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PRINCIPAL INVESTIGATOR:	Dr. Britton Trabert
CONTRACTING ORGANIZATION:	The Geneva Foundation 950 Broadway Suite #307 Tacoma, WA 98402
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6. AUTHOR(S)

Dr. Britton Trabert

britton.trabert@hci.utah.edu (preferred)
britton.trabert@nih.gov

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The Geneva Foundation
917 Pacific Avenue. Suite 600
Tacoma, WA 98402

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Objective: We hypothesize that the use of updated exposure information in cohort analyses will clarify and refine the ovarian cancer risk reduction associated with aspirin, that there are subgroups of women who will derive the most benefit from daily aspirin use with respect to ovarian cancer chemoprevention, and that aspirin will preferentially reduce risk for ovarian cancers dependent on the tumor immune microenvironment.
Impact: The proposed research directly addresses the OCRP vision – to eliminate ovarian cancer, by addressing critical questions related to the prevention of ovarian cancer. This research also addresses OCRP research objectives related to cancer etiology, primary prevention, and understanding the mechanism(s) by which aspirin can prevent ovarian cancer. By leveraging and expanding upon the OC3 infrastructure through collection of updated exposure information and tumor tissue this well-powered investigation of aspirin use with ovarian cancer risk will address key questions needed to develop recommendations for aspirin-based chemoprevention. The identification of women who will derive the most benefit from aspirin for ovarian cancer chemoprevention will guide future clinical trials in high-risk populations. Further, our examination of potential biologic mechanisms using tumor tissue expression of COX-1/2 and immune/inflammation markers will help strengthen the causal link between daily aspirin use and ovarian cancer development and inform potential co-testing of immune-modulators and daily aspirin use to improve cancer prognosis and/or progression-free survival. Since aspirin generally has few side effects, the potential for public health impact is substantial, particularly if risk reductions are identified among women at moderate to high risk of ovarian cancer. Ultimately, this innovative application combines epidemiologic and tumor tissue data to improve both the mechanistic understanding of ovarian carcinogenesis and the ability to make recommendations regarding the prevention of this fatal disease that will benefit all women, including military Service members, their families, and other military beneficiaries.

15. SUBJECT TERMS
Oncology, Pharmacology, Women's Health, Cancer, Ovarian Cancer, Prevention, Force Health Protection

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1. INTRODUCTION:

The research conducted as part of this project aims to address the unresolved questions related to the potential prevention of ovarian cancer associated with frequent aspirin use and provide mechanistic insight by collecting updated analgesic exposure information in cohort studies to refine risk assessment and clarify associations, combining cohort and case-control study data to evaluate the ability of aspirin to reduce ovarian cancer risk among high-risk subgroups of women, and to create/evaluate tumor tissue microarrays (TMAs) from cohort studies to explore possible mechanisms by which aspirin may reduce ovarian cancer risk.

2. KEYWORDS:

Ovarian cancer, prevention, aspirin, mechanism, epidemiology, etiology, tumor tissue, immune response

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aims: The aims of the study are to:
1) Evaluate the relationship of daily aspirin use over the life course, including updated information on dose, duration, and frequency post-baseline, and ovarian cancer risk using data from 12 studies in the Ovarian Cancer Cohort Consortium (OC3);
2) Identify subgroups of women who could most benefit from aspirin chemoprevention in a well powered study using harmonized case-control data from Ovarian Cancer Association Consortium (OCAC) and cohort data from OC3;
3) Explore mechanisms by which aspirin reduces ovarian cancer risk by utilizing ovarian tumor tissue from seven OC3 cohorts.

Major Task 1: Update data use/data transfer agreements to include aims and sign Material Transfer Agreements for transfer of biologic specimens for assays. *(100% Complete)*
Major Task 2: Submission of institutions IRB approval and related materials for DOD's HRPO approval. *(100% Complete)*
Major Task 3: Collect and harmonize questionnaire data from non-baseline time points across 12 cohorts, conduct analyses of analgesic use with ovarian cancer risk using updated follow-up data. *(95% Complete, manuscript in progress)*
Major Task 4: Obtain OCAC dataset and conduct study-specific analyses. Conduct meta-analyses to evaluate aspirin-ovarian cancer associations by risk factors. *(100% Complete)*
Major Task 5: Collect Tissue microarray (TMA) slides and create TMAs for studies with tumor tissue only. Complete molecular analysis of TMAs. *(100% Complete)*
Major Task 6: Integrate TMA expression data with OC3 dataset. Analyze tumor expression data to evaluate heterogeneity in aspirin association by tumor markers. *(85% Complete, final data analyses in progress, manuscript pending.)*

What was accomplished under these goals?

