2020 NCI Cohort Consortium ANNUAL MEETING
LIGHTNING TALK ABSTRACTS
NOVEMBER 16–17, 2020

**Project Title**: Appendiceal Cancer Consortium (APPECC)
**First and Last Name**: Andreana N. Holowatyj, Ph.D., M.S.
**Title**: Assistant Professor of Medicine and Cancer Biology
**Organization:** Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center
**Email:** Andreana.holowatyj@vumc.org
**Cohort Affiliation (if applicable):** Shanghai Men's Health Study (SMHS), Shanghai Women's Health Study (SWHS), Southern Community Cohort Study (SCCS)
**NCI Cohort Consortium Project Group Affiliation (if applicable)**: Appendiceal Cancer Consortium (APPECC) (*new consortium project approved in 2020*)

**Background and Significance:** In 2020, an estimated 333,680 cases of cancers of the digestive system will be diagnosed in the U.S.—of which 2.3% (7,600 cases) include appendiceal carcinomas (AC) and other rare digestive system tumors. As a rare malignancy, little is currently known about the risk factors and etiologies of AC. Strikingly, as the overall incidence of malignant AC has risen over the last two decades in the U.S. by 232%, rates have increased from older to younger generations. However, rates of appendectomies have remained stable over this period—suggesting that the rising AC incidence is likely not related to an increase in diagnosis of incidental, asymptomatic tumors.

**Why a Cohort Consortium approach is necessary (if new project idea)**:

**Aims:** Our overarching goal is to understand risk factors, etiologies, and prognostic factors of appendiceal cancer, and utilize this knowledge to reverse the increasing disease burden, as well as inform clinical, molecular, and population-level features that contribute to appendiceal cancer disparities.

**Approach / Methods:** We are utilizing a nested case-control study approach, including incident appendiceal cancer cases identified during follow-up of cohorts, as well as cohort-matched non-cancer controls and cohort-matched colorectal cancer cases.

**Results (as appropriate):** We will discuss the current enrollment status of APPECC, which includes 25 participating cohorts with over 1,240 incidental appendiceal cancer cases. We will also discuss that we are open to enrolling NCI Cohort Consortium cohorts with interest in participation for APPECC and with available appendiceal cancer cases.

**Conclusion (as appropriate):** As a rare cancer, with an age-adjusted incidence rate of 0.12 per 1,000,000 person years, the study of appendiceal cancer is limited in individual cohorts. By leveraging a cohort consortium approach and pooling cases from large cohort studies, we will

have sufficient statistical power to discover novel appendiceal cancer risk factors and etiologies to advance our understanding of this malignancy worldwide.

**Next Steps / Future plans**: We will apply for a grant to support data preparation for each cohort and to evaluate the association of lifestyle factors with appendiceal cancer risk, and to explore potential appendiceal cancer biomarkers, in this proposed study.

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**Project Title**: How to add free & secure interactive data visualizations to your cohort or project's website

**First and Last Name**: Jim Lacey & Emma Spielfogel
**Title**: Professor and Research Data Analyst, respectively
**Organization:** City of Hope
**Email:** jlacey@coh.org and espielfogel@coh.org, respectively
**Cohort Affiliation (if applicable):** California Teachers Study (CTS)
**NCI Cohort Consortium Project Group Affiliation (if applicable)**: Not applicable

**Background and Significance:** A common challenge facing all Cohort Consortium stakeholders is data exploration. How many cancers of a specific type exist in a cohort? What specific data does each cohort have? What has the cohort previously published on? Interactive web-based data visualizations could accelerate user-driven discovery across the Cohort Consortium, but few cohorts offer this feature. The California Teachers Study (CTS) has developed a web-based interactive visualization strategy that can be readily reused by other cohorts.

**Why a Cohort Consortium approach is necessary (if new project idea)**: N/A

**Aims:** We will demonstrate three of our web-based data visualizations and describe how other cohorts could securely, using entirely free software and tools, copy and use these visualizations for their own data.

**Approach / Methods:** The CTS created non-identifiable summary data and metadata about essential cohort characteristics and data: topic areas for the types of data it has collected, numbers of biospecimens, and summaries of CTS publications.

**Results (as appropriate):**
The three visualizations are available here:

Data collection topic areas & biospecimens: https://www.calteachersstudy.org/cts-data

CTS publications: https://www.calteachersstudy.org/study-findings

**Conclusion (as appropriate):** Increased use of interactive data visualizations could improve information exchange and project development in multiple cohorts and across the NCI Cohort Consortium. Adoption of these types of free and secure data visualizations could accelerate knowledge transfer and data sharing.

