CCSS Analysis Concept Proposal
February 13, 2012

STUDY TITLE: Evaluation of the association between lifestyle factors, psychological status and adverse pregnancy outcomes in the Childhood Cancer Survivor Study cohort

WORKING GROUP AND INVESTIGATORS

Working groups: Cancer Control, Epidemiology/Biostatistics, Psychology

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1. BACKGROUND AND RATIONALE:

Approximately 83% of the children diagnosed with cancer when younger than 15 years of age will survive for at least five years.[1] The majority of this growing population of cancer survivors will successfully reach reproductive age; therefore, their pregnancy outcomes are a matter of significant concern. Fortunately, the risk of stillbirth, miscarriage and abortion among childhood cancer survivors is no greater when compared to their siblings.[2] However, female survivors of childhood cancer are at an increased risk for adverse pregnancy outcomes such as preterm birth, low birth weight, small for gestational age (SGA) infants and low rates of live birth compared to their siblings.[2-4]

In the general population, the association between lifestyle factors such as smoking and alcohol, body composition, physical activity (PA), and adverse pregnancy outcomes has been extensively studied.[5-14] _ENREF_5 Smoking and heavy alcohol consumption, both before and during pregnancy are strongly associated with increased risk of preterm birth, low birth weight and SGA.[5-7,10,11,14] A higher pre-pregnancy body mass index (BMI) has been associated with increased risk of medically necessary preterm delivery, spontaneous abortion, miscarriage and stillbirth.[13,15] A lower pre-pregnancy BMI has been linked with increased risk of spontaneous and medically necessary preterm birth as well as with low birth weight infants.[16]

The effect of physical activity (PA) on pregnancy outcomes such as preterm birth, low birth weight and SGA varies based on the intensity of PA.[8,9] A recent European population cohort study of 11,759 participants reported that a sedentary lifestyle during pregnancy is associated with low birth weight.[17] Sedentary lifestyle including excessive television viewing has also been associated with preterm birth.[18] Although, a modest to heavy leisure time physical activity during pregnancy is reported to be beneficial in reducing the risk of preterm birth,[18-20] _ENREF_6excessive physical exertion, particularly late in pregnancy increases the risk of preterm birth and low birth weight.[8,9]

_ENREF_15 Similar to lifestyle factors, psychological stress and depression both before and during pregnancy have been associated with preterm birth, low birth weight and SGA in the general population.[6,21-27] Maternal stress and depression are also strongly associated with their health related quality of life (HRQOL)[28-30] which is reported to be associated with preterm birth[31] and low birth weight.[32,33] It has been hypothesized that stress during pregnancy elevates corticotrophin releasing hormone (CRH)[34,35] and C-reactive protein[36] causing preterm birth. Depression during pregnancy reduces natural killer cell activity and elevates pro-inflammatory cytokines which have also been hypothesized as reasons for preterm birth.[37] Pathways hypothesized for low birth weight and SGA include higher levels of placental CRH, a stress hormone and subsequent reduction in utero-placental blood flow resulting in hypoxemia.[38,39] While considering the effect of stress on adverse pregnancy outcomes the timing of stress is also important.[40] Pre-pregnancy stressors have been strongly associated with both preterm births and SGA,[25,26] _ENREF_25 stress in early pregnancy is believed to initiate CRH gene expression in the placenta which may reduce the length of gestation.[41-43] Stressful stimuli in late pregnancy appear to have lesser impact when compared to stress in early pregnancy.[41,44]

There is a higher prevalence of low BMI, low PA as well as psychological distress and psychosocial impairment in female cancer survivors compared to the general population.[45-49] Unfortunately, all of these are also potential risk factors for adverse pregnancy outcomes. Female survivors of leukemia and brain tumors are at an increased risk for higher body mass index (≥ 30 kg/m^2) compared to the general population.[46] This risk of obesity is even higher if a woman has a history of cranial irradiation with doses exceeding 20 Gy.[49] Moreover, female cancer survivors are more likely to lead an inactive lifestyle when compared to their siblings.[45,49] Cancer survivors are less likely to take up smoking[50] and risky drinking[51] than similar age and sex members of the general population. However, adult female cancer survivors are known to have greater risk for psychological distress[47] and psychosocial impairment[48] than are siblings or male survivors.

