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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
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Making the CASE: Chemopreventive use of Aspirin for Ovarian Cancer- Integrating Epidemiological Data to Evaluate Population Subgroups and Tumor Expression

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6. AUTHOR(S)
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5e. TASK NUMBER

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The Geneva Foundation
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U.S. Army Medical Research and Materiel Command
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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

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

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: *Provide a brief list of keywords (limit to 20 words).* Ovarian cancer, chemoprevention, aspirin, mechanism, epidemiology, etiology, tumor tissue

3. ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project? *List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.*

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.
Major Task 2: Submission of institutions IRB approval and related materials for DOD's HRPO approval.
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.
Major Task 4: Obtain OCAC dataset and conduct study-specific analyses. Conduct meta-analyses to evaluate aspirin-ovarian cancer associations by risk factors.
Major Task 5: Collect Tissue microarray (TMA) slides and create TMAs for studies with tumor tissue only. Complete molecular analysis of TMAs.
Major Task 6: Integrate TMA expression data with OC3 dataset. Analyze tumor expression data to evaluate heterogeneity in aspirin association by tumor markers.

What was accomplished under these goals?

For this reporting period we completed major tasks 1 and 2, and made substantial progress toward completed major tasks 3, 4, and 5.
For Major Task 1, Dr. Trabert 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 (11 cohorts in total) and baseline data as well as harmonization code was transferred between Brigham and Womens