**Next Steps / Future plans**: Our lightning talk will conclude by describing specific steps other cohorts can take to create these types of interactive data visualizations.

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**Project Title**: Population Attributable Fraction (PAF) project

**First and Last Name**: Robert MacInnis
**Title**: Associate Professor
**Organization:** Cancer Council Victoria, Australia
**Email:** macinnis@unimelb.edu.au
**Cohort Affiliation (if applicable):** Melbourne Collaborative Cohort Study (MCCS), Breast Cancer Family Registry (BCFR)
**NCI Cohort Consortium Project Group Affiliation (if applicable)**: Population Attributable Fraction (PAF) project (*new consortium project approved in 2020*), Diet and Cancer Pooling Project (DCPP)

**Background and Significance:** The disease burden measure population attributable fraction (PAF) estimates the proportion of cancer that could be prevented if exposure to its risk factors were removed or reduced. PAFs are increasingly used to evaluate the national and global burden of cancer and to advocate for changes in public health policy and activity settings to reduce the prevalence of causal risk factors. Most previous studies that estimated PAFs, however, had focused on past burden rather than future burden, and had not accounted for joint effects of risk factors, competing risks, or misclassification error. Also, most previous studies had not tested for differences in PAFs by subgroups.

**Why a Cohort Consortium approach is necessary (if new project idea)**: Previous attempts at estimating PAFs have been narrow in scope and taken a single-study approach. There is the need, however, to investigate more broadly in a large international pooled cohort where we can identify and compare subgroups and countries with high burdens of disease. The Cohort Consortium will allow us to have better precision in estimating joint effects, particularly for less common cancers.

**Aims:** Our overarching objective is to estimate PAFs and their confidence intervals for cancer incidence, allowing analysis of the simultaneous effects of multiple factors and accounting for competing risks, and using representative external exposure prevalence data.

To calculate fractions of cancers causally related to smoking, alcohol consumption, body mass index (BMI), physical activity, fruit consumption, vegetable consumption, red and processed meat consumption, multivitamin use, oral contraceptive use, menopausal hormone therapy use, and breastfeeding. The cancers we seek to investigate include prostate (aggressive), breast, colorectal, upper aerodigestive tract, kidney, bladder, pancreas, stomach, and thyroid cancer and non-Hodgkin lymphoma.

**Approach / Methods:** To achieve this, we will leverage the existing resources of the Pooling Project of Prospective Studies of Diet and Cancer (DCPP) in the National Cancer Institute Cohort Consortium. The DCPP has an existing data repository to support evaluation of different cancer sites and has examined previously associations with several of the proposed cancers. The data needed for this project is currently being or has already been harmonized. We have developed methods to overcome some of the limitations of previous publications as part of an Australian PAF-consortium and have published several papers for various cancer outcomes in the last 3 years.

We will estimate pooled relative risks between lifestyle-related risk factors and the cancers of interest in the participating cohorts. Repeated measures of exposure will be utilized, if available. We will estimate the country-specific population-level prevalence of the risk factors from the latest representative national health surveys for U.S., western European countries, Australia, etc. Using the RRs and the prevalence estimates for each exposure, we will calculate PAFs for different lengths of follow-up (to assess the impact of competing risks). We will analyze potential between-cohort heterogeneity. Through a process of co-design, partnership, and engagement, we will seek to translate the findings to improve evidence-based population- and population-subgroup health promotion policies.

**Results (as appropriate):**

**Conclusion (as appropriate):**

**Next Steps / Future plans**: We will apply for funding (initially to WCRF) to support data preparation and produce evidence-based, up-to-date novel data on the population-level relevance of risk factors for cancer internationally.

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**Project Title**: Opioid cohort consortium (OPICO) to investigate the effects of regular opioid use on cancer development

**First and Last Name**: Mahdi Sheikh
**Title**: Postdoctoral Scientist
**Organization:** International Agency for Research on Cancer (IARC)

**Email:** sheikhm@fellows.iarc.fr
**Cohort Affiliation (if applicable):** Golestan Cohort Study / EPIC
**NCI Cohort Consortium Project Group Affiliation (if applicable)**: N/A

**Background and Significance:** The recent opioid crisis has resulted in thousands of deaths annually and billions in economic losses worldwide. Opioids are categorized into opiates (the natural/minimally-processed subgroup including opium and heroin), and pharmaceutical opioids (the semi-synthetic/synthetic subgroup). The acute health hazards of opioid misuse are well characterized, but the long-term health consequences of regular use of opioids remain unknown. Opium consumption was recently classified as "Group1, carcinogenic to humans" by the IARC Monographs. However, it is still unclear whether pure forms of naturally occurring opiates (e.g., morphine) or semi-synthetic or synthetic opioids (e.g., fentanyl and tramadol) also cause cancer.