Compared to the general population, cancer survivors have a higher prevalence of not only potentially modifiable lifestyle factors but also adverse pregnancy outcomes. This increased risk of adverse pregnancy outcomes has been associated with various cancer treatment exposures such as cranial, spinal, uterine and pelvic irradiation as well as use of non-alkylating chemotherapeutic agents.[2,52] However, lifestyle factors and psychological status have not been evaluated as potential risk factors for adverse pregnancy outcomes in cancer survivors. These factors may explain a portion of the risk for adverse pregnancy outcomes not explained by

treatment exposures (Fig 1). Thus, to develop interventions that might reduce the adverse outcomes among female cancer survivors it is important to understand the impact of modifiable lifestyle factors and psychological status on pregnancy outcomes.

We propose to study the association between lifestyle factors such as smoking and alcohol, body composition, PA, and adverse pregnancy outcomes such as preterm birth, low birth weight, SGA, lower rate of live birth, miscarriage, abortion and stillbirth in the Childhood Cancer Survivor Study (CCSS) cohort. In the same cohort, we also propose to study the association of psychological status and adverse pregnancy outcomes. The previous CCSS reports based on questionnaires before 2000 that compared the rate of low birth weight between offspring of cancer survivors and their siblings using multivariable regression controlled for smoking and alcohol but did not find them significant.[2,4] _ENREF_19 No analysis has specifically examined the association of lifestyle factors, psychological status and adverse pregnancy outcomes in the CCSS cohort. Female childhood cancer survivors of reproductive age could significantly benefit from knowing if these factors could impact pregnancy outcomes by modifying their lifestyle or seeking psychological interventions.
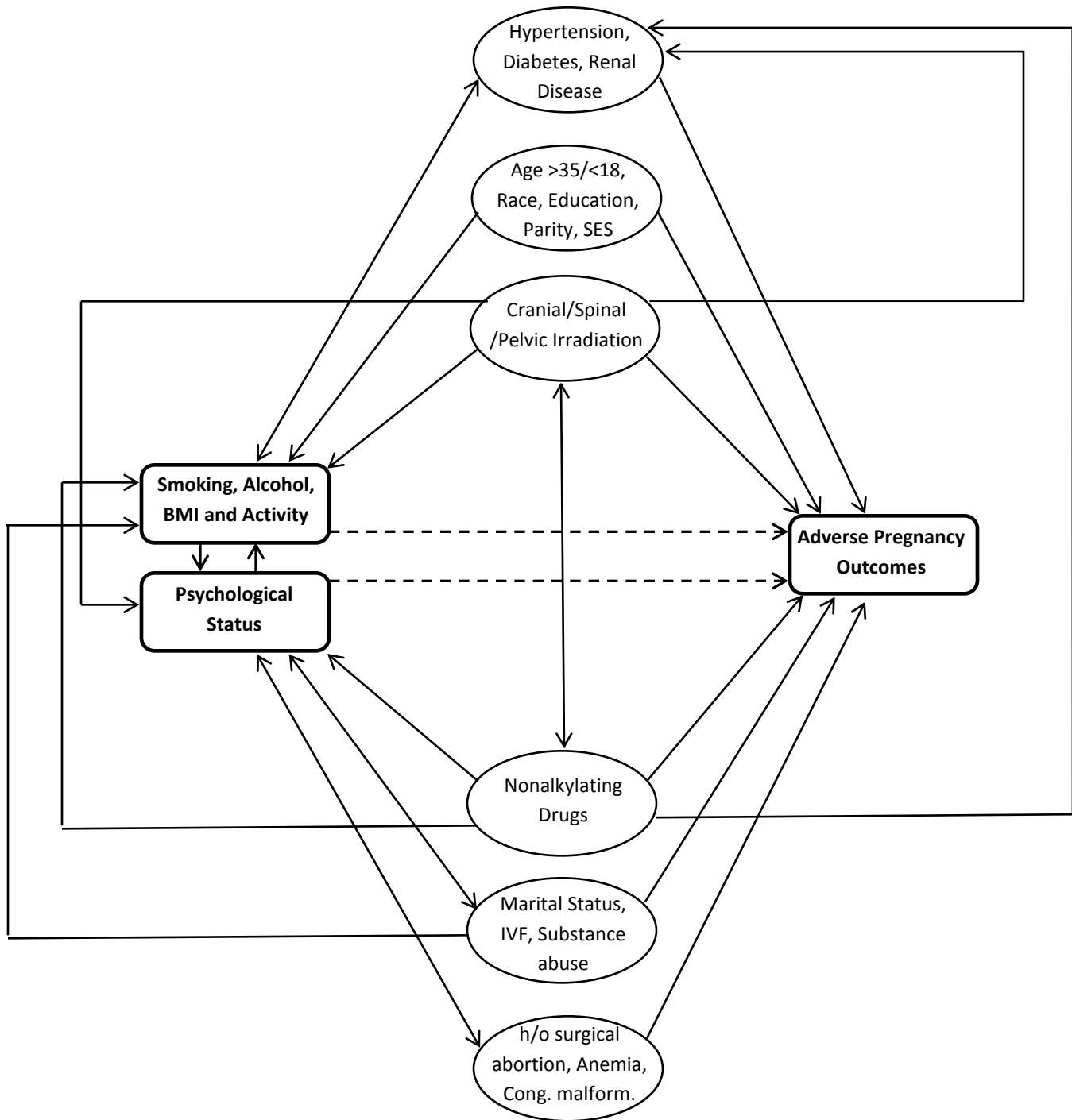
Fig 1. Causal diagram illustrating possible pathways between lifestyle factors, psychological status and adverse pregnancy outcomes

