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TITLE: Dietary Polyunsaturated Fatty Acids, Inflammatory Index, and Circulating Endocannabinoids/Oxylipins in Relation to Colorectal Carcinogenesis in Black Women

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14. ABSTRACT

This study aims to determine the role of dietary inflammation and circulating lipid mediators in colorectal carcinogenesis among Black women. Data and blood specimens for this study have been previously collected in the Black Women's Health Study, a prospective cohort of 59,000 Black women. To examine the role of dietary inflammation, including polyunsaturated fatty acids and fish intake, we are using data from food frequency questionnaires (Aim 1). To examine lipid mediators, we are conducting targeted assays using liquid chromatography/mass spectrometry to quantify levels of endocannabinoids and oxylipins in plasma samples (Aim 2). Finally, we will then leverage the published literature to assess the contribution of polyunsaturated fatty acids and fish intake to racial disparities in colorectal cancer and adenoma risk (Aim 3). This project consists of selecting appropriate individuals with dietary data and/or blood samples available, accessing samples for biospecimen assays, meta-analyzing the literature, and conducting analyses. To date, we have created data sets and started data analysis for Aim 1, we have selected individuals with blood samples available for Aim 2, and we have begun the systematic review of the literature for Aim 3. Analysis is ongoing; we have no results to present at this time.

15. SUBJECT TERMS
Colorectal adenoma, colorectal cancer, Dietary Inflammatory Index, epidemiology, food frequency questionnaire, health disparities, lipid mediators, meta-analysis, polyunsaturated fatty acids, risk factors

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TABLE OF CONTENTS

1. **INTRODUCTION:**

Black Americans have the highest CRC incidence and mortality rate of any racial/ethnic group, in addition to having a high prevalence of the CRC precursor—adenomas. Epidemiologic studies have shown that diets high in fish consumption and low in inflammation are inversely associated with colorectal carcinogenesis (normal tissue → adenoma → CRC). Cold-water fish, especially the dark meat fish (e.g., salmon and tuna), are rich sources of long-chain n-3 PUFAs, which have anti-inflammatory properties, influence the gut microbiota composition, suppress tumor progression, and are hypothesized to account for the reduced risk of CRC from fish consumption. Lipid mediators are bioactive PUFA metabolites, including endocannabinoids and oxylipins, and have been implicated in gastrointestinal disease. Evidence suggests that the beneficial effect of dietary n-3 PUFAs depends on the formation of lipid mediators. Black Americans have higher fish consumption than White Americans. However, Black Americans are over 3-times more likely to consume fried fish. Frying fish with cooking oils adds high amounts of fat and n-6 PUFAs. The objective of this proposal is to determine the role of dietary inflammation and lipid mediators in colorectal carcinogenesis among Black women. Data and blood specimens for this study have been previously collected in the Black Women's Health Study, a prospective cohort of 59,000 Black women. To examine the role of dietary inflammation, including polyunsaturated fatty acids and fish intake, we are using data from food frequency questionnaires (Aim 1). To examine lipid mediators, we are conducting targeted assays using liquid chromatography/mass spectrometry to quantify levels of endocannabinoids and oxylipins in plasma samples (Aim 2). Finally, we will leverage the published literature to assess the contribution of polyunsaturated fatty acids and fish intake to racial disparities in colorectal cancer and adenoma risk (Aim 3). This project consists of selecting appropriate individuals with dietary data and/or blood samples available, accessing samples for biospecimen assays, meta-analyzing the literature, and conducting analyses.

2. **KEYWORDS:**

colorectal adenoma, colorectal cancer, Dietary Inflammatory Index, epidemiology, food frequency questionnaire, health disparities, lipid mediators, meta-analysis, polyunsaturated fatty acids, risk factors

3. **ACCOMPLISHMENTS:**

   a. **What were the major goals of the project?**

      i. **Major Task 1:** Determine if dietary polyunsaturated fatty acids, fish intake, and the Dietary Inflammatory Index are associated with a) adenoma and b) colorectal cancer risk in Black women.

      ii. **Major Task 2:** Quantitate circulating levels of endocannabinoids and oxylipins in adenoma cases and matched controls, using liquid chromatography/mass spectrometry.

      iii. **Major Task 3:** Determine if circulating endocannabinoids/oxylipins are associated with a) adenoma and b) colorectal cancer risk in Black women.