Major Activities

For Major Task 1, Dr. Trabert initially completed and received approved OHSRP exemption paperwork from NIH. Dr. Tworoger and colleagues at Moffitt Cancer Center with the assistance of Dr. Trabert updated all cohort data transfer agreements (12 cohorts in total) and baseline data as well as harmonization code was transferred between Brigham and Womens Hospital and Moffitt Cancer Center. Dr. Trabert then completed and received IRB approval from her new institution (University of Utah) for the project (April 2021). Dr. Tworoger and colleagues at Moffitt Cancer Center with the assistance of Dr. Trabert updated all necessary information at the Moffitt Cancer Center related to Dr. Trabert's change in institution. Major Task 1 was completed in its entirety in April 2021.

For Major Task 2, Drs. Trabert and Tworoger completed necessary IRB agreements with Moffitt and ensured that appropriate data access and data use agreements were in place for Dr. Trabert and Dr. Lauren Hurwitz to conduct analyses. In conjunction with completing major task 2, we also submitted and received paperwork and approval back from DOD HRPO that the project was approved. Subsequently, Dr Trabert submitted a revised DOD HRPO submission with the updated IRB approval from the University of Utah and the updated SOW that added University of Utah as an additional research site. The HRPO concurrence correspondence (E01116.1b - HRPO Concurrence Memorandum (IRB Study Number 00043994, Proposal Number OC180339, Award Number W81XWH-19-1-0346).) was received on July 16, 2021, thus completing Major Task 2 in its entirety.

For Major Task 3, Dr. Trabert created a data request form with data abstracting instructions for cohorts and data requests were formally submitted to the cohorts in Jan 2020. By October 2021 data have been received from all 12 cohorts requested. As part of subtask 2, we (Drs. Townsend, Tworoger, and Trabert) with the support of the Biostatistics Core at Moffitt

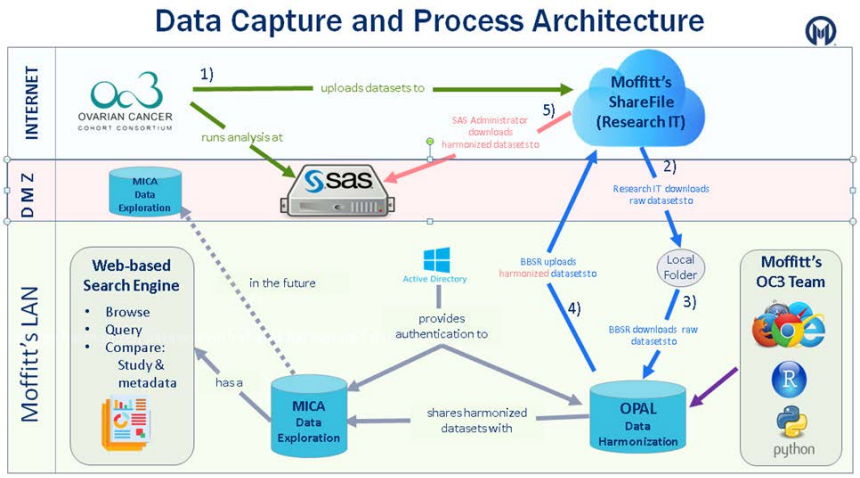


Figure 1: Accomplishment: Working with staff at H. Lee Moffitt Cancer Center, we developed a data capture and process architecture for the harmonization, storage, and analysis of data related to the studies primary aims. This infrastructure will be used to support OC3 research projects going forward and represents a substantial amount of effort and person-time funded by this project.

Cancer Center implemented a data capture and processing architecture as summarized in Figure 1 to harmonize the data. We consulted biostatisticians to develop a macro to generate the harmonized variables necessary and format the data for the planned pooled logistic regression analyses to update the follow-up data at 2-year time windows. Throughout the duration of the grant and no-cost-extension we continued to have biweekly conference calls with a group of ~12 individuals to review data and discuss progress and troubleshoot any issues we were having with harmonization. In the most recent reporting periods this has included presentations from biostatistical experts to answer questions related to the pooled logistic regression data structure and analysis.