2. AIMS AND HYPOTHESES:

Primary Aims:

1. To evaluate the association between lifestyle factors including smoking and alcohol consumption <u>during</u> pregnancy and adverse pregnancy outcomes (preterm birth, low birth weight, SGA, lower rate of live birth, miscarriage, abortion and stillbirth) among female survivors in the CCSS who were pregnant at least once.

2. To evaluate the association between lifestyle factors including smoking, alcohol consumption, body composition and physical activity <u>before</u> pregnancy and adverse pregnancy outcomes (preterm birth, low birth weight, SGA, lower rate of live birth, miscarriage, abortion and stillbirth) among female survivors in the CCSS who were pregnant at least once.

3. To evaluate the association between psychological distress, depression, anxiety, somatization, anxiety about cancer, poor health related quality of life and life satisfaction <u>before</u> pregnancy and adverse pregnancy outcomes (preterm birth, low birth weight, SGA, lower rate of live birth, miscarriage, abortion and stillbirth) among female survivors in the CCSS who were pregnant at least once.

Hypotheses:

1. Smoking during pregnancy will be associated with adverse pregnancy outcomes in female childhood cancer survivors. The number of pack years of smoking during pregnancy will be directly associated with adverse pregnancy outcomes in female childhood cancer survivors.

2. Alcohol consumption during pregnancy will be associated with adverse pregnancy outcomes in female childhood cancer survivors. The number of drinks per month during pregnancy will be directly associated with adverse pregnancy outcomes in female childhood cancer survivors.

3. Smoking before pregnancy will be associated with adverse pregnancy outcomes in female childhood cancer survivors. The number of pack years of smoking before pregnancy will be directly associated with adverse pregnancy outcomes in female childhood cancer survivors.

4. Risky drinking defined as exceeding the NIAAA guidelines of 3 drinks/day or 7 drinks/week before pregnancy will be associated with adverse pregnancy outcomes in female childhood cancer survivors.

5. There will be a "J" shaped association between BMI and adverse pregnancy outcomes in female childhood cancer survivors with increased risk associated with both lowest and highest BMI.

6. There will be a "J" shaped association between physical activity and adverse pregnancy outcomes in female childhood cancer survivors with increased risk associated with both lowest and highest physical activity levels.

7. Psychological distress, depression, anxiety, somatization, poor health related quality of life and poor life satisfaction will be associated with adverse pregnancy outcomes in female childhood cancer survivors.

3. ANALYSIS FRAMEWORK:

Population:

We propose to conduct our analysis in two follow up intervals of the Childhood Cancer Survivor Study (CCSS) (Fig 2). Female CCSS participants who are alive and completed the 1) Baseline and 2000 and/or 2) 2003 and 2007 questionnaires will be included in the analysis. Only those who reported being pregnant at least once either between Baseline and 2000 or between 2003 and 2007 questionnaire will be eligible for this study.

Female participants who had not reached menarche at Baseline would be excluded from the first follow up interval (Baseline to 2000, Fig 2). Participants who were pregnant at the time of exposure and outcome measurement (Baseline, 2000, 2003 and 2007 Questionnaire) will be excluded from the study. Only female participants who completed the "2000 Pregnancy survey" and who reported their smoking and alcohol habits during pregnancy will be used to evaluate primary aim no. 1 (Fig 2.).