      iv. **Major Task 4:** Conduct a systematic review and meta-analysis of literature on dietary polyunsaturated fatty acid and fish intake in relation to a) adenoma and b) colorectal cancer risk.

      v. **Major Task 5:** Assess the extent to which dietary polyunsaturated fatty acid and fish intake contributes to racial disparities in a) adenoma and b) colorectal cancer risk.

   b. **What was accomplished under these goals?**

i. **Major Task 1:** Determine if dietary polyunsaturated fatty acids, fish intake, and the Dietary Inflammatory Index are associated with a) adenoma and b) colorectal cancer risk in Black women. *33% complete*

Subtasks	**Timeline (months)**	**Status**
Subtask 1: Submitted IRB application and received approval	Pre-start date	Complete
Subtask 2: Submitted HRPO application and received approvals.	1-2	Complete
Subtask 3: Finalized study protocols.	3	Complete
Subtask 4: Study-specific *adenoma* dataset creation. We created a dataset, using the Black Women's Health Study (BWHS) data, that includes information on dietary variables (reported on food frequency questionnaires completed by BWHS participants) and information on potential covariates. Included in this task is construction of dietary polyunsaturated fatty acids, fish, and Dietary Inflammatory Index variables. This dataset includes all participants that have reported a colonoscopy or sigmoidoscopy and provided dietary information (n=31,881) and includes 1,817 outcomes of adenoma.	3-8	Complete
Subtask 4: Study-specific *colorectal cancer* dataset creation. We created a dataset, using the BWHS data, that includes information on dietary variables and on potential covariates. Included in this task is construction of dietary polyunsaturated fatty acids, fish, and Dietary Inflammatory Index variables. This dataset includes all participants that have reported dietary information (n=52,754) and will include 687 incident colorectal cancers.	3-8	Complete
Subtask 5: Descriptive data analysis examining baseline frequency (n) and relative frequency (%) of *adenoma* cases and non-cases, polyunsaturated fatty acid and fish intake, Dietary Inflammatory Index and potential covariates.	8-9	In Progress
Subtask 6: Descriptive data analysis examining baseline frequency (n) and relative frequency (%) of *colorectal cancer* cases and non-cases, polyunsaturated fatty acid and fish intake, Dietary Inflammatory Index and potential covariates.	10-11	Complete
Subtask 7: Use logistic regression models to calculate odds ratios, as an estimate of relative risk, and 95% confidence intervals for the association between dietary polyunsaturated fatty acids, fish, and Dietary Inflammatory Index variables and *adenomas,* overall and by size (i.e., ≥ 1 cm) and anatomic location. In a sensitivity analysis, we will restrict to participants who underwent at least two colonoscopies or sigmoidoscopies and were adenoma-free at the first procedure.	12-15	In Progress
Subtask 8: Use Cox proportional hazards regression models to calculate hazard ratios, as an estimate of relative risk, and 95% confidence intervals for the association between dietary polyunsaturated fatty acids, fish, and Dietary Inflammatory Index variables and incidence of *colorectal cancer* overall and by site (proximal and distal colon, rectal cancer).	16-19	In Progress
Subtask 9: Prepare and submit manuscripts.	15-20	Not Initiated

1. Progress and delays: We originally planned to conduct the adenoma analysis first. However, as the colorectal cancer dataset was already partially created for another project, we initiated this analysis first and are farther along with that than originally planned. This change will not affect our overall progress.

2. Preliminary Data: We have preliminary data examining the association between dietary polyunsaturated fatty acids, fish, and colorectal cancer.

   Methods. *Study Population.* The Black Women's Health Study (BWHS) is an ongoing prospective cohort study, which was designed to assess risk factors for

disease outcomes in US Black women. In 1995, 59,000 women aged 21–69 years were recruited by mailing questionnaires primarily to subscribers of *Essence* magazine. To enroll in the study, participants filled out a self-administered questionnaire on medical history, lifestyle factors, demographics, and diet. Participants have completed a questionnaire, either by mail or online, every 2 years since recruitment, so follow-up has continued for over 25 years. Follow-up is complete for about 85% of potential person-years. The BWHS protocol has been approved by the Institutional Review Board of Boston University and the study is reviewed annually.

