially unique features of our proposed study design is the extension of such methods to the study of outcomes following cancer therapy (vs. that related to normal aging), the specific requirement for temporal overlap in the selection of patient cohorts needed to facilitate the direct estimation of biomarker changes across the entire time spectrum, and also the study of potential biomarkers in relation to a downstream clinical outcome. Studies to date have typically focused on the assessed parameter (e.g., cognitive performance) alone in relation to some dimension of time, but not necessarily in its relationship with some more downstream clinical phenotype (e.g., dementia).

Study Population

Subjects will include all ALL patients who have not relapsed or developed SMNs as of the CCSS baseline survey, and who have not been exposed to spinal XRT. Although chemotherapy for ALL may not be uniform over the CCSS time period (diagnosis years 1970-86), and there may be some secular effects on BMI during this time period, the major influence on BMI (other than chronologic age) is thought to be CRT, and stratification/adjustment of any analysis by the primary CRT categories should result in relatively homogeneous treatment groups. Given the potential added effects of spinal XRT to both height (and thus BMI indirectly) and potential radiation scatter to the pancreas, kidneys, and heart, the small minority of ALL patients who received spinal XRT will be excluded.

Similarly, BSI-18 has been collected uniformly across multiple time points by CCSS. Survivors exposed to CRT, even at lower doses, have reported greater distress as measured by the BSI-18 compared with non-irradiated survivors [10,11]. While the BSI-18 does change with chronologic age, larger shifts tend to occur in the elderly and not as much in the age range of the target CCSS population [12-14]. Thus, demonstrating the feasibility and applicability of this alternative "tiled" study design to examine psychological outcomes among cancer survivors would be attractive and an extension of the original cross-sequential study methods proposed by psychologists [4].

Separate from CRT level, it will be possible to identify 3 distinct cohorts based on diagnosis time period (1970-75, 1976-80, 1981-86; each identified by a different color in Figure 5). Although, the baseline CCSS questionnaire was administered over a relatively long time period (primarily 1995-2000, with some participants responding 1992-94, and 2001-02), temporal overlap among these 3 cohorts can still be identified and relationships examined both longitudinally within a given cohort (e.g., A1 vs. A2 vs. A3) as well as across cohorts at the same time since diagnosis (e.g., B1 vs. A2). The observation period that this CCSS example requires under the standard biomarker study design will thus be 15 years (1995-2009), well beyond a typical 5-year grant period, but the methods developed should still apply to cohorts that have shorter follow-up but are more densely sampled. The maximum duration of follow-up that this cohort will allow study on would extend to 39 years (patient treated in 1970, surveyed in 2009), well beyond the actual 15 years of observation.

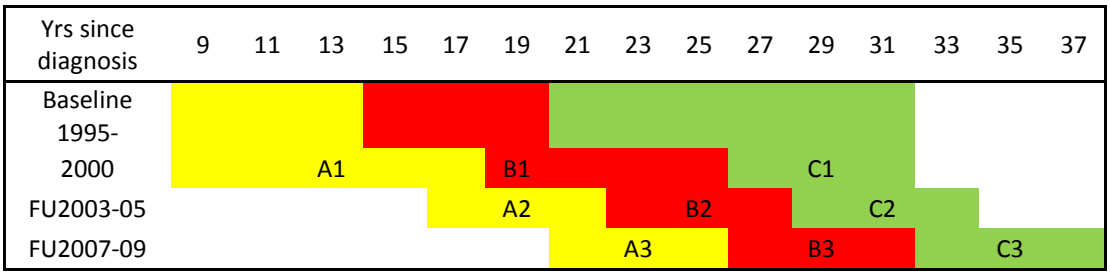

FIGURE 5. *Temporal overlap of subcohorts selected within CCSS (A: 1981-86; B: 1976-80; C: 1970-75)*

Outcome Variables (Table 1)

- Scenario 1: clinical end phenotype: diabetes and hypertension, as defined by medication use in Armstrong, et al., JCO 2013 [15]. These will be examined as separate outcomes.
- Scenario 2: clinical end phenotype: psychoactive medication use, as defined in Brinkman, et al., J Cancer Surviv 2013 [16]. In subanalyses, if sufficient sample size, we will explore specific classes of psychoactive medications in relation to BSI-18 subscales (see biomarker section below).

Primary "biomarker"s of interest (independent variable)

- Scenario 1: BMI as defined in Garmey et al., JCO 2008 [17]. Given issues of translating BMI values in children to those in adults, we will restrict our analyses to those with values reported at age ≥18 years, similar to Garmey et al.
- Scenario 2: BSI-18, as used in Brinkman et al., Br J Cancer 2013 [11]. This instrument was only collected among participants age ≥18 years, at baseline, follow-up 2 (2003-2005), and follow-up 3 (2007-2009). In addition to providing a global measure of psychological distress, it also provides subscales related to anxiety, depression, and somatization, which if sufficient sample size exists, we will examine in relation to anxiolytic, anti-depressant, and analgesic medication use, respectively, as defined in Brinkman, et al., J Cancer Surviv 2013 [16].

Treatment and Other Variables Considered

- Treatment exposures
    - CRT as part of initial therapy: this will be categorized as none, <20 Gy, and ≥20 Gy as in Chow et al, J Pediatr 2007 [18]. We will initially plan on stratifying our analyses by CRT category, but will also examine if more simple multivariate adjustment in a combined model will be sufficient.
    - Spinal radiotherapy: patients receiving this will be excluded upfront.
- Late relapse or secondary malignancy following the baseline CCSS survey. These will be classified as competing risk events for any time-to-event analysis. For logistic regression, we will exclude individuals with these events.
- Sex. Given differences in BMI and BSI-18 by sex, analyses can be stratified by sex, though we will also explore a combined analysis based on sex-specific normative data to see if that will be sufficient.
- Age and time since cancer diagnosis.