The data harmonization process took much longer than estimated but ran very smoothly, and in total we have harmonized 2686 variables across 109 timepoints for 12 cohorts (Summarized in Table 1 and Figure 2) for the time-updated aspirin analysis outlined in Aim 1.

The data cleaning and harmonization included 5 variables related to aspirin exposure updated every 2 years depending on the cohort (Figure 2), updated ovarian cancer outcome data from individual cohorts, harmonized covariate data including age, oral contraceptive use duration, parity, updated information on body mass index and smoking status, family history of breast or ovarian cancer, updated tubal ligation and hysterectomy status, duration of menopausal hormone therapy use, and additional information to facilitate analyses. Harmonization was completed early summer of 2023 and we have been analyzing and cleaning the data since then and are

Table 1. Summary of study participants, number of time points of data collection, and number of variables harmonized across all timepoints for the funded project.

Study	# participants	# time points	# variables
AARP	225,384	3	69
CPS2	94,538	10	190
CTS	109,752	6	119
BGS	113,219	2	66
IWHS	41,836	6	121
MCCS	23,249	1	47
MEC	90,072	3	101
NHS	120,653	20	527
NHS2	116,412	14	569
PLCO	76,099	3	101
SCCS	50,342	4	104
SIS	50,884	5	258
SMC	38,923	3	100
WHI	161,808	29	314
TOTAL	**1,313,171**	**109**	**2686**

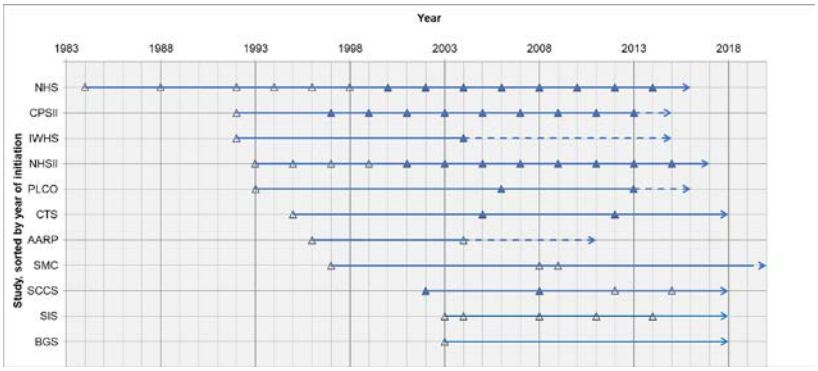


Figure 2. Time points for aspirin data collection in the eleven cohort studies included in this analysis. Blue triangles indicate the timing of the questionnaires that collected information on frequency of aspirin use. Triangles are shaded for questionnaires that also collected information on dose of aspirin use. Arrow lines indicate the follow-up period for ascertainment of ovarian cancer incidence, with solid lines indicating active follow-up and dashed lines indicating passive follow-up.

in the process of drafting a manuscript which will be the final deliverable for Major Task 3. It is important to note that even with delays related to the COVID19 pandemic and work from home requirements we met our goal of receiving all data for Aim 1 by the end of the 3rd quarter of CY21. Summary of results (Major Task 3, Aim 1): There were 815,972 individuals

included in the time-updated aspirin analysis. At baseline, 12.4% of individuals reported frequent aspirin use. During subsequent questionnaire cycles, an additional 23.4% of participants reported frequent aspirin use. Of the frequent aspirin users, 2% first reported frequent aspirin use before age 40, 11% first reported use between age 40 and 49, 25% first reported use between ages 50 and 59, 35% first reported use between ages 60 and 69, and 28% first reported use at age 70 or older (Table 2). There were 6,480 ovarian cancers diagnosed during the follow-up period (median follow-up=16 years). Overall, there was no association between cumulative, time-updated frequent aspirin use and ovarian cancer risk (HR (95% CI): 0.97 (0.89-1.05)), with consistent associations found in models varying lag and minimum inclusion age as well as in time-updated Cox proportional hazards models. Importantly, when we examined the association by dose of aspirin, a protective association was observed for frequent use of low-dose aspirin (HR (95% CI): 0.87 (0.76-0.99), n=352 exposed cases) but not for adult strength aspirin (HR (95% CI): 1.15 (0.96-1.39), n=134 exposed cases. This manuscript will be circulated to co-authors in early 2024 and submitted to a journal for publication shortly thereafter, representing the final product from Major Task 3.