Outcome. For this analysis, incident cases were classified as women diagnosed with primary colon or rectal cancer [definition based on the International Classification of Diseases for Oncology, Third Edition (ICD-0-3); codes C18.0-C18.9, C19.9, C20.9, and C21.8] from July 1st, 1996, 1 year after the first questionnaire, through December 31st, 2021. Colorectal cancer was further examined by anatomic location, defined as proximal (ICD-O-3 codes C18.0, C18.2-C18.5), distal (C18.6-C18.7), and rectal cancer (C19.9 and C20.9). Cases were ascertained by self-report on follow-up questionnaires, the National Death Index, and cancer registry data from 24 states (covering 95% of participants). Hospitals or cancer registries provided pathology data for 75% of cases, of which 95% were confirmed. Unless disconfirmed by review of pathology data, self-reported colorectal cancer cases are included. Colorectal cancer arising in women younger than 50 was defined as early-onset, while colorectal cancer arising in women of at least 50 years of age was defined as late-onset.

Dietary Assessment. Dietary data were first collected in 1995 based on the Block short-form FFQ from the National Cancer Institute (68 line items), and a second time in 2001 (85 line items). The BWHS FFQ was slightly modified to include food items commonly consumed by Black Americans not previously included in the Block FFQ. Three 24-hour recalls were used as criterion instruments to validate the BWHS FFQ. The deattenuated and energy-adjusted Pearson correlation coefficients between the FFQ and the 24-hour recalls for protein and saturated fat were 0.78 and 0.63, respectively.

For each line item, a medium portion size was defined, and participants were asked to report how frequently they had eaten the food in the last year and the approximate portion size consumed. The portion sizes for the 1995 questionnaire were small, medium, and large; a super-size portion was included on the 2001 questionnaire. In relation to the medium serving size, a small portion was specified as one-half or less; a large portion was 1.5 times the medium serving; a super-size portion was double the medium serving. Response options for frequency of food consumption ranged from least frequently, or "never or less than 1 per month," to most frequently, or "2 or more per day." To calculate consumption of fish in grams, serving size-adjusted frequency of food intake was multiplied by the estimated number of ounces in a medium portion (~3 oz). To calculate intakes of fatty acids, the serving size-adjusted grams/day for each food item was multiplied by its grams of fat content per 100 g fresh food weight, utilizing DIETCALC software, version 1.4.1 (National Cancer Institute).

Total fish included baked or broiled fish, tuna fish, and fried fish. The 2001 FFQ differentiated dark meat fish from baked or broiled fish intake and included a line

item for shellfish. Thus, we examined dark meat fish and shellfish intake for a subset of participants that returned the 2001 FFQ. n-3 PUFA intake included α-linolenic acid (18:3), stearidonic acid (18:4), eicosapentaenoic acid (20:5), docosapentaenoic acid (22:5), and docosahexaenoic acid (22:6); n-6 PUFA intake included linoleic acid (18:2) and arachidonic acid (20:4). We also examined the ratio of n-3:n-6 PUFAs and, separately, the long-chain n-3:n-6 ratio, which excludes α-linolenic acid, stearidonic acid, and linoleic acid.

Fish (oz/day) and PUFA intake (g/1,000 kilocalories) were categorized into quartiles, based on the distribution of intake among all study participants. Linear trend tests were performed based on quartile-specific medians of fish or PUFA intake. Distributions of continuous fish and PUFA intake were skewed, so intakes were $\log_{10}$-transformed for the analysis. A 1-unit change in log-transformed intake corresponded to 1 oz/day of fish intake, 10 g/day of total PUFA intake, and 1 g/day of individual fatty acids.

The cumulative average approach was used to examine dietary intake; in 2001, food frequency data collected from the 1995 and 2001 questionnaires were averaged. This method provides a more statistically powerful test of diet-disease relationships and reduces measurement error. For participants who did not fill out the 2001 FFQ, their 1995 dietary data was carried forward.

Covariates. Values for covariates and potential effect modifiers were obtained at baseline in 1995 and updated in 2001. Potential covariates included: age, total energy intake (kcal/day), type 2 diabetes, body mass index (BMI: ≥30, 25-29.9, or <25 kg/m^2), smoking (never, former, current; cigarettes/day), alcohol intake (drinks/week), red and processed meats (servings/day), fruits and vegetables (servings/week), education (≤12, 13-15, 16, ≥17 years), family history of colorectal cancer, aspirin and non-steroidal anti-inflammatory (NSAID) use, vigorous physical activity (hours/week), menopausal status, and menopausal hormone use.