Baseline (1994-96) ⟶ 2000   --------   2003 ⟶ 2007

Interval 1   **Interval 2**

N=1366   **N=1232**

Exposures   **Outcomes**   **Exposures**   **Outcomes**

(No SF-36 and   (**recall of Exposures**   (No Alcohol data)   (No Birth Weight data)
Cantril Ladder   Smoking, Alcohol,
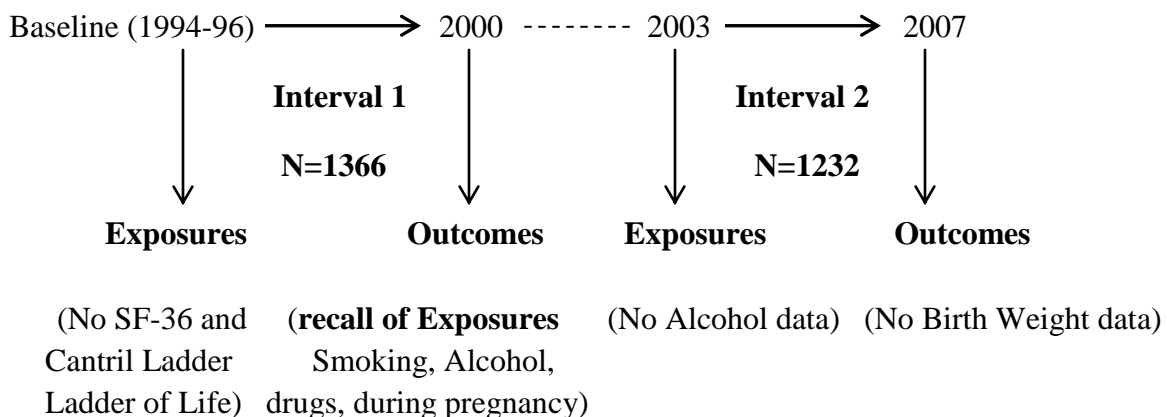Ladder of Life)   drugs, during pregnancy)

Fig 2. Study population from CCSS cohort proposed to evaluate the association of lifestyle factors and psychological distress, depression, anxiety, somatization, and poor health related quality of life with adverse pregnancy outcomes.

Exposures of Interest (Baseline, Pregnancy Survey FU2000 and FU2003):

The information on lifestyle factors and the psychological status will be retrieved from;

a) Physical activity (N9-14 Baseline, D1-7 FU2003)
b) Body mass index (A10-11 Baseline, 7-8 FU2003)
c) Smoking (N1-2 Baseline, Pregnancy Survey B2 FU2000, L1-6 FU2003)
d) Alcohol consumption (N3-8 Baseline, Pregnancy Survey B3 FU2000)
e) Psychological status
    i. Distress, Depression, Somatization and Anxiety
       (Brief Symptom Inventory-18 (BSI-18), J16-35, 37 Baseline and G1-18, 20 FU2003)
    ii. Health Related Quality of Life (HRQOL)
       (Medical Outcomes Survey Short Form-36 (SF-36), F1-14 FU2003)
    iii. Life satisfaction
       (Cantril Ladder of Life I1-3 FU2003)

Categorization of Exposure:

a) Physical activity:
    i. Binary: (Yes/No)-Centers for Disease Control and Prevention (CDC) guidelines for physical activity (30 minutes of moderate intensity physical activity on 5 or more days of the week or 20 minutes of vigorous activity 3 or more days a week)
    ii. Ordinal: Tertiles of metabolic equivalent (MET) min/week of physical activity
b) Body Mass Index:
    i. Ordinal: WHO classification of BMI; $< 18.5 \text{ kg/m}^2$, 18.5 to 24.99 kg/m^2, 25.0 to 29.99 kg/m^2 and $\geq 30 \text{ kg/m}^2$
    ii. Continuous: In the absence of a non-linear association we will explore BMI as a continuous variable (unit: 1 kg/m^2).
c) Smoking:
    i. Status: Current, Ever, Never
    ii. Pack Years
d) Alcohol:
    i. Current Drinker: Yes/No
    ii. Drinking Frequency:
       a. less than monthly, 1-3 x/month, 1-2 x/week, 3-4 x/week, Daily
       b. less than 1 drinks/month, 1-4 drinks/month, 5-10 drinks/month, 11-30 drinks/month and > 30 drinks/month
    iii. Risky Drinking, NIAAA: Yes/No (More than 3 drinks on any day or 7 drinks/ week)

