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**TITLE:** Making the CASE: Chemopreventive use of ASpirin for ovarian cancer - integrating Epidemiological data to evaluate population subgroups and tumor expression

**PRINCIPAL INVESTIGATOR:** Dr. Britton Trabert

**CONTRACTING ORGANIZATION:** The Geneva Foundation, Tacoma, WA

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<b>14. ABSTRACT</b> 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.					
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## 1. INTRODUCTION:

The research conducted as part of this project aims to address the unresolved questions related to the potential chemoprevention 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, chemoprevention, aspirin, mechanism, epidemiology, etiology, tumor tissue

## 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. *(75% Complete)*

**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. *(75% Complete)*

**Major Task 6:** Integrate TMA expression data with OC3 dataset. Analyze tumor expression data to evaluate heterogeneity in aspirin association by tumor markers. *(25% Complete)*

## What was accomplished under these goals?

Major Tasks 1, 2, and 4 were completed in previous reporting periods.

For this reporting period we continued to make substantial progress toward completing major tasks 3 (Aim 1) and 5 (Aim 3). We have begun work on Major Task 6 (Aim 3); however, completion of this task is contingent on completing Major Task 5.

### Major Activities:

For Major Task 4, the primary manuscript summarizing results was submitted to Journal of Clinical Oncology (IF 44.5) in the previous reporting period, and was published July 22, 2022 after two rounds of revisions. <https://pubmed.ncbi.nlm.nih.gov/35867953/>

For this task the specific objectives were to combine individual participant data from 17 studies to describe the association between frequent aspirin use and ovarian cancer risk, overall and across subgroups of women with other ovarian cancer risk factors. Previous studies have suggested that frequent use of aspirin (i.e., 6-7 days per week of use) may be associated with lower risk of ovarian cancer, but there are also known potential side effects to taking aspirin frequently. We wanted to determine whether the apparent protective association of aspirin for ovarian cancer was also observed in subgroups of women at higher ovarian cancer risk due to the presence of other risk factors, since the benefits of aspirin might be more likely to outweigh the harms within these subgroups.

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. We submitted this manuscript to a journal earlier this year, the primary findings are as follows: 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 the final deliverable from Aim 2/Major Task 4 in the Statement of Work.

The progress we have made towards completing Major Task 3 is as follows: 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 and at the time of the previous progress report (Oct 2021), data had been received from 12 cohorts of the 12 cohorts requested. As part of subtask 2, we are continuing to use the data capture and processing architecture as provided in the Quad chart (upper right-hand corner) to harmonize the data and have solicited support from the Biostatistics Core at Moffitt Cancer Center 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. As of this progress report we have completed harmonization of all necessary study data including 5 variables related to aspirin exposure updated every 2 years depending on the cohort, 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 (summarized in Figure 1), this equated to approximately 147 variables per cohort from 12 cohorts with a maximum of 450 variables for the Nurses’ Health Study. We continue to have biweekly conference calls with a group of ~12 individuals to review data and discuss progress and troubleshoot any issues we are having. The data harmonization process has been very successful and we are in the process of finalizing the analytic dataset. 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 3<sup>rd</sup> quarter of CY21. Harmonization took much longer than estimated, primarily due to the sheer quantity of work that was required and was completed by August 2022 (delayed by ~10 months). As a result data analysis for this aim was delayed substantially and will begin by the end of CY22. With the resulting manuscript being written and submitted by the end of our No Cost Extension (NCE, September 2023).

**Figure 1. Summary of participants, timepoints, and number of variables harmonized for the 12 cohorts included in the harmonized dataset for Aim 1.**

Study	# participants	# timepoints	# variables
California Teachers Study	109,851	6	99
Cancer Prevention Study II	94,538	10	149
Iowa Women’s Health Study	41,836	6	101
Generations Study	113,399	2	49
Multiethnic Cohort Study	90,072	3	96
NIH AARP Diet and Health Study	225,384	3	51
Nurses’ Health Study	120,653	20	450
Nurses’ Health Study II	116,412	14	395
PLCO Screening Trial	76,099	3	98
Sister Study	41,257	5	94
Southern Community Cohort Study	50,342	4	92
Swedish Mammography Cohort	38,923	3	91

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

Professional development opportunities have been provided to trainees at both Moffitt Cancer Center and NCI. Dr. Hurwitz worked one-on-one with her 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?**

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:



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?**

Over the next reporting period (NCE) we will complete Aim 1 (Major Task 3) and submit the resulting manuscript to a journal for publication. We will complete the molecular assays for Aim 3 (Major Tasks 5 and 6) and will complete data analysis and manuscript preparation for Major Task 6.