Exclusions. From the 58,973 participants enrolled at baseline, those missing dietary data (i.e., >10 blank items) or reporting an implausible total energy intake (i.e., ≤500 kcal/day or ≥3800kcal/day) in 1995 (n = 6084) were excluded. Other exclusions included cases of prevalent colorectal cancer (n = 135) at baseline, or death within one year of enrollment (n = 0). Thus, the analytic sample consists of 52,754 women.

Statistical Analysis. Cox-proportional hazards regression models, with follow-up time as the underlying time metric, were used to estimate HRs and 95% confidence intervals (CIs) for association between fish and PUFAs with incidence of colorectal cancer. Follow-up time was calculated from baseline to the first of the following events: occurrence of incident colorectal cancer, loss to follow-up, date of death, or end of study follow-up in 2021. Proportional hazards assumptions were tested utilizing the Cox ZPH test on models with no covariates, and no violations of the assumption are reported ($p>0.05$).

All models were stratified by continuous age and time-period (2-year questionnaire cycle) and adjusted for energy (kcal/day), utilizing the standard multivariate approach. Next, we examined potential covariates and evaluated the extent to which they altered the log(HR) by ≥10%. Covariates retained in the final models included

total energy intake (kcal/day), type 2 diabetes, BMI (in kg/m^2) <25, 25-29.9, or ≥30 kg/m^2, red and processed meats (servings/day), and education (≤12, 13-15, 16, ≥17 y). Effect measure modification by age, BMI, and diabetes was assessed using likelihood ratio tests comparing regression models with and without a multiplicative term. All p-values are two-sided. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results. After exclusions, the analysis included 687 incident colorectal cancer cases over a median follow-up of 24 years. Compared with women consuming the lowest quartile of fish intake, women in the highest quartile of fish intake were more likely at baseline to be older, have higher educational attainment, smoke cigarettes, drink alcohol, and be physically active (**Table 1**).

Total fish intake was not associated with risk of colorectal cancer ($HR_{Q4\ vs.\ Q1}$=0.98, 95% CI: 0.78–1.23, P_{trend}=0.97, **Table 2**). There was also little to no association between fish intake and colorectal cancer when considering preparation method, baking ($HR_{Q4\ vs.\ Q1}$=0.82, 95% CI: 0.66–1.02, P_{trend}=0.12) or frying ($HR_{Q4\ vs.\ Q1}$=0.93, 95% CI: 0.75–1.15, P_{trend}=0.43). Intake of tuna fish was associated with a modest increased risk of colorectal cancer ($HR_{Q4\ vs.\ Q1}$=1.28, 95% CI: 1.02–1.61, P_{trend}=0.03). Associations were similar when considering age at colorectal cancer onset.

Table 1. Age-Standardized Baseline Characteristics by Quartiles of Total Fish Intake.

	Total Fish Intake oz/day			
	Quartile 1: <0.18 (n=13,174)	Quartile 2: 0.18-0.37 (n=13,423)	Quartile 3: 0.38-0.72 (n=13,091)	Quartile 4: >0.72 (n=13,066)
Age	37.0 ± 10.5	38.6 ± 10.7	39.4 ± 10.6	40.3 ± 10.7
BMI, kg/m^2	27.7 ± 6.6	27.9 ± 6.6	28.0 ± 6.7	28.1 ± 6.6
Waist-to-Hip Ratio	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
Cigarettes/day	2.0 ± 5.7	2.2 ± 5.9	2.1 ± 5.8	1.9 ± 5.7
Education				
≤ 12 years, %	20	19	17	15
13-15 years, %	36	37	36	35
16+ years, %	44	44	47	49
Smoking Status				
Never, %	67	65	64	63
Past, %	18	19	21	22
Current, %	14	16	16	15
Alcohol Use				
Never, %	61	57	55	51
Past, %	14	14	15	15
Current, %	24	29	30	34
Vigorous Physical Activity				
None, %	37	34	30	26

Table 1. Age-Standardized Baseline Characteristics by Quartiles of Total Fish Intake.

	Total Fish Intake oz/day			
	Quartile 1: <0.18 (n=13,174)	Quartile 2: 0.18-0.37 (n=13,423)	Quartile 3: 0.38-0.72 (n=13,091)	Quartile 4: >0.72 (n=13,066)
<5 hrs/wk, %	48	52	53	53
≥ 5 hrs/wk, %	12	12	13	17
History of diabetes				
Yes, %	4	4	4	5

Values are means ± SD or percentages and are standardized to the age distribution of the study population.