      iv.   Heavy Drinking, 5+/6+: Yes/No

e) Psychological status:

      i.   BSI-18 - T score from ≥ 63 classified as psychological distress: Yes/ No

      ii.   BSI-18 - Depression: Yes/No

      iii.   BSI-18 - Anxiety: Yes/No

      iv.   BSI-18 - Somatization: Yes/No

      v.   SF-36 - T score from ≤ 40 classified as poor HRQOL: Yes/No

      vi.   Cantril Ladder of Life: Ordinal; cutoff (>8 found to be most predictive-depends on the outcome)

Outcomes of Interest (FU2000 and FU2007):

We will use number of pregnancies as our total sample because same women can have multiple pregnancies with different outcomes. The adverse pregnancy outcomes (8 & 8a-b FU2000, B8-9, C1 & D3 Pregnancy Survey FU2000, Q5 FU2007)

a) Preterm birth: Birth before 37 weeks of gestational age.

b) Low Birth Weight: Infant birth weight less than 2,500 g (up to and including 2,499 g)

c) Small for Gestational age: Infants with birth weight less than 10th percentile for their gestational age.

d) Live births: Fetus shows any signs of life after delivery

e) Stillbirths: Fetal demise after 20 weeks of gestation either in the uterus or during labor

f) Miscarriages: Spontaneous, expulsion of a nonviable embryo or fetus from the uterus before the 20th week of gestation.

g) Abortions: Induced (elective) termination of pregnancy

Based on the participants responses in both the questionnaires regarding pregnancy outcomes we will dichotomize all the outcome variables.

Covariates:

1. Date of birth (A1 Baseline, FU2003)
2. Sex (A2 Baseline, FU2003)
3. Date of questionnaire completion (Baseline, FU2000, FU2003 and FU2007)
4. Menarche (yes/no E16 Baseline, FU2003)
5. Marital Status (L1-13 Baseline, 2 FU2003)
6. Pregnancy within interval 1 or interval 2 (8 FU2000, Q1 FU2007 and Overall Pregnancy Database created by John A. Whitton at Fred Hutchinson Cancer Research Center)
7. Currently Pregnant (M4 Baseline, B10 FU2000, N2 FU2003, Q2 FU2007)
8. Maternal, Obstetric and Neonatal Characteristics (A-D Pregnancy Survey FU2000)
9. Previous history of adverse pregnancy outcome (M10-11 Baseline, FU2003)

10. Cancer diagnosis (eight level diagnosis: Leukemia, Central Nervous System, Hodgkin's, Non-Hodgkin's lymphoma, Kidney (Wilm's tumor), Neuroblastoma, Soft tissue sarcoma, Bone cancer)

11. Age at cancer diagnosis (calculated from date of birth and date of diagnosis abstracted from medical record)

12. Age at pregnancy (A1 Pregnancy Survey FU2000, Q3 FU2007)

13. Race/ethnicity (A4 Baseline, Race 5 code, African-American vs. Non-African American)

14. Highest level of educational attainment (< high school, high school graduate, college graduate – O1-4 Baseline, 1 FU2003 and A3 FU2007)

15. Employment status (working/caring for home or family, student, unemployed, unable to work – O5-11 Baseline, 4-6 FU2003 and A4 FU2007)

16. Annual household income (<$20000, ≥$20000 – Q8-9 Baseline, S1-3 FU2003 and A6-8 FU2007)

17. Insurance (Q1-6 Baseline, 16 FU2000, M1 FU2003, B1 FU2007)

18. Recreational drugs, marijuana, cocaine during pregnancy (Yes/No – B7 Pregnancy Survey FU2000)

19. Radiation therapy (RT) (site and dosage from MRAF summary and database created by Rita Weathers at MD Anderson)
    a. Cranial or spinal radiation therapy
        - No radiation
        - Cranial and spinal
        - Cranial only
        - Spinal only
        - No cranial/spinal radiation therapy
        - Unknown
    b. Ovarian radiation therapy
        - No radiation
        - Ovaries in radiation field
        - Ovaries near radiation field
        - Ovaries shielded
        - No ovarian radiation therapy
        - Ovarian radiation unknown
    c. Ovarian/Uterine radiation dosage: ordinal variable
    d. Total Body Irradiation (Yes/No)

