Section: Contact Information

First Name : **Yan**
Last Name : **Yuan**
Institution : **The School of Public Health, University of Alberta**
Address 1 : **3-299 C05 Edmonton Clinic Health Academy 11405 - 87 Ave NW Edmonton AB T6G 1C9**
Address 2 :
City : **Edmonton**
State/Province/Region : **International Location: Alberta**
Country : **Canada**
Zip/Postal Code : **T6G 1C9**
Phone Number : **+17805663036**
Alternate Phone Number :
Email Address : **yyuan@ualberta.ca**

Section: Project Requirements and Description

Group: Requirements to submit AOI

A comprehensive review of previously published data has been completed. : **Yes**
The specific aims are clear and focused. : **Yes**
The investigator has appropriate experience and expertise to develop the concept proposal; if not, has identified a mentor or senior co-investigator. : **Yes**
The investigator agrees to develop an initial draft of the concept proposal within 6 weeks of approval of the AOI and to finalize the concept proposal within 6 months. : **Yes**
Project Title : **Risk Prediction of Menarche and Menopause-related Phenotypes in Childhood Cancer Survivors Using Polygenic Risk Scores and Clinical Predictors**
Planned research population (eligibility criteria) :
The planned study population is female childhood cancer survivors in CCSS who were treated between Jan. 1, 1970 and Dec 31, 1999.

Inclusion criteria:
1. Female survivors with at least 5 years survival, diagnosed before the age of 21 years with eligible cancer types.
2. Provided menstrual history information, including age at menarche, age at last menstrual period, current menstrual status, and causes of menopause (surgical or non-surgical).
3. Provided biospecimens for DNA genotyping.

Exclusion criteria:
1. Exposed to a cranial or pituitary radiation dose higher than 30 Gy.
2. History of tumors in the hypothalamus or pituitary region.
3. History of Turner or Down's Syndrome
4. Female survivors who had had second malignant neoplasm (smn) within five years of primary cancer diagnosis
Proposed specific aims :
Aim 1: Identify published polygenic risk scores (PRS) for menarche/menopause-related phenotypes, including age at menarche and menopause, if available, or develop PRS using susceptibility variants identified to date for menarche-/menopause-related

phenotypes in genome-wide association studies (GWAS) conducted in the general population. Use summary-statistic based methods (e.g., LDpred, Lassosum, PRS-CS, etc.) to construct PRS and validate candidate PRS using general population genotype data (e.g., UK Biobank), if none exists.

Aim 2: Develop and validate predictive models that include both validated PRS and clinical predictors to accurately predict the risk of developing menarche-/menopause-related phenotypes among childhood cancer survivors, and translate the predicted risk of menarche-/menopause-related phenotypes into a clinical and genetic risk score system.

2a) Use existing baseline predictive models for menarche-/menopause-related phenotypes if available, or develop and validate new predictive models that only include the clinical predictors (e.g., demographic information, cancer treatment, etc.), if none exists;

2b) Include both the PRS (derived from aim 1) and clinical predictors (identified in aim 2a) in the predictive models for these menarche-/menopause-related phenotypes and compare their prediction performance.

Aim 3: Assess whether PRS that includes or reconciles treatment-specific SNP effects identified in previous GWAS conducted in female cancer survivors improves the predictive models' prediction performance for menarche-/menopause-related phenotypes in comparison to PRS constructed from general population studies.

Will the project require non-CCSS funding to complete? : **Yes**

If yes, what would be the anticipated source(s) and timeline(s) for securing funding? : **2020 Applied Research in Cancer Control (ARCC) studentship; timeline: Sep 1, 2020 - Aug. 31, 2021**

Group: Does this project require contact of CCSS study subjects for:

Additional self-reported information : **No**

Biological samples : **No**

Medical record data : **No**

If yes to any of the above, please briefly describe. :

Group: What CCSS Working Group(s) would likely be involved? (Check all that apply)

Second Malignancy :

Chronic Disease : **Secondary**

Psychology / Neuropsychology :

Genetics : **Primary**

Cancer Control : **Secondary**

Epidemiology / Biostatistics : **Secondary**

Section: Outcomes or Correlative Factors

Late mortality :

Second Malignancy :

Group: Health Behaviors

Tobacco : **Correlative Factors**

Alcohol : **Correlative Factors**
Physical activity :
Medical screening :
Other :
If other, please specify :

Group: Psychosocial

Insurance :
Marriage :
Education :
Employment :
Other :
If other, please specify :

Group: Medical Conditions

Hearing/Vision/Speech :
Hormonal systems :
Heart and vascular :
Respiratory :
Digestive :
Surgical procedures :
Brain and nervous system :
Other : **Primary, Correlative Factors**
If other, please specify : **Primary: reproductive system: including the reproductive lifespan length and timing of puberty, menopause (e.g., primary ovarian insufficiency, which includes acute ovarian failure and non-surgical premature menopause). Correlative Factors (exclusion criteria): Turner or Down's syndrome, tumors in the hypothalamus or pituitary region**

Group: Medications

Describe medications :

Group: Psychologic/Quality of Life

BSI-18 :
SF-36 :
CCSS-NCQ :
PTS :
PTG :
Other :
If other, please specify :

Group: Other

Pregnancy and offspring :
Family history :
Chronic conditions (CTCAE v3) :
Health status :

Group: Demographic

Age : **Correlative Factors**

Race : **Correlative Factors**
Sex : **Correlative Factors**
Other :
If other, please specify :

Group: Cancer treatment

Chemotherapy : **Correlative Factors**
Radiation therapy : **Correlative Factors**
Surgery : **Correlative Factors**

Section: Anticipated Sources of Statistical Support

CCSS Statistical Center : **Yes**
Local institutional statistician : **Yes**
If local, please provide the name(s) and contact information of the statistician(s) to be involved. :
Name: Yan Yuan
Address: 3-299 C05 Edmonton Clinic Health Academy 11405 - 87 Ave NW Edmonton AB T6G 1C9
Phone: +1(780) 566-3036
Email address: yyuan@ualberta.ca
Will this project utilize CCSS biologic samples? : **Yes**
If yes, which of the following? : **Buccal cell DNA**
If other, please explain :

Section: Other General Comments

Other General Comments :
I agree to share this information with St. Jude : **Yes**