Table 2. Adjusted HRs and 95% CIs for associations of fish intake with risk of CRC by age in the BWHS[1]

	All Ages			**≥50 years**			**<50 years**		
	Cases, n	Person-y	HR (95% CI)[2]	Cases, n	Person-y	HR (95% CI)[2]	Cases, n	Person-y	HR (95% CI)[2]
Total fish, oz/day									
<0.25	161	348,631	1.00	115	151,286	1.00	46	197,345	1.00
0.25-0.47	163	333,507	0.95 (0.76, 1.18)	120	168,607	0.93 (0.72, 1.20)	43	164,900	0.98 (0.65, 1.50)
0.48-0.87	165	339,400	0.91 (0.73, 1.14)	127	183,689	0.90 (0.70, 1.17)	38	155,711	0.91 (0.59, 1.41)
>0.87	198	341,048	0.98 (0.78, 1.23)	151	196,788	0.93 (0.72, 1.21)	47	144,260	1.13 (0.73, 1.76)
P_{trend}[3]			0.97			0.75			0.53
Continuous, per 1 oz/day			0.95 (0.75, 1.21)			0.94 (0.71, 1.25)			0.97 (0.61, 1.55)
Total baked fish, oz/day									
0	167	335,692	1.00	120	139,134	1.00	47	196,558	1.00
0.02-0.16	166	338,903	0.92 (0.74, 1.14)	110	168,703	0.78 (0.60, 1.02)	56	170,200	1.31 (0.88, 1.96)
0.17-0.40	161	328,630	0.85 (0.68, 1.06)	121	180,569	0.78 (0.60, 1.01)	40	148,061	1.04 (0.67, 1.60)
>0.40	187	350,676	0.82 (0.66, 1.02)	157	206,744	0.81 (0.63, 1.04)	30	143,933	0.76 (0.47, 1.23)
P_{trend}[3]			0.12			0.25			0.23
Continuous, per 1 oz/day			0.86 (0.69, 1.07)			0.88 (0.69, 1.13)			0.80 (0.51, 1.24)
Total fried fish, oz/day									
<0.02	196	351,289	1.00	149	170,311	1.00	47	180,979	1.00
0.04-0.09	141	329,043	0.76 (0.61, 0.95)	100	168,095	0.72 (0.56, 0.93)	41	160,947	0.89 (0.59, 1.37)
0.09-0.18	172	368,835	0.81 (0.66, 1.00)	131	192,292	0.81 (0.64, 1.04)	41	176,543	0.80 (0.52, 1.23)
>0.18	175	306,632	0.93 (0.75, 1.15)	131	166,303	0.90 (0.70, 1.15)	44	140,329	1.00 (0.65, 1.55)
P_{trend}[3]			0.43			0.36			0.99
Continuous, per 1 oz/day			0.94 (0.69, 1.28)			0.93 (0.65, 1.33)			0.96 (0.52, 1.77)
Total tuna fish, oz/day									
≤0.02	138	312,082	1.00	93	148,588	1.00	45	163,494	1.00
0.04-0.10	181	364,776	1.09 (0.87, 1.36)	145	184,544	1.27 (0.98, 1.65)	36	180,232	0.70 (0.45, 1.08)
0.10-0.20	175	363,850	1.02 (0.81, 1.28)	135	194,654	1.15 (0.88, 1.51)	40	169,196	0.73 (0.47, 1.13)

>0.20	191	313,443	1.28 (1.02, 1.61)	138	168,084	1.33 (1.01, 1.75)	53	145,359	1.20 (0.79, 1.81)
P_{trend}[3]			0.03			0.04			0.46
Continuous, per 1 oz/day			1.34 (1.02, 1.76)			1.33 (0.97, 1.82)			1.38 (0.80, 2.35)

[1]BWHS, Black Women's Health Study; CRC, colorectal cancer.
[2]The model was adjusted for age, time-period, total energy intake (kcal/day), type 2 diabetes, BMI (≥30, 25-29.9, or <25 kg/m^2), red and processed meats (servings/week), and education (≤12, 13-15, 16, ≥17 years).
[3]Tests of linear trend were calculated by assigning the median of each category as scores.

ii. **Major Task 2:** Quantitate circulating levels of endocannabinoids and oxylipins in adenoma cases and matched controls, using liquid chromatography/mass spectrometry. *25% Complete*