For Major Task 4, (Drs. Trabert and Hurwitz) completed the manuscript evaluating frequent aspirin use and ovarian cancer risk by strata of defined effect modifiers in both OCAC and OC3. The primary manuscript summarizing results was submitted to Journal of Clinical Oncology (IF 44.5) and was published July 22, 2022 after two rounds of revisions.
https://pubmed.ncbi.nlm.nih.gov/35867953/

Subtask 1 involved requesting the OCAC data and Dr. Trabert did that directly through the OCAC data coordinating center at Duke University. Dr. Trabert and Hurwitz then conducted study-specific unconditional logistic regression with adjustment for harmonized confounders to estimate odds ratios and 95% confidence intervals of the frequent aspirin use exposure with ovarian cancer risk by strata of ovarian cancer risk factors (i.e., age, endometriosis, family history of breast and/or ovarian cancer, body mass index, oral contraceptive use, parity, and tubal ligation status. Dr. Trabert accessed the baseline OC3 data and completed analyses using study-specific cox proportional hazards models with adjustment for harmonized confounders to estimate hazards ratios and 95% confidence intervals of frequent aspirin use exposure and ovarian risk by strata of ovarian cancer risk factors. Individual effect estimates and standard errors for the aspirin-ovarian cancer association by strata of risk factor and study were then transferred to Stata and meta-analyses were conducted by study design and overall. We tested for heterogeneity in the findings across the strata of risk factors overall and by study design. To complete the analyses by histologic subtype we first estimated associations in individual studies, however, given the rarity of many of the ovarian cancer subtypes, we conducted analyses by study design (case-control and cohort) and pooled the study design specific estimates using meta-analysis. We reviewed results from these analyses 3 times on the OC3 bi-weekly programming conference call to solicit feedback and input on the methods and results and received input from all co-authors/collaborating studies and incorporated that feedback into the manuscript.

The resulting manuscript (referenced above) was then circulated to Drs. Penny Webb and Shelley Tworoger for completed technical and scientific review and then circulated to all OCAC and OC3 study authors. Once the manuscript revision process was completed, the

manuscript was submitted through clearance at the National Cancer Institute and through cohort specific clearance processes (Nurses' Health Study). This was a major accomplishment as we have completed Aim 2 of the proposed study. The submitted manuscript is attached to this report. We included 9 cohort studies from the Ovarian Cancer Cohort Consortium (OC3) and 8 case-control studies from the Ovarian Cancer Association Consortium (OCAC), the totality of studies with exposure data on frequent aspirin use.

Significant results included the observation of a protective association between frequent aspirin use and ovarian cancer risk that was generally consistent across subgroups of women with other ovarian cancer risk factors. There was also a protective association among women with multiple ovarian cancer risk factors. Furthermore, this manuscript received considerable press attention, including multiple interviews by various news outlets for Drs. Trabert and Hurwitz.

In addition to the main effect modification analysis, we also evaluated associations by genetic susceptibility to ovarian cancer as specified in our study aims. This manuscript was published in JAMA Network Open in February 2023 https://pubmed.ncbi.nlm.nih.gov/36826816/. The purpose of this manuscript was to expand on Aim 2; frequent aspirin use is associated with reduced ovarian cancer risk, but it is unknown whether genetic factors modify this association. We tested for effect modification by a polygenic score (PGS) for non-mucinous ovarian cancer. Pooling eight case-control studies from the Ovarian Cancer Association Consortium, we used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs), and likelihood ratio tests to investigate effect modification by the PGS. Overall, among n=6,659 controls and n=4,476 non-mucinous cases, frequent aspirin use was associated with 13% lower risk of ovarian cancer (OR: 0.87, 95% CI: 0.76-0.99). The association was not modified by the PGS, and a similar OR was observed among women with the highest PGS (quintile 5: OR 0.87, 95% CI 0.70-1.07). Results were consistent across histotype. This study suggests that frequent aspirin use may lower risk of ovarian cancer among women with increased genetic susceptibility to ovarian cancer. Our findings complement the main manuscript published based on study Aim 2, and represent an additional deliverable from Aim 2/Major Task 4 in the Statement of Work. Both manuscripts for Aim 2 are in the attached appendix.