20. Chemotherapy (MRAF summary, yes/no)
    a) Anthracycline agents (yes/no, 1-100 mg/m^2, 101-400mg/m^2, >401 mg/m^2)
    b) Alkylating agents (yes/no, dose score tertile:1-2, 3-4, > 5)
    c) Epipodophyllotoxin (yes/no, 1 - 982 mg/m^2; 983- 4108mg/m^2; > 4109 mg/m^2)
    d) Bleomycin (yes/no, 1-59 mg/m^2; 60-118 mg/m^2; > 119 mg/m^2)

21. Surgery (MRAF summary, amputation of lower limb/other surgery/none)
22. Medication for Hypothyroidism, Diabetes, Epilepsy, Hypertension (yes/no - B8 Baseline and Q4-6, C8.5, 8.7, 8.8 FU2003)
23. Thyroid disease, Diabetes (E1-7 Baseline)
24. Heart diseases (F4-10 Baseline, 10d-h FU2000)
25. Epilepsy (J4-5 Baseline, 12g-h FU2000)
26. Neonatal Death (Q3 FU2007)

Statistics:

Our unit of measurement will be "pregnancies" and not "individual women" because it is possible for the same woman to have multiple pregnancies within an interval. The pregnancies from two intervals will be combined together to create a single sample for the analysis.

Univariate analysis: The distribution of demographic, obstetric and medical characteristics of the study population in follow-up interval 1 (Baseline to 2000), follow-up interval 2 (2003 to 2007) and total sample (both intervals combined) will be presented as number and percentage or mean and standard deviation (Table 1).

Univariable and Multivariable analysis: The distribution of smoking and alcohol consumption during pregnancy measured in 2000 (Pregnancy Survey FU2000) and lifestyle factors (smoking, alcohol, BMI and PA), psychological status measured in 1994-96 (Baseline) and 2003 would be compared across the respective adverse pregnancy outcomes (preterm birth, low birth weight, SGA, lower rate of live birth, miscarriage, abortion and stillbirth) that occurred between baseline to 2000 and 2003 to 2007 (Table 2).

Statistical analysis will be performed using regression models with logit link and based on a generalized estimating equation (GEE)[53-55]_ENREF_54 adjustment to handle correlated outcome data from women who had >1 pregnancies within an interval. We will model the relationship between the eight exposures 1) Smoking (including during pregnancy exposure from Pregnancy Survey 2000) 2) Alcohol (including during pregnancy exposure from Pregnancy Survey 2000) 3) BMI 4) PA and 5) Stress, 6) HRQOL, 7) Life satisfaction and 8) Anxiety due to cancer and seven outcomes 1) preterm birth, 2) low birth weight, 3) SGA, 4) live birth, 5) miscarriage, 6) abortion and 7) stillbirth after controlling for potential confounders and evaluating interaction. The results will be presented as odds ratio (OR) and 95% confidence interval (CI) (Table 3).

Initial models will be univariable assessments of the impact of risk factors on outcomes (Table 2. An asterisk (*) will denote that P value from regression models is less than significance level (α=0.05)). Next, we will use a two-step approach to select potential confounders which includes first using directed acyclic graphs (DAG)[56] to select minimally sufficient adjustment set and second using the change-in-estimate[57] strategy because relying solely on data-dependent change in effect estimate strategy is deleterious.[58] A DAG visually represents our assumptions about the causal relations between exposure outcome and covariates. Assuming negligible uncontrolled confounding, all important covariates will be used for plotting the DAG. After deleting all the pathways emanating from the exposure (lifestyle factors and psychological status) the rest of the acyclic pathways will be analyzed for unblocked pathways from exposure to outcome (adverse pregnancy outcomes). The 'minimally sufficient adjustment' set of confounders will be selected after excluding colliders[59,60]_ENREF_56 and will be included in the model even if does not change

the effect estimate by more than 10%. Other covariates will then be added in the model only if they change the effect estimate by more than 10%.[57]

We believe that the association between lifestyle factors, psychological status and adverse pregnancy outcomes would be stronger among older, multiparous, African American women, those who received pelvic radiation and, some form of chemotherapy. We would therefore evaluate interaction by age ($\geq$ 30 vs. <30 years), parity, race, pelvic radiation and chemotherapy using a significance level of $\alpha=0.15$ for interaction terms in the GEE models.