Subtask 1: We identified *adenoma* cases (n=349) with available plasma samples and 2:1 matched controls (n=698).	7-8	Complete
Subtask 2: We identified *colorectal cancer* cases (n=52) with available plasma samples and 2:1 matched controls (n=104).	7-8	Complete
Subtask 3: Have biorepository pull blood samples, aliquot, and ship to the NIH West Coast Metabolomics Center, including samples from the BWHS cases (n=349 adenoma and 52 colorectal), controls (n=698 and 104, respectively), and 60 commercially acquired quality control samples (n=1,263 total samples).	9-12	In Progress
Subtask 4: Conduct assays using liquid chromatography/mass spectrometry at NIH West Coast Metabolomics Center for 30 endocannabinoids and 90 oxylipins.	13-24	Not Initiated
Subtask 5: Examine quality control sample data to assess technical and batch-to-batch variability within the laboratory by calculating the coefficient of variation and interquartile range.	25-26	Not Initiated

1. Progress and delays: We have selected cases and matched and controls. We are now waiting in the queue for the laboratory to pull and aliquot the samples. We anticipate that this will be completed in the next 1-2 months.

iii. **Major Task 3:** Determine if circulating endocannabinoids/oxylipins are associated with a) adenoma and b) colorectal cancer risk in Black women. *Not Complete*

Subtask 1: Descriptive data analysis examining baseline frequency (n) and relative frequency (%) of *adenoma* cases and non-cases, endocannabinoid and oxylipin values, and potential covariates.	25-26	Not Initiated
Subtask 2: Descriptive data analysis examining baseline frequency (n) and relative frequency (%) of *colorectal cancer* cases and non-cases, endocannabinoid and oxylipin values, and potential covariates.	27-28	Not Initiated
Subtask 3: Use conditional logistic regression models to calculate odds ratios and 95% confidence intervals for the association between endocannabinoids and oxylipins and *adenomas.*	27-30	Not Initiated
Subtask 4: Use conditional logistic regression models to calculate odds ratios and 95% confidence intervals for the association between endocannabinoids and oxylipins and *colorectal cancer incidence.*	31-34	Not Initiated
Subtask 5: Prepare and submit manuscript(s).	31-36	Not Initiated

iv. **Major Task 4:** Conduct a systematic review and meta-analysis of literature on dietary polyunsaturated fatty acid and fish intake in relation to a) adenoma and b) colorectal cancer risk. *40% Complete*

Subtask 1: We conducted a systematic review of the literature for the association between dietary polyunsaturated fatty acid and fish intake and *adenomas.* We identified 7 relevant studies.	3-7	Complete
Subtask 2: We conducted a systematic review of the literature for the association between dietary polyunsaturated fatty acid and fish intake and *colorectal cancer.* We identified 21 relevant studies.	8-12	Complete
Subtask 3: Perform a meta-analysis of the existing literature together with the BWHS results from Major Task 1, and estimate the relative risks for the association between dietary polyunsaturated fatty acid and fish intake and *adenomas.*	16-17	Not Initiated
Subtask 4: Perform a meta-analysis of the existing literature with the BWHS results from Major Task 1, and estimate the relative risks for the association between dietary polyunsaturated fatty acid and fish intake and *colorectal cancer*.	20-21	Not Initiated

v. **Major Task 5:** Assess the extent to which dietary polyunsaturated fatty acid and fish intake contributes to racial disparities in a) adenoma and b) colorectal cancer risk. *Not Complete*

Subtask 1: Extract race- and sex-specific distribution of dietary polyunsaturated fatty acid and fish intake from the (publicly available) National Health and Nutrition Examination Survey.	9-12	In Progress
Subtask 2: Calculate race- and sex-specific population attributable fractions (using the relative risks calculated in the meta-analysis in Major Task 4), which will represent the proportion of *adenoma* cases that can be attributed to dietary polyunsaturated fatty acid or fish intake.	18-23	Not Initiated
Subtask 3: Calculate race- and sex-specific population attributable fractions, which will represent the proportion of *colorectal cancer* cases that can be attributed to dietary polyunsaturated fatty acid or fish intake.	24-29	Not Initiated
Subtask 4: Prepare and submit manuscripts.	24-30	Not Initiated

1. Progress and delays: We experienced delays in staffing at the beginning of the project, which is not uncommon in research studies like ours. Staff were not immediately available to work on this project at full effort when we received the award because they needed to complete work on other projects. Instead of hiring new personnel, which would also have delayed staffing, we planned to shift staff from the Black Women's Health Study so that the project would have experienced staff working on data analysis. We are now fully staffed and anticipate finalizing the extraction of dietary distributions in the next 3 months.

c. **What opportunities for training and professional development has the project provided?**

i. Nothing to report

d. **How were the results disseminated to communities of interest?**

i. Nothing to report

e. **What do you plan to do during the next reporting period to accomplish the goals?**

i. In the next reporting period, we plan to finalize any remaining subtasks from year 1 (i.e., aliquoting and shipping blood samples and extracting dietary intake distributions from NHANES). We will also complete the study activities that are expected for year 2.

