ARIC Manuscript Proposal # 3285

PC Reviewed: 11/13/18    Status: _____    Priority: 2
SC Reviewed: _________   Status: _____   Priority: ____

1.a. Full Title: Yogurt consumption and colorectal cancer (CRC) risk in Atheroclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Yogurt and CRC

2. Writing Group:
Writing group members: Samara Rifkin, Francis Giardiello, Linda Hylind, Cynthia Sears Anna Prizment, Casey Rebholz, Corinne Joshu, and all interested ARIC investigators welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___SBR___ [please confirm with your initials electronically or in writing]

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3. Timeline:
We will spend 3 months analyzing the data and additional three months composing the manuscript. Finally, we will likely require 4-6 months to submit the manuscript depending on whether it gets accepted initially.
4. **Rationale:**

A majority of colorectal (CRC) cases are attributed to modifiable lifestyle factors including diet, physical activity, alcohol intake, and tobacco use. Dietary behavior modification represents a potential strategy to prevent CRC. Mounting evidence suggests red and processed meat and saturated fats increase the risk of CRC, whereas fiber, fruits and vegetables may protect against colon carcinogenesis. Fermentable dairy foods and specifically, yogurt may also offer protection against colon cancer although accumulating evidence is limited and inconclusive.

Compelling evidence supports an anti-tumor effect of lactic acid-producing bacteria, including *Lactobacillus bulgaricus*, *Streptococcus thermophiles*, *Lactobacillus acidophilus*, and *Bifidobacterium*, contained in yogurt and probiotics. There are several proposed mechanisms by which these bacteria may prevent colon carcinogenesis. Lactic acid bacteria may decrease the risk of colon polyp formation by stimulating the immune system, increasing the mucosal immune response through cytokine production, T cell function modification, increased concentration of natural killer (NK) cells and IgA secreting lymphocytes. In addition, these bacteria may also act to decrease CRC risk by decreasing inflammation. In a case series of patients with active ulcerative colitis, use of probiotics decreased mucosal inflammation in 77% of the population. There is also evidence that lactic acid bacteria reduce the concentration of secondary bile acids and dietary carcinogenic metabolites produced by meat ingestion including N-nitroso compounds and heterocyclic aromatic amines (HCAs) by binding to and inactivating them which effectively reduces their bioavailability. In addition, certain bacterial strains may reduce bacterial enzyme activity present in the colon such as β-glucuronidase and nitroreductase. These bacterial enzymes hydrolyze and activate carcinogenic molecules contained in burnt and processed meat products. Finally, lactic acid bacteria produce short chain fatty acids, including butyrate, known to promote colon epithelial cell health, as the primary colonocyte energy source and contain antitumorigenic properties. Butyrate inhibits histone deacetylase and thereby decreases cell proliferation and promotes apoptosis. Decreases in butyrate-producing bacteria and enrichment of pathogenic bacteria is a common finding in studies comparing differences between CRC cases and controls.

There are a limited number of epidemiological studies evaluating the relationship between yogurt and CRC risk and the cumulative results of these prior studies have been inconclusive. In case-control and cohort studies, there have been reports of inverse and null associations with CRC risk. A pooled analysis of 10 cohort studies examined 5,734 CRC cases observed a weak association between consumption of yogurt with CRC risk that was of borderline significance. The heterogeneity in the study design of these prior studies may contribute to these differences including exposure definition (several assessed broader categories including fermented dairy products), variation in lactic acid bacteria strains, differences in target population and underlying diet and differences in analysis including controlling for confounders.

Animal models and epidemiologic studies have also suggested a link between dairy products and colon cancer with the main hypothesis being that calcium decreases the risk of colon cancer.
Calcium may protect against colon cancer by reducing cellular proliferation, stimulating differentiation, and inducing apoptosis in colon epithelial cells. Additionally, calcium may reduce damage to colon mucosa by binding to bile and fatty acids. Given that yogurt like other dairy products contains high calcium levels and may, thus, protect against colon cancer, we aim to assess the association between yogurt and colon cancer as well as non-yogurt dairy products and colon cancer in attempt to unravel a potential link. We hypothesize that the lactic acid-producing bacteria contained in yogurt are protective against tumor development beyond the protective effect of calcium. Thus, we plan to evaluate the association between yogurt and CRC independent of calcium. Evidence also suggests that the effects of probiotics may be stronger when fed in conjunction with prebiotics, indigestible fiber that lactic acid bacteria consumes. We hypothesize that increased indigestible fiber intake will increase the strength of the association between yogurt and colon cancer.

Since polyp type, CRC histopathology and genetic mutations differ in anatomical distribution along the length of the colon and suggest carcinogenic processes may differ along the colonic axis, we will also investigate differences in a potential association between yogurt consumption and colon cancer by anatomical location along the colon.

5. Main Hypothesis/Study Questions:
   i) We will examine the association between frequency of yogurt consumption and colorectal cancer risk in the ARIC population after adjusting for non-yogurt dairy intake, calcium intake and Vitamin D levels. We hypothesize that increased frequency of yogurt consumption will be inversely associated with colorectal cancer independent of non-yogurt dairy intake, calcium intake and Vitamin D intake.
   ii) We will confirm the association between non-yogurt dairy intake and calcium intake and colorectal cancer in ARIC. We hypothesize non-yogurt dairy intake and calcium intake will both be inversely association with colorectal cancer.
   iii) We will examine whether fiber intake modifies an association between frequency of yogurt consumption and colon cancer. We hypothesize that fiber intake will strengthen the inverse association between frequency of yogurt consumption and colorectal cancer.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

**Study design:** Prospective cohort of all ARIC participants without prevalent cancer at Visit 1.

**Independent variables:** Yogurt intake frequency will be defined as never/rarely, monthly but less than weekly (1-3/month), weekly but less than daily (1-6/week), and daily (1+/day). We will calculate quartiles for average daily yogurt consumed. In addition, we will calculate quartiles for daily non-yogurt dairy consumed. We will explore how best to express yogurt intake frequency and average daily yogurt consumed in relation to colorectal cancer risk and mortality. We will
categorize participants based on their baseline intake, using updated and cumulative updated measures of intake (measured at Visits 1 and 3).