Experimental studies have shown the presence of opioid receptors in some cancer tissues and documented their role in tumor initiation and progression. Also, some studies have illustrated the tumor-promoting effects of opioids and documented chromosomal damage in association with exposure to these drugs. Finally, evidence from registry data linkage studies has shown associations between regular use of pharmaceutical opioids and increased risk of several cancer types including lung, liver, and urogenital cancers. However, the nature of these studies does not allow addressing the role of important confounders including smoking, alcohol intake, and underlying health conditions that can bias the results.

In this project we aim to address the relationship between using opioids and the development of cancers. The overarching aim of this project will be to characterize the long-term health consequences of regular opioid use. By providing insights on the harms of regular opioid prescriptions, our results could aid in the development of evidence-based guidelines for using opioids in chronic pain management, as well as comprehensive prevention policies to reduce the long-term health-related and economic harms of opioid use.

**Why a Cohort Consortium approach is necessary (if new project idea)**: To our knowledge, the association between using pharmaceutical opioids and cancer incidence has not been evaluated in any large prospective cohort, likely because detailed data on opioid use have not been gathered in most cohorts, while in cohorts with opioid use data, the number of long-term opioid users is limited and therefore a single cohort often cannot provide sufficient power to evaluate cancer incidence outcomes among opioid users. Further, the types, patterns of use, accessibility, and underlying health conditions differ among opioid users in various countries, and thus performing a single analysis in one cohort might not be generalizable to other regions. Due to these limitations, a comprehensive consortium-based approach is needed to address this issue.

**Aims:**

1. Organize data on opioid use from large-scale prospective cohorts around the world
2. Where feasible, compile new data on opioid use in large prospective cohorts through linkage to prescription registries
3. Assess the type, distribution, and extent of opioid use across diverse populations
4. Determine the association of regular opioid use with cancer incidence
5. Determine the association of regular opioid use with all-cause and cause-specific mortality

**Approach / Methods:** The International Hundred K+ Cohort Consortium (IHCC) has recently approved our application to build the opioid cohort consortium (OPICO) as part of the 2020 IHCC pilot project awards. Up to now, nine large-scale cohorts across Asia, Europe, Australia, and North America have agreed to join the OPICO. We would like to invite the eligible cohorts within the NCI Cohort Consortium to join this global initiative.

We will gather detailed information on baseline covariates, cancer incidence in the follow-up, and illicit use of opiates (if available) from each participating cohort. We will also gather detailed data of used medications at enrollment from each participating cohort to extract the use of pharmaceutical opioids. Datasets from participating cohorts will be received at IARC and will be standardized and harmonized by a uniform protocol and codebook, building from our resources established for the Lung Cancer Cohort Consortium (LC3). Data sharing will be supported, in particular for participating members of OPICO, to increase scientific impact.

There are very good national resources in some countries for registering the prescription or dispensing of medications. In OPICO, we hope to gather detailed opioid use data from some large-scale cohorts by linking their data to the national prescription registries. We started to assess the feasibility of this approach in the 45 & Up study in Australia, and in the Generation Scotland study in Scotland.

The outcome of interest for the cancer incidence analysis would be the diagnosis of any cancer type, and the subcategories of digestive cancers, respiratory cancers, urinary tract cancers, and brain cancer that were associated with using opiates in our previous investigations. We will compare risk of cancer incidence among opioid users and nonusers and then we will perform stratified analyses on opiates and pharmaceutical opioids. We will also perform a detailed dose-response evaluation between the estimated daily amount of opioid use and risk of outcomes. To address the indication bias, we will perform stratified analysis based on the presence of chronic illness, the type of pain medications used (opioids/NSAIDs), and the indication of opioid use, and compare the risk of outcomes in the strata.

**Results (as appropriate):** N/A

**Conclusion (as appropriate):** N/A

**Next Steps / Future plans**: In the subsequent phase of OPICO, we plan to link the harmonized opioid use data to the whole genome sequencing data from the participating cohorts with

available genetic data, and perform a genome-wide association study (GWAS) to investigate the mechanisms of regular opioid use (in comparison to regular use of non-opioid pain medications and/or non-regular opioid use) at the genetic level, and if applicable perform a Mendelian Randomization study to investigate regular use of opioids and cancer risk.