For major task 5: In the first year of the grant we established an agreement with the University of Iowa (Dr. Charles Lynch, IWHS samples) to obtain tumor samples for the cases from their cohort and create a TMA. Creation of the TMA occurred at Moffitt Cancer Center (site 2). For major task 5 our initial plan was to obtain TMA from 5 cohorts, including IWHS, NHS, NHSII, BGS, and PLCO. We were not able to complete sample acquisition from the Breakthrough Generations Study since they had a leadership change and priorities in terms of contributing to ovarian cancer projects were re-evaluated and we were not able to obtain the samples. We have been able to collect TMAs from all other listed studies. As part of Major Task 5, the analytic core at Moffitt Cancer Center completed staining of the aspirin pathway, T-cell/B-cell markers, and tumor associated macrophages on 7 TMAs from NHS/NHSII, 4 TMAs from IWHS, and 8

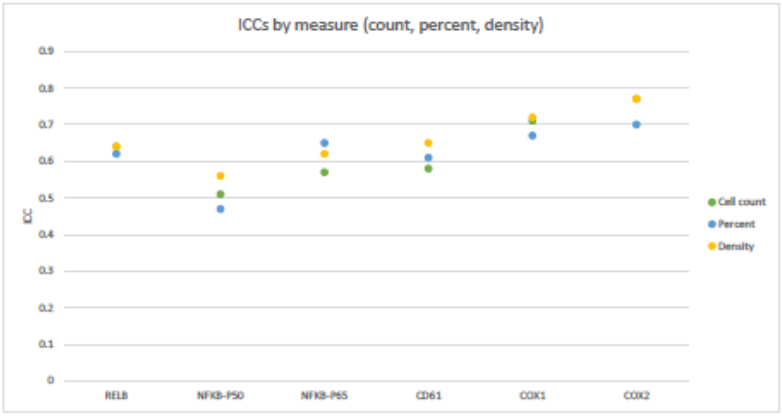
TMAs from PLCO resulting in tumor marker data on 908 total cases (532 NHS/NHSII, 142 IWHS, 234 PLCO).

As part of this project we worked with the laboratory to develop a panel that quantified aspirin pathway-associated markers including COX 1&2 and NFkB markers. This panel passed quality control testing (Major task 5, subtask 3 assay QC): Below are the results of the preliminary analysis of the inflammatory marker panel: In summary, the ICCs for the markers on the panel were all above acceptable (0.47 and greater, mean 0.62). Thus completing Major Task 5.

Preliminary data, Distribution of immune cells (percent positive) in Tester TMA (204 cores), Inflammation-related tumor marker panel.

Cell type	Location	% >0	% >3%	% >5%	P0	P20	P40	P50	P60	P80	P100	Mean	ICC	ICC CI
RelB	Overall	98.0	76.5	70.1	0.0	2.3	10.0	17.7	28.2	52.3	99.7	27.4	0.62	(0.50, 0.73)
NFKB-p50	Overall	99.5	97.1	97.1	0.0	36.5	59.6	68.7	77.6	87.5	98.9	62.9	0.47	(0.33, 0.62)
NFKB-p65	Overall	97.6	95.1	94.6	0.0	42.7	67.9	75.9	81.8	92.6	99.7	66.4	0.65	(0.53, 0.75)
CD61	Overall	99.0	68.1	53.4	0.0	1.8	3.9	5.8	9.1	19.2	80.8	12.7	0.61	(0.49, 0.72)
COX1	Overall	93.6	76.4	48.0	0.0	0.3	2.5	4.4	9.4	33.9	90.4	16.5	0.67	(0.56, 0.76)
COX2	Overall	90.7	57.8	49.5	0.0	0.2	2.6	4.9	11.1	41.5	97.9	19.2	0.70	(0.60, 0.79)

Cell marker	Measure	ICC
RELB	Cell count	0.64
NFKB-P50	Cell count	0.51
NFKB-P65	Cell count	0.57
CD61	Cell count	0.58
COX1	Cell count	0.71
COX2	Cell count	0.77
RELB	Percent	0.62
NFKB-P50	Percent	0.47
NFKB-P65	Percent	0.65
CD61	Percent	0.61
COX1	Percent	0.67
COX2	Percent	0.7
RELB	Density	0.64
NFKB-P50	Density	0.56
NFKB-P65	Density	0.62
CD61	Density	0.65
COX1	Density	0.72
COX2	Density	0.77



For Major Task 6 we are working to integrate TMA expression data with the OC3 dataset, we have completed this task for NHS/NHSII/IWHS and are working to complete this for PLOC. We have conducted preliminary analyses using the NHS/NHSII/IWHS samples and summarized the marker distributions among ovarian cancer cases on the TMA by frequent and infrequent aspirin use for the 3 marker panels developed and analyzed as part of major task 5. These distributions are summarized in table 2 below. Analyses and manuscript writing are ongoing for this final major task and are expected to be completed in the coming months.