TABLE 1. *Numbers of ALL survivors with BMI information and who developed diabetes or hypertension, and/or with BSI-18 data who reported psychoactive medication use at each study time point (age≥18 years), excluding survivors with history of relapse, SMN, or exposure to spinal RT.*

Questionnaire	Diabetes		Hypertension		Psychoactive Medication Use	
	Yes N (%)	No N (%)	Yes N (%)	No N (%)	Yes N (%)	No N (%)
Baseline						
No CRT	5 (1.1)	436 (98.9)	10 (2.3)	431 (97.7)	88 (22.7)	299 (77.3)
15-19 Gy CRT	3 (0.6)	520 (99.4)	5 (1.0)	518 (99.0)	96 (19.7)	392 (80.3)
20-29 Gy CRT	5 (0.7)	751 (99.3)	30 (4.0)	726 (96.0)	171 (23.8)	549 (76.3)
FU2003*						
No CRT	7 (0.9)	741 (99.1)	27 (3.6)	721 (96.4)	130 (20.0)	521 (80.0)
15-19 Gy CRT	9 (1.3)	659 (98.7)	28 (4.2)	640 (95.8)	120 (20.4)	469 (79.6)
20-29 Gy CRT	23 (3.9)	573 (96.1)	42 (7.0)	554 (93.0)	100 (18.9)	428 (81.1)
FU2007*						
No CRT	14 (2.1)	654 (97.9)	44 (6.6)	624 (93.4)	54 (8.0)	623 (92.0)
15-19 Gy CRT	13 (2.2)	571 (97.8)	35 (6.0)	549 (94.0)	63 (10.5)	539 (89.5)
20-29 Gy CRT	15 (2.9)	498 (97.1)	57 (11.1)	456 (88.9)	49 (9.1)	489 (90.9)

*Number of cases (e.g. Scenario 1 [diabetes, hypertension]; Scenario 2 [psychoactive medication use]) shown reflect individuals newly reporting these outcomes since the prior survey.

Statistical Analyses

To validate the proposed approach, we will compare a hypothetical scenario of 3 cross sectional surveys of 3 cohorts that mimic the proposed study design with a conventional analysis of the CCSS data, i.e., time-to-event analysis for BMI and cardiometabolic outcomes[15], logistic regression for BSI-18 and psychoactive medication use[11]. Specifically, using the schema shown in Figure 5, we will examine in separate models, the relationships between 1) BMI and our cardiometabolic outcome(s) of interest, and 2) BSI-18 and psychoactive medication use, for the 3 subcohorts (chosen by original diagnosis years (A) 1981-86, (B) 1976-80, and (C) 1970-75) across 3 sampling time points (baseline survey, FU2003-05, and FU2007-09). At each sampling time point, prevalent cases will be excluded and only newly incident cases will be counted for that particular time period.

We will characterize the association using Poisson regression models for BMI-cardiometabolic outcomes and logistic regression models for BSI-18-psychoactive medication use. Specifically, we will model the outcomes (rates of cardiometabolic outcomes; odds of psychoactive medication use) as a function of BMI and BSI-18 in the most recent questionnaire, respectively, accounting for the other covariates listed earlier. The key to this modeling is the hypotheses of how biomarker-outcome relationships change or not change longitudinally within cohort and by years since treatment: we are assuming that eras of treatment have no effect as we focus on specific treatment exposures offered over different treatment eras. Specifically, we will use these models to specifically test the hypotheses on time-related changes in the biomarker-outcome relationship of interest and develop a final model that describes the relationship over time concisely.

The resulting relationships between BMI and the cardiometabolic outcome(s) of interest, and separately between BSI-18 and subsequent psychoactive medication use, will then be compared to

results where the entire eligible CCSS population is analyzed together using conventional analytic methods for each of our 2 scenarios[11,15].

If sample size considerations allow doing so, random subsets of the eligible CCSS population of varying sizes, sampled according to time since diagnosis as well as CRT level can also be examined. This will provide a more robust test of the sample size requirements that the proposed study design would require, in comparison to results generated from a conventional analysis using the entire eligible CCSS population. We will use simulation based on real CCSS data to address this question as we need to assess patterns associated with sample sizes, which cannot be done unless we examine a large number of datasets.

Other Considerations

Biomarkers may present in several different ways:

- Acute marker – only present early on following exposure.
- Chronic marker – only present later on following exposure.
- Acute on chronic marker – presents early on and then diminishes before increasing again later on.

Use of BMI and BSI-18 as markers in the CCSS example would only allow us to explore the behavior of a "chronic" marker, particularly as we lack either covariate at time of treatment and with the earliest value only being for those who are at least 6 years post-diagnosis (diagnosed 1986, baseline survey completed in 1992). Other cohorts or simulated data will be required to further explore the characteristics of acute markers and acute on chronic markers. Examples of these, using cardiotoxicity as an example, may include such things as troponin and natriuretic peptide levels, respectively [1]. In the situation with "acute" markers, such studies would need to first establish the relationship between any "acute" marker with an intermediate end-point (e.g. select echocardiogram parameter using cardiotoxicity as an example), and then determine the pattern of change of the intermediate end-point over time in relation to the late outcome of interest (e.g. heart failure).

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