The overarching aim of OPICO is to build a cohort consortium that includes large-scale cohort studies from low-, middle-, and high-income countries with detailed and harmonized data on opioid use to provide a strong international resource for multidisciplinary scientific studies on the use of opioids and their long-term hazardous effects. In the future, this consortium will also facilitate genetic and biomarker studies to understand the underlying mechanisms related to this exposure and its association with different outcomes.

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**Project Title**: Metabolomics of obesity and obesity-related cancers

**First and Last Name**: Deirdre K. Tobias, Sc.D.
**Title**: Assistant Professor, Epidemiologist
**Organization:** Brigham and Women's Hospital and Harvard Medical School
**Email:** dtobias@bwh.harvard.edu
**Cohort Affiliation (if applicable):** Women's Health Study (WHS)
**NCI Cohort Consortium Project Group Affiliation (if applicable)**: N/A

**Background and Significance:** Excess body weight is a recognized risk factor for at least 13 cancer sites, contributing up to 9% of the cancer burden in developed countries. Overweight- and obesity-related cancers disproportionately affect women, accounting for 55% of cancers diagnosed in U.S. women and 24% of those in men. Furthermore, while the incidence of malignancies overall has declined over the past two decades, obesity-related cancers continue to rise. As the prevalence of overweightness and obesity in the U.S. and globally increases, a downstream surge in obesity-related cancers is inevitable without effective strategies for prevention. The metabolic consequences of excess adiposity are diverse and diffuse, yet its role in mediating cancer risk is poorly understood. In addition, interventions and therapies targeting upstream modifiable obesity-related mechanisms may provide powerful broad-spectrum strategies for the prevention of several cancer sites among high-risk individuals.

**Why a Cohort Consortium approach is necessary (if new project idea)**: Improve power for site-specific obesity-related cancers and investigation in under-represented minorities.

**Aims:** We will conduct targeted analyses evaluating the associations between previously identified obesity-related metabolites and incident composite endpoint of obesity-related cancer risk. We will also estimate the proportion of obesity's relationship with cancer explained by the significant metabolites.

**Approach / Methods:** For this analysis, we will include cohort participants participating in the blood sample collection, excluding those with missing information on baseline height and weight, from which body mass index (BMI kg/m2) is derived; those with baseline BMI < 18.5 kg/m2; or those with a diagnosis of cardiovascular disease or cancer prior to baseline. Individual metabolites will be determined prior to the published literature of metabolomics with obesity, body weight, waist circumference, and other anthropometrics. We will log transform to improve normality as needed. We will classify obesity-related cancers based on the 2016 IARC report of 13 cancer sites or types with sufficient strength of evidence for an association with body fatness, including: adenocarcinoma of the esophagus, gastric cardia, colon and rectum, liver, gallbladder, pancreas, postmenopausal breast, corpus uteri, ovary, renal cell, meningioma, and multiple myeloma. Thyroid cancers are not included given the potential for surveillance bias. Cox proportional hazards regression models are used with follow-up from the date of baseline blood draw to date of first invasive cancer diagnosis, death, or administrative censoring, whichever comes first. Models will be adjusted for age (years) and cancer risk factors. Metabolites are to be analyzed continuously per 1 SD difference in concentration, and categorically across quartiles or quintiles (sample sizes permitting). A summary metabolite score will also be derived across all candidate metabolites and evaluated continuously in the same manner as individual metabolites for the relationship with obesity-related cancers.

**Results (as appropriate):** We recently completed an analysis in the Women's Health Study longitudinal cohort for the relationship of plasma branched-chain amino acids (BCAAs) with incident obesity-related cancers (Tobias DK, et al., Scientific Reports, Oct 2020). Baseline BMI ≥ 30 kg/m2 compared with BMI 18.5–25.0 kg/m2 was associated with 23% greater risk of obesity-related cancers (n = 2,751 events; multivariable HR 1.23, 95% CI 1.11–1.37). However, BCAAs were not associated with obesity-related cancers (multivariable HR per SD = 1.01 [0.97–1.05]). Results for individual BCAA metabolites suggested a modest association for leucine with obesity-related cancers (1.04 [1.00–1.08]), and no association for isoleucine or valine (0.99 [0.95–1.03] and 1.00 [0.96–1.04], respectively). Exploratory analyses of BCAAs with individual sites included positive associations between leucine and postmenopausal breast cancer, and isoleucine with pancreatic cancer. Total circulating BCAAs were unrelated to obesity-related cancer incidence, although a positive association was observed for leucine with incident obesity-related cancer.

**Conclusion (as appropriate):**

**Next Steps / Future plans**: Collaborate with additional cohorts with metabolomics assayed among pre-diagnosis blood samples for the analysis proposal above.