Study Title:

Diet, Adiposity, and Metabolic Alterations

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Background

According to the International Agency for Research on Cancer (IARC), there is sufficient evidence that avoidance of weight gain reduces the risk of several cancers, including colorectal, breast (postmenopause), pancreatic, endometrial, kidney (renal-cell), liver, gallbladder, oesophageal (adenocarcinoma), multiple myeloma, meningioma, ovarian, thyroid and stomach (cardia) cancer[1]. Several mechanisms have been suggested to mediate the obesity-cancer association, including increased insulin levels and bioavailability of insulin like growth factor 1 (IGF-I), altered secretion of adipokines and inflammatory cytokines, and changes in sex hormone levels [2,3]. The mechanisms are likely to vary depending on cancer site and patient subgroup [3].

In previous studies, we have identified five heterogeneous trajectory groups of body fatness from age five and up to 60 years (lean-stable, lean-moderate increase, lean-marked increase, medium-stable, and heavy-stable/increase) [4]. These trajectories have been associated with distinct patterns of cancer incidence [4] and mortality [5]. Having excess body weight at any life period have been associated with increased risk of total and obesity related cancers with distinct adiposity-cancer associations depending on cancer site and patient subgroup [4]. How the various trajectories of body shape relate to cancer relevant risk biomarkers is however yet to be determined.

In addition, how dietary factors may influence the levels of these biomarkers remains largely unknown. For example, epidemiological evidence indicates that habitual coffee consumption is inversely associated with total and cancer-specific mortality[6,7]. A recent umbrella review of the evidence across meta-

analyses of studies on coffee consumption also showed its robust risk reduction for numerous health outcomes [8]. However, potential mechanisms underlying the associations remain largely unknown.

To gain a better understanding of the complex interplay between obesity, diet (e.g., coffee consumption), plasma biomarkers and cancer development, we aim to investigate the longitudinal associations between trajectories of body fatness, diet, and cancer-relevant risk biomarkers in the Nurses' Health Study and Health Professionals Follow-up Study.

Hypothesis

In the current project, we aim to examine the relationship of the five trajectory groups of body fatness, diet with levels of obesity-related risk biomarkers. Furthermore, we will explore the influence of early vs late life adiposity on these biomarkers, by comparing extreme trajectories in which body shape is similar at one end of life and substantially different at the other. We will also explore whether the trajectory/diet-biomarker associations vary depending on subgroup (e.g. sex, smoking status, physical activity level, aspirin/NSAIDs use, statin use and use of hormone replacement therapy (HRT) (in women only).

We hypothesize that in general individuals who have excess body weight at any life period will have a more unfavorable biomarker profile than those who are lean across the lifespan, although a different pattern may be expected for some markers. Early vs late life adiposity is associated with distinct biomarker profiles and that trajectory-biomarker associations vary across subgroups. Moreover, we hypothesize that women and men consuming a healthy diet (e.g., higher coffee consumption) have a healthier biomarker profile.

Study population: Nurses' Health Study and Health Professionals Follow-up Study.

Exposures:

- Trajectories of body fatness based on self-reported somatotypes at age 5, 10, 20, 30 and 40 as well as BMI at age 50 and 60.
- Dietary consumption: derived from the food frequency questionnaires (FFQ). For example, total coffee calculated as the sum of intakes of caffeinated and decaffeinated coffee. Cumulative averages of coffee intake were calculated by using the 1984, 1986 and 1990 FFQs in the NHS, and the 1986, 1990 and 1994 FFQs in the HPFS to account for long-term coffee exposure and reduce within-person variability.

Outcome: Biomarkers suggested to mediate the obesity-cancer relationship, including:

- Biomarkers of the insulin/IGF system: C-peptide, IGF-I, IGFBP1, IGFBP3
- Inflammation biomarkers: CRP, IL-6, sTNFR2
- Adipokines: Adiponectin (total and HMW adiponectin), leptin, leptin receptor
- Sex hormones: Estradiol, estrone, testosterone, SHBG

We will extract the biomarker data from previous nested case-control studies for various endpoints (see the attached tables).

Inclusion criteria: Available biomarker and trajectory/diet data.

Exclusion criteria: History of cancer (other than non-melanoma skin cancer) at blood draw, missing values related to assay difficulties or low blood volume, statistical outliers.

Covariates: Age at blood draw, time of blood draw, analysis batch and laboratory, fasting status, sex, race, smoking status, dietary intake including energy intake and intake of macronutrients, alcohol consumption, multivitamin use, regular aspirin/NSAIDs use, physical activity, duration of past oral contraceptive use, menopausal status, parity and history of having breastfed (for women only).

Statistical analysis:

Available biomarker data from the two cohort studies will be merged to create one final data set. Biomarker measurements will be corrected for laboratory and analysis batch using the average batch correction method [9] with adjustments for age, BMI and physical activity.

Difference in biomarker level across trajectories of body fatness/diet will be analyzed using multivariable linear regression models. Data will be presented as adjusted arithmetic mean of the various biomarkers by categories of exposure. Stratified analysis will be performed to evaluate whether trajectory-biomarker associations vary by subgroups (e.g. sex, smoking status, physical activity level, aspirin/NSAIDs use, statin use and use of hormone replacement therapy (HRT) (in women only). To test for interaction, we will include cross-product terms between the stratification factor and trajectories/diet in our models, and use a likelihood ratio test to calculate the p value.

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