Table 2. Summary of tumor tissue microarray (TMA) distributions; number and percent above median marker expression by frequent aspirin use vs. infrequent aspirin use among ovarian cancer cases in NHS, NHSII, and IWHS.

	Infrequent aspirin use (n=484)		Frequent aspirin use (n=58)	
Aspirin-related marker panel	N	%	N	%
COX1	228	47%	23	40%
COX2	235	49%	20	34%
p65	230	48%	24	41%
p50	236	49%	24	41%

Rel B	233	48%	24	41%
ITGB3	221	46%	34	59%
Tumor associated macrophage (TAM) panel				
CD68	221	46%	25	43%
CD86	205	42%	23	40%
CD163	217	45%	22	38%
PSTAT	223	46%	26	45%
CD206	208	43%	29	50%
M1 TAMs	230	48%	19	33%
M2 TAMs	219	45%	22	38%
T-cell/B-cell marker panel				
CD3	235	49%	22	38%
CD8	234	48%	24	41%
CD4	233	48%	27	47%
CD19	200	41%	21	36%
CD138	238	49%	26	45%

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

Professional development opportunities have been provided to trainees and staff at both Moffitt Cancer Center and NCI. Dr. Hurwitz worked one-on-one with mentor Dr. Trabert to complete the analysis and manuscript for Aim 2 and submitted an abstract for that project to an internal award. Dr. Hurwitz reported the results of Aim 2 analyses to the Cancer Prevention Fellowship Program as part of her Fellows Research Meeting in February 2021, her talk was titled: "Aspirin for ovarian cancer chemoprevention: Building the epidemiologic evidence". Dr. Hurwitz also presented the results of a subset of Aim 2 at the American Society of Preventive Oncology Annual Meeting in Tucson AZ this past Spring (March 2022. Hurwitz LM, Webb PM, Jordan SJ, Doherty JA, Harris HR, Goodman MT, Modugno F, Schildkraut JM, Anton-Culver H, Menon U, Wu AH, Pharaoh PDP, Trabert B. Does polygenic risk score modify the association between frequent aspirin use and ovarian cancer risk? An analysis within the Ovarian Cancer Association Consortium (OCAC)). Dr. Hurwitz has also had the opportunity to lead data analysis calls and participate in dissemination of study results to collaborators and study PIs and most recently participated in media interviews related to our JCO publication and participated in media training at the NCI.

How were the results disseminated to communities of interest?

Annual results were shared with the OC3 community and steering committee at the NCI Cohort Consortium Annual Meetings. This included a poster presentation at the meeting in November 2019 summarizing details of the data harmonization process through the Opal system. The Results of our JCO manuscript were shared with the Society of Gynecologic Oncology via news briefs and interviews with *Women's Cancer News Daily.* As a result our paper was leading the SGO news feed for at least two weeks; Excerpt below:

SGO Society of Gynecologic Oncology women's cancer A daily briefing for SGO members NEWS

Leading the News

Frequent Aspirin Use Tied To Lower Ovarian Cancer Risk Regardless Of Other Risk Factors

HealthDay (8/12) reported that "frequent aspirin use is associated with lower ovarian cancer risk regardless of the presence of most other ovarian cancer risk factors, according to a" 17-study meta-analysis. The "association was not seen among women with endometriosis;

however, consistent risk reductions were seen among all other subgroups defined by ovarian cancer risk factors, including women with two or more risk factors." The results were published in the Journal of Clinical Oncology.

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

Nothing to report (final report)

4. **IMPACT:**

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

Our recently published study found that frequent aspirin use is associated with reduced ovarian cancer risk, and that the protective association is not modified by other ovarian cancer risk factors. These results suggest that primary prevention of ovarian cancer is an added benefit of frequent aspirin use that could be incorporated into composite risk-benefit calculations. Because the observed protective association does not appear to be modified by other ovarian cancer risk factors, women with these ovarian cancer risk factors may also potentially benefit from frequent aspirin use for ovarian cancer prevention.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

- Nothing to report

What was the impact on society beyond science and technology?