#### 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.

*Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an 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 is taking much longer than estimated to complete major tasks 3, 5, and 6. Details of the delays encountered and efforts to resolve these delays are described in the next section.

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

Major task 3 was delayed due the longer than expected time it took to clean and harmonize ~150 variables across 12 studies. Analysis will begin on this task by then end of CY2022 and the manuscript will be written and submitted by the end of the NCE. Major task 5 was delayed due to COVID-19-related laboratory queue delays, however substantial progress has been made on the molecular assays in the latter half of this year, and we anticipate integrating the molecular data with the OC3 dataset in early 2023 with the goal of completing major task 5 by March 2023. Major task 6 is dependent on the completion of Major task 5 and the analyses for Major task 6 and manuscript generation will be completed by the end of the NCE. We have the appropriate staff in place to make progress on these aims as necessary to complete the work under the expanded timeline.

### **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:**

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

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.

**Manuscripts submitted:**

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, Pharaoh PDP, Trabert B. Frequent aspirin use and ovarian cancer risk according to genetic susceptibility.

**Books or other non-periodical, one-time publications.**

Nothing to report.

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

**Virtual presentation:**

Hurwitz L, Trabert B. Effect modification of the aspirin-ovarian cancer association. Ovarian Cancer Association Consortium (OCAC) Epidemiology Meeting, Virtual

- **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**

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 at Moffitt Cancer Center. 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.

## **7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

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

<i>Name:</i>	<i>Britton Trabert</i>
<i>Project Role:</i>	<i>PI</i>
<i>Researcher Identifier (e.g. ORCID ID):</i>	<i>0000-0002-1539-6090</i>
<i>Nearest person month worked:</i>	<i>No change</i>
<i>Name:</i>	<i>Shelley Tworoger</i>
<i>Project Role:</i>	<i>Site PI</i>
<i>Researcher Identifier (e.g. ORCID ID):</i>	<i>0000-0002-6986-7046</i>
<i>Nearest person month worked:</i>	<i>No change</i>
<i>Name:</i>	<i>Mary Townsend</i>
<i>Project Role:</i>	<i>Applied Research Scientist</i>
<i>Researcher Identifier (e.g. ORCID ID):</i>	<i>0000-0003-2452-4477</i>
<i>Nearest person month worked:</i>	<i>No change</i>
<i>Name:</i>	<i>Lauren Hurwitz</i>
<i>Project Role:</i>	<i>Cancer Prevention Postdoctoral Fellow</i>
<i>Researcher Identifier (e.g. ORCID ID):</i>	<i>0000-0001-8932-5028</i>
<i>Nearest person month worked:</i>	<i>No change</i>

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

Active support for PI Dr. Britton Trabert has not changed.

Active support for co-PI Dr. Shelley Tworoger totals 6.87 calendar months and has changed as follows: Remained active support (no change to effort): W81XWH1910346 (Trabert, 0.72 calendar), OC190330 (Tworoger, 0.6 calendar), P30 CA076292 (Cleveland, 2.4 calendar), NIH/NCI - 5U01CA164973-09 (Administrative Supplement: LeMarchand, 0.24 calendar), W81XWH2010488 (Tworoger, 0.48), NCI 1R01CA258679-01 (Terry, 0.84 calendar), W81XWH2110914 (Merritt, 0.6 calendar), W81XWH2110326 (Kubzansky, 0.39 calendar), NIH/NHLBI K01HL143034 (Huang, 0 calendar – in kind).  
Additions to active support: RSG2204701HOPS (ACS, Harris, 0.6)

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

Nothing to report

**8. SPECIAL REPORTING REQUIREMENTS**

**COLLABORATIVE AWARDS:**

**QUAD CHARTS:**

**9. APPENDICES:**