4. **IMPACT:**

    a. **What was the impact on the development of the principal discipline(s) of the project?**

        i. Nothing to report

    b. **What was the impact on other disciplines?**

        i. Nothing to report

    c. What was the impact on technology transfer?

        i. Nothing to report

    d. **What was the impact on society beyond science and technology?**

        i. Nothing to report

5. **CHANGES/PROBLEMS:**

    a. **Changes in approach and reasons for change**

        i. Nothing to report

    b. **Actual or anticipated problems or delays and actions or plans to resolve them**

        i. Nothing to report

    c. **Changes that had a significant impact on expenditures**

        i. Nothing to report

    d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents** – Nothing to report

    e. **Significant changes in use or care of human subjects** – Nothing to report

    f. **Significant changes in use or care of vertebrate animals** – Nothing to report

    g. **Significant changes in use of biohazards and/or select agents** – Nothing to report

6. **PRODUCTS:**

    a. **Publications, conference papers, and presentations**

        i. **Journal publications.**

            1. **Petrick JL**, Barber LE, Rosenberg L. What are the Factors Underlying Colorectal Cancer Health Disparities? *Cancer Prev Res (Phila)* 2022;15:561-563. PMID: 36047055.

                a. Published

b. Acknowledgement of federal support: Yes

ii. **Books or other non-periodical, one-time publications.** - Nothing to report

iii. **Other publications, conference papers, and presentations.**

1. "The association between the oral microbiome and body mass index among Black women". The 15th American Association for Cancer Research Conference on the Science of Health Disparities in Racial/Ethnic Minorities and the Medically Underserved. September 18th, 2022. Philadelphia, PA.

b. **Website(s) or other Internet site(s)** – Nothing to report

c. **Technologies or techniques -** Nothing to report

d. **Inventions, patent applications, and/or licenses** – Nothing to report

e. **Other Products** – Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. **What individuals have worked on the project?**

Name:	Jessica Petrick
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-6580-450X
Nearest person month worked:	3
Contribution to Project:	PI responsible for all aspects of the study
Funding Support:	N/A

Name:	Nuo Xu
Project Role:	Research data analyst
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Data analyst responsible for creating datasets and data analysis
Funding Support:	N/A

b. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

PAST/COMPLETED SUPPORT – Jessica Petrick

Title:	Improving Breast Cancer Risk Prediction for African American Women: Consideration of Estrogen Receptor Subtype-Specific Risk Factors
Effort:	4.2 calendar months
Supporting Agency:	National Cancer Institute
Grants Officer:	Stefanie A. Nelson stefanie.nelson@nih.gov
Performance Period:	1/8/2019 – 12/31/2022
Funding Amount:	
Project Goals:	To develop a breast cancer risk prediction model for AA women that takes into account etiologic differences in major subtypes.
Specific Aims:	**Aim 1. Develop and test a clinically useful breast cancer risk prediction tool for AA women that takes into account differential risk factors and age-incidence curves for ER+ and ER- breast cancer** 1. Use case-control data to estimate relative risk estimates for each of ER+ and ER- breast cancer. Combine with ER-specific SEER age-incidence rates for AA women to build separate absolute risk models for ER+ and ER- breast cancer. Use competing risks methods to derive the probability of developing the first of either ER+ or ER- breast cancer over a pre-specified time interval given an individual's age and risk factors 2. Develop an alternative model using traditional methods that treat breast cancer as a single disease. 3. Test the two models in an independent prospective study, the BWHS. Assess calibration and discriminatory accuracy of the models overall and within strata of age and family history of breast cancer. 4. Compare performance of the new models with the two previous models developed for AA women using net reclassification index and alternative reclassification methods. 5. Develop a brief web-based questionnaire and statistical program for computing absolute risks. **Aim 2. Assess whether model performance is improved by addition of common, low-penetrance genetic variants associated with breast cancer in AA women.** 1. Using odds ratios and risk allele frequencies for genetic variants associated with AA breast cancer in a large collaborative study, already published, redo the steps of model development to obtain models that include both non-genetic and genetic factors 2. Test these new models in BWHS data and compare performance with performance of the Aim 1 models using net reclassification index and other methods
Overlap:	None