- Nothing to report

5. CHANGES/PROBLEMS:

We requested and received a no cost extension (approved 8/30/2022) to continue to complete this work with an additional year of time. The extension was requested given that it took much longer than estimated to complete major tasks 3, 5, and 6. We were able to resolve these delays with the no cost extension and have nothing further to report.

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report. At all institutions (NCI, Moffitt, and Univ. of Utah) our work is considered not human subjects research since it involves de-identified data and previously collected tumor specimens. There is no anticipated change to this status through the duration of the project.

Significant changes in use or care of vertebrate animals

Not applicable, nothing to report.

Significant changes in use of biohazards and/or select agents

Not applicable, nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

- **Journal publications.**

Posters presented at International Meetings:

2023 Hurwitz LM, Webb PM, Jordan SJ, Doherty JA, Harris HR, Goodman MT, Modugno F, Schildkraut JM, Anton-Culver H, Menon U, Wu AH, Pharaoh PDP, Trabert B. Does polygenic risk score modify the association between frequent aspirin use and ovarian cancer risk? An analysis within the Ovarian Cancer Association Consortium (OCAC). American Society of Preventive Oncology

Annual Meeting, Tucson, AZ

2019 Hurwitz LM, Michels KA, Trabert B. Modification of the association between daily aspirin use and ovarian cancer risk by potentially modifiable risk factors. American Association of Cancer Research Molecular Epidemiology Meeting – Modernizing Population Sciences in the Digital Age, San Diego, CA

Manuscript published:

Hurwitz LM, Townsend MK, Jordan SJ, Patel AV, Teras LR, Lacey JV Jr, Doherty JA, Harris HR,
Goodman MT, Shvetsov YB, Modugno F, Moysich KB, Robien K, Prizment A, Schildkraut JM, Berchuck A, Fortner RT, Chan AT, Wentzensen N, Hartge P, Sandler DP, O'Brien KM, Anton-Culver H, Ziogas A, Menon U, Ramus SJ, Pearce CL, Wu AH, White E, Peters U, Webb PM, Tworoger SS, **Trabert B** (2022). Modification of the association between frequent aspirin use and ovarian cancer risk: A meta-analysis using individual-level data from two ovarian cancer consortia. (Epub ahead of print) *J Clin Oncol*, JCO2101900.

Hurwitz LM, Webb PM, Jordan SJ, Doherty JA, Harris HR, Goodman MT, Shvetsov YB, Modugno F, Moysich KB, Schildkraut JM, Berchuck A, Anton-Culver H, Ziogas A, Menon U, Ramus SJ, Wu AH, Pearce CL, Wentzensen N, Tworoger SS, Pharoah PDP, **Trabert B**. Association of Frequent Aspirin Use With Ovarian Cancer Risk According to Genetic Susceptibility. JAMA Netw Open. 2023 Feb 1;6(2):e230666. doi: 10.1001/jamanetworkopen.2023.0666.
PMID: 36826816

Manuscripts submitted: none – two additional manuscripts under development

Oral presentations

2023 "Chemoprevention of ovarian cancer: The promising role of aspirin"
Grand Rounds, Roswell Park Comprehensive Cancer Center, Buffalo, NY

2023 "Aspirin for ovarian cancer prevention in higher-risk subgroups"
Clinical and Translational Epidemiology Unit, Massachusetts General Hospital, Boston, MA (virtual presentation)

2023 "Aspirin for ovarian cancer prevention in higher-risk subgroups"
Fellow's Research Meeting, Cancer Prevention Fellowship Program, National Cancer Institute, Rockville, MD (virtual presentation)

2022 "Prevention of reproductive cancers: Epidemiologic investigation into potential risk factors"
Seminar, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD

2022 "Modification of the association between frequent aspirin use and ovarian cancer risk: Ongoing projects within OCAC
Ovarian Cancer Association Consortium (OCAC) Virtual Meeting (virtual presentation)

2020 "Aspirin for ovarian cancer chemoprevention: Building the epidemiologic evidence"
Fellow's Research Meeting, Cancer Prevention Fellowship Program, National Cancer Institute, Rockville, MD (virtual presentation)

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

Other publications, conference papers and presentations.

Related poster presentations:
2020 "Aspirin use and ovarian cancer risk using extended follow-up of the PLCO Cancer Screening Trial"
Society for Epidemiologic Research Annual Meeting (virtual meeting)

2020 "Associations between daily aspirin use and cancer risk across strata of major cancer risk factors in two large U.S. cohorts"
American Association for Cancer Research Annual Meeting (virtual meeting)

Media Interviews

2023 MedicalResearch.com Interview. "NCI Study Evaluates Aspirin Use with Ovarian Cancer." https://medicalresearch.com/cancer-_-oncology/nci-study-evaluates-aspirin-use-with-ovarian-cancer-risk/

2023 Medscape Medical News. "Ovarian Cancer Risk Lower With Daily Aspirin, Despite Genetics." https://www.medscape.com/viewarticle/989002

2022 MedPage Today. "Lauren Hurwitz, PhD, on Aspirin Use and Ovarian Cancer." http://www.medpagetoday.com/asco/gynecological-cancers/100835

2022 MedPage Today. "Another Possible Use for Aspirin: Reducing Ovarian Cancer Risk." https://www.medpagetoday.com/hematologyoncology/ovariancancer/99928

2022 Training Matters Magazine. “High hopes for aspirin.” https://www.tmmagazine.co.uk/in-depth/high-hopes-for-aspirin

- **Website(s) or other Internet site(s)**

The Ovarian Cancer Cohort Consortium website provides details about data resources, data access, publications, and funding that support the OC3, https://www.theoc3.org/

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

- **Other Products**

Data/databases: For this project, the data types include: 1) self-reported data from questionnaires or interviews; 2) medical history data obtained via national registry, medical record abstraction, or self-report; and 3) biomarker data from biospecimen assays (tissue). The analytic datasets

(which includes harmonized OC3 variables only) and statistical analysis programs used to generate the published results will be preserved at the OC3 DCC. Harmonization documentation for the variables in the dataset, data dictionary, and metadata related to the questionnaires administered in each study (i.e., year(s) of administration) are also stored at the DCC and are being entered into the Maelstrom software via the MICA program to enable easy queries by interested researchers.

Analytic code/macros: three SAS macros were developed to handle the longitudinal data harmonized in Aim 1 of this grant. Longitudinal harmonized data are stored in a vertical file format (one record per subject, multiple variables for repeat exposure assessment). The first macro was developed to convert this longitudinal data to an interval dataset (called Interval Dataset Macro). The purpose of this macro was to reformat the data into a horizontal file (in 2-year increments) with options for carrying forward or backward exposure variables as well as covariates. This macro creates a uniform risk interval dataset for each cohort in a 2-year format. Exposure is defined at the start of each interval and the outcome can occur at any time during the interval. Optional formatting for a lag between exposure and risk period, minimum age at inclusion, cancer risk and cancer survival outcomes, as well as carry forward/backward for exposures and covariates are coded in the the Interval Dataset Macro. The second macro created was the Pooled Logistic Regression Macro. This macro utilizes the Interval Dataset created with the first macro, and conducts the time updated pooled logistic regression using the CLOGLOG link to estimate the odds ratio that approximates the hazard ratio. The third macro created was the Time-dependent Cox Proportional Hazards macro, that utilizes the time-varying verticle file, to conduct analyses incorporating random effects, baseline stratification, and interaction. Histologic subtype macro add ons were also created for this macro that allowed histotype heterogeneity testing to accomplish the stated research aims. These macros are available from the DCC through the SAS software via the remote secure server where all data analyses take place and can be shared with other investigators on request.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Britton Trabert*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-1539-6090*
Nearest person month worked:	*No change*
Name:	*Shelley Tworoger*
Project Role:	*Site PI*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-6986-7046*
Nearest person month worked:	*No change*
Name:	*Mary Townsend*
Project Role:	*Applied Research Scientist*
Researcher Identifier (e.g. ORCID ID):	*0000-0003-2452-4477*
Nearest person month worked:	*No change*
Name:	*Lauren Hurwitz*
Project Role:	*Cancer Prevention Postdoctoral Fellow*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-8932-5028*
Nearest person month worked:	*No change*
Name:	*Brett Reid*
Project Role:	*Data analyst, developed SAS macros for pooled logistic regression analysis*
Researcher Identifier (e.g., ORCID ID):	
Nearest person month worked:	*0.6 person months*

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

Nothing to report (final report)

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *N/A*

QUAD CHARTS: *N/A*

9. APPENDICES: *N/A*