To evaluate the association between smoking and alcohol consumption during pregnancy and adverse pregnancy outcomes (primary aim no.1) we will have to rely on self-reported information based on maternal recall (Pregnancy Survey FU2000) which can be subject to recall bias.[61] However, Yawn et al[62] found that smoking during pregnancy is well reported with an accuracy of 99.5% (Kappa= 0.88 agreement with medical records) irrespective of adverse outcomes. Information on alcohol consumption during pregnancy on the other hand, has its problem with misclassification[63] and is highly susceptible to underreporting[64]. However, this misclassification of alcohol and smoking has minimal influence on the effect estimates in retrospective data.[65] We will conduct a sensitivity analysis concerning the potential effect of misclassification of alcohol and smoking in the Pregnancy Survey FU2000 questionnaire. Sensitivity analysis for smoking and alcohol will be conducted by method proposed by Fox et al[66] which accounts for both systematic and random error. The ranges of sensitivity and specificity of misclassification of smoking and alcohol will be decided based on previous literature.[61,65] ENREF_66

Specific Tables:
Table 1. Demographic and treatment characteristics of pregnant CCSS participants

	Baseline to 2000 (N=), *n (%)*	2003 to 2007 (N=), *n(%)*	Total (N=), *n(%)*
Women with >1 pregnancies			
Age at start of pregnancy (y)			
<15			
15-20			
21-25			
26-30			
31-35			
>35			
Age at diagnosis (y)			
0-4			
5-9			
10-14			
15-20			
Race/ethnicity			
White, NH			
Black, NH			
Other, NH			
Hispanic/Latino			
Not indicated			
African American			
Yes			
No			
Annual household income (US$)			
<20,000			
≥ 20,000			
Education level			
Did not graduate high school			
Graduated from high school			
Graduated from College			
Not indicated			
Insurance			
Yes			
No			
Current Marital Status			
Married or living as married			

Single or widowed or divorced

Table 1. Demographic and treatment characteristics of pregnant CCSS participants (cont.)

	Baseline to 2000 (N=), *n (%)*	2003 to 2007 (N=), *n(%)*	Total (N=), *n(%)*
Employment			
Working/caring for home or family			
Student			
Unemployed/looking for work			
Unable to work			
Not indicated			
Multiple gestations			
Yes			
No			
Previous preterm birth			
Yes			
No			
Parity (≥3, 2, 1)			
Diabetes Mellitus			
Yes			
No			
Hypertension			
Yes			
No			
Thyroid disease			
Yes			
No			
Epilepsy			
Yes			
No			
Recreational drugs, cocaine, marijuana			
Yes			
No			
Cancer diagnosis			
Leukemia			
Central nervous system			
Hodgkin's lymphoma			
Non-Hodgkin's lymphoma			
Kidney (Wilm's tumor)			
Neuroblastoma			
Soft tissue sarcoma			

Bone cancer

Table 1. Demographic and treatment characteristics of pregnant CCSS participants (cont.)

	Baseline to 2000 (N=), *n (%)*	2003 to 2007 (N=), *n(%)*	Total (N=), *n(%)*
Treatment			
Chemotherapy only			
Surgery only			
Radiation therapy only			
Chemotherapy+Surgery			
Chemotherapy+Radiation			
Surgery+Radiation			
Chemotherapy+Surgery+Radiation			
Unknown			
Chemotherapy drug			
Anthracycline			
Not exposed			
1-100 mg/m2			
101-400 mg/m2			
>401 mg/m2			
Alkylating agent score			
Not exposed			
1-2			
3-4			
>5			
Epipodophyllotoxin			
Not exposed			
1-982 mg/m2			
983-4108 mg/m2			
>4109 mg/m2			
Bleomycin dose			
Not exposed			
1-59 mg/m2			
60-118 mg/m2			
>119 mg/m2			
Cranial or spinal radiation therapy			
No radiation			
Cranial+spinal			
Cranial only			
Spinal only			
No cranial/spinal radiation therapy			

Unknown

Table 1. Demographic and treatment characteristics of pregnant CCSS participants (cont.)