**Dependent Variable:** Colorectal cancer incidence (~300 cases) and CRC-specific mortality (~100 cases) through 2012.

**Other variables of interest:** age, race, sex, study site, education, BMI, smoking status, number of pack-years of smoking, alcohol consumption, physical activity, diabetes, hypertension, hyperlipidemia, NSAID use, dietary energy intake (kcal/day), use of post-menopausal hormones (current/former/never use) for women, and diet/calorie intake, adjusted for dietary calcium (divided into quartiles), Vitamin D levels (ng/ml) (divided into quartiles), Vitamin D intake (IU) (divided into quartiles), frequency of non-yogurt dairy intake (never/rarely, monthly less than weekly, weekly less than daily, daily). Vitamin D levels will be taken from Visit 2. Other variables will be taken from the questionnaire at the first visit.

**Analysis plan:** We will use Cox proportional hazard models to estimate the multivariate adjusted risk of colorectal cancer risk and mortality (separately) in relation to all markers at Visit 1. Participants began contributing time at risk at the first visit (1988-1990) and are followed from baseline until diagnosis of first primary colorectal cancer, diagnosis of another cancer, loss to follow-up, or 12/31/12, whichever comes first. The proportional hazards assumption will be tested by graphing the log(-log(survival)) versus log(time). We will also explore the association between yogurt intake and risk of colon (overall, proximal and distal) and rectal cancers to assess for differences in association between yogurt and colon cancer by anatomical location of the colon cancer.

We will stratify by fiber intake based on the median level intake into higher and lower consumers of fiber and assess for an association between yogurt frequency intake and colorectal cancer in both groups.

The following models will be used:
Model 1: adjusted for age, sex, race*ARIC study site.

Model 2: Model 1 additionally adjusted for education, BMI, smoking status, number of pack-years of smoking and dietary energy intake (kcal/day).

Model 3: Model 2 adjusted for frequency of non-yogurt dairy intake (never/rarely, monthly less than weekly, weekly less than daily, daily).

Model 4: Model 2 adjusted for dietary calcium, Vitamin D levels (ng/ml), Vitamin D intake (IU).

Model 5: Model 2 adjusted for dietary fiber intake and fitted for an interaction term between dietary fiber and frequency of yogurt consumption. We will also stratify Model 2 by dietary fiber intake and assess if the association between yogurt intake frequency and colorectal cancer differs between higher and lower fiber intake.
Inclusion/Exclusion: inclusion: all ARIC Visit 1 participants free of cancer; exclusion: those who
did not give consent to participate in cancer studies, participants with missing data for serum
biomarker in a corresponding analysis.

Power calculation: Using a Chi square power calculation with 364 colorectal cases, 18%
prevalence of at least weekly yogurt consumption, 0.05 of Type error probability and based on
prior studies, an OR of 0.65, we found a power of 0.779. We may have limited power to detect
an association between yogurt and colon cancer, but this diverse cohort population will offer
significant variability in the exposure to yogurt consumption.

7.a. Will the data be used for non-CVD analysis in this manuscript? _x___ Yes    ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons
with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA
analysis RES_DNA = “CVD Research” would be used? _x___ Yes    ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains
the responses to
consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? _____ Yes    _x___ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating
Center must be used, or the file ICTDER03 must be used to exclude those with value
RES_DNA = “No use/storage DNA”? __x__ Yes    _____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC
Study manuscript proposals and has found no overlap between this proposal and
previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of
the web site at:  http://www.cscc.unc.edu/ARIC/search.php

____x___ Yes     _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to
contact lead authors of these proposals for comments on the new proposal or
collaboration)?
#2604 - Vitamin D, parathyroid hormone (PTH) and fibroblast growing factor (FGF) 23 in
relation to colorectal cancer risk and mortality in the Atherosclerosis Risk in Communities
Study. Anna Prizment, lead author, is a collaborator on this study. This study will use Vitamin D
as a potential confounder only; Vitamin D will be adjusted for in analyses and not evaluated as a
predictor of CRC.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any
ancillary study data? __X__ Yes    ____ No
11.b. If yes, is the proposal
   ___ A. primarily the result of an ancillary study (list number* 1995.04, 2011.07, 2009.17)
   ___ B. primarily based on ARIC data with ancillary data playing a minor role
      (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a
      manuscript is not submitted for ARIC review at the end of the 3-years from the date of the
      approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public
      has access to the published results of NIH funded research. It is your responsibility to upload
      manuscripts to PubMed Central whenever the journal does not and be in compliance with this
      policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in
      http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals
      automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be
    submitted by the Coordinating Center to CMS for informational purposes prior to
    publication. Approved manuscripts should be sent to Pingping Wu at CC, at
    pingping_wu@unc.edu. I will be using CMS data in my manuscript ___ Yes ___ No.
References