Title:	Exploring factors related to racial disparities in ovarian cancer incidence and survival: the OCWAA consortium
Effort:	1.2 calendar months
Supporting Agency:	NIH
Grants Officer:	Lisa M Gallicchio Lisa.gallicchio@nih.gov
Performance Period:	04/01/17-03/31/22
Funding Amount:	
Project Goals:	The goal of this project is to assess racial differences in incidence and survival in relation to reproductive and lifestyle factors that differ in prevalence or timing between African American and white women, using data from a consortium of studies of ovarian cancer in African American and white women.
Specific Aims:	**Aim 1.** To harmonize risk factor, clinical and outcome data from the participating sites in the OCWAA consortium. We will pool and harmonize questionnaire and pathology/clinical data from existing case--control and cohort studies in AA women. We will also harmonize data for white cases and controls enrolled in a subset of the studies in OCWAA. This effort will establish an infrastructure for pooling data from existing studies, resulting in an increased sample size and a core database of epidemiologic and clinical information to build future epidemiologic research on ovarian cancer in AA women. **Aim 2.** To estimate the contribution of reproductive and lifestyle exposures, which differ in *prevalence* and/or *timing* between AA and white women, to racial differences in *incidence* of IEOC. 1) We will estimate race--specific patterns of exposure for tubal ligation, oral contraceptive use (OC), menopausal hormone use, parity, hysterectomy, endometriosis, talc use, aspirin use, non-steroidal anti-inflammatory drug (NSAID) use, and body mass index (BMI), and we will pay special attention to duration and temporal factors (e.g., age at first and last exposure, duration of exposure) when applicable. 2) We will estimate race--specific associations between these exposures and IEOC incidence. 3) We will estimate separate race--specific population attributable risk percent (PAR%) for each risk factor, both individually and in aggregate. In exploratory analyses, we will also estimate race--specific PAR% using simulation modeling and compare results to those obtained using conventional methods. We will repeat Aim 2 analyses specifically for high grade serous ovarian cancer. **Aim 3.** To estimate the contribution of personal and lifestyle characteristics, treatment and tumor characteristics, as well as ovarian cancer risk factors which differ between AA and white women, to differences in *survival* of IEOC. 1) We will estimate race--specific associations of tumor histology, stage at diagnosis, tumor grade and treatment, along with the exposures listed in Aim 2.1, and address factors affecting access to care. 2) We will estimate race--specific associations between covariates and IEOC survival. 3) As in Aim 2.3, we will estimate race--specific PAR% for individual and aggregate prognostic factors using both conventional approaches and simulation modeling. We will repeat Aim 3 analyses specifically for high grade serous ovarian cancer.

Overlap:	None

NEW/ADDED SUPPORT – Jessica Petrick

Title:	A Follow-up Study for Causes of Cancer in Black Women
Effort:	1.2 calendar months
Supporting Agency:	National Cancer Institute
Grants Officer:	Danielle M. Carrick Danielle.Carrick@nih.gov
Performance Period:	9/1/2022-8/31/2027
Funding Amount:	
Project Goals:	The Black Women's Health Study (BWHS), initiated in 1995, is the largest follow-up study of the health of self-identified Black women yet conducted (n=59,000). The goals of this study are to identify and evaluate causes and risk factors for breast cancer, other cancers, and other serious illnesses in Black women, including genetic, behavioral, and environmental factors. This infrastructure grant supports data and specimen collection in the BWHS.
Specific Aims:	**Aim 1:** Continue and enhance data collection and follow-up of the BWHS cohort. **Aim 2:** Manage/collect/assay biospecimens. **Aim 3:** Participate in consortial projects, data sharing, data analysis, and manuscript preparation.
Overlap:	None

c. **What other organizations were involved as partners?**

i. Nothing to Report.

8. **SPECIAL REPORTING REQUIREMENTS**

a. **COLLABORATIVE AWARDS:** N/A

b. **QUAD CHARTS:** N/A

9. **APPENDICES:** N/A