	Baseline to 2000 (N=), *n (%)*	2003 to 2007 (N=), *n(%)*	Total (N=), *n(%)*
Ovarian radiation therapy			
No radiation			
Ovaries in radiation field			
Ovaries near radiation field			
Ovaries shielded			
No ovarian radiation therapy			
Ovarian radiation unknown			
Ovarian radiation dosage (Gy)			
Total Body Irradiation (Yes/No)			

Table 2. Distribution of lifestyle factors and psychological status measured at baseline, 2000^ and 2003 across adverse pregnancy outcomes (assessed at 2000 and 2007) of CCSS. (*Data will be presented as number (%) & mean ± standard deviation*)

	Preterm birth		Low birth wt.		SGA		Live births		Stillbirths		Miscarriages		Abortions	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Smoking														
Status														
Current														
Ever														
Never														
Not indicated														
Pack years														
Smoking assessed in 2000^														
During Pregnancy														
Yes														
No														
Months of Pregnancy														
1-3														
4-6														
7-9														
Cigarettes per day														
Alcohol														
Current drinker														
Yes														
No														
Drinking frequency														
LT monthly														
1-3 x/month														

1-2 x/week							
3-4 x/week							
Daily							
Risky Drinking$							
Yes							
No							
Heavy drinking							
≥ 5 drinks/week							
< 5 drinks/week							
Alcohol assessed in 2000^							
During Pregnancy							
Yes							
No							
Months of Pregnancy							
1-3							
4-6							
7-9							
Drinks/month							
<1 drink							
1-4 drinks							
5-10 drinks							
11-30 drinks							
> 30 drinks							
Physical activity							
Meets CDC guidelines							
Yes							
No							
Not indicated							
Inactive lifestyle							

Yes							
No							
Not indicated							
MET min/week							
1st tertile							
2nd tertile							
3rd tertile							
Body Mass Index							
Underweight							
Normal weight							
Overweight							
Obese							
Psychological status							
Stress - BSI-18							
T score							
≥ 63							
< 63							
Depression							
Abnormal							
Normal							
Anxiety							
Abnormal							
Normal							
Somatization							
Abnormal							
Normal							
HRQOL - SF-36							
Poor (Score ≤ 40)							
Good							

Life Satisfaction - Cantril Ladder of Life							
Abnormal							
Normal							
Anxiety about cancer							
Abnormal							
Normal							

^ smoking and alcohol intake during pregnancy were also assessed using a separate self-reported Pregnancy Survey in 2000;

$ Risky drinking: exceeds the NIAAA guidelines of 3 drinks/day or 7 drinks/week,

* will denote that P value from regression models is less than significance level (α=0.05)

Table 3. Multivariate odds ratios from GEE models for adverse pregnancy outcomes in two follow up intervals$^@$ of CCSS

	Preterm birth		Low birth wt.		SGA		Live births		Stillbirths		Miscarriages		Abortions	
	1	2	1	2	1	2	1	2	1	2	1	2	1	2
Physical activity														
Meets CDC guidelines														
Yes (ref)														
No														
Inactive lifestyle														
Yes														
No (ref)														
MET min/week														
1st tertile (ref)														
2nd tertile														
3rd tertile														
Body Mass Index														
Underweight														
Normal weight (ref)														
Overweight														
Obese														
Smoking														
Status														
Current														
Ever														
Never (ref)														
Increment of 10 Pack years														
Alcohol														
Current drinker														

Yes							
No (ref)							
Drinking frequency							
LT monthly (ref)							
1-3 x/month							
1-2 x/week							
3-4 x/week							
Daily							
Risky Drinking$							
Yes							
No (ref)							
Heavy drinking							
≥ 5 drinks/week							
< 5 drinks/week (ref)							
Psychological status							
Stress - BSI-18							
T score							
≥ 63							
< 63 (ref)							
Depression							
Abnormal							
Normal (ref)							
Anxiety							
Abnormal							
Normal (ref)							
Somatization							
Abnormal							
Normal (ref)							
HRQOL - SF-36							

Poor (T score 1SD ≤ 40)							
Good (ref)							
Life Satisfaction - Cantril Ladder of Life							
Abnormal							
Normal (ref)							
Anxiety about cancer							
Abnormal							
Normal (ref)							

@ *Follow up interval:1- Baseline to 2000, 2- 2003 to 2007; $Risky drinking: exceeds the NIAAA guidelines of 3 drinks/day or 7 drinks/week , Data will be presented as Odds Ratio (95% confidence interval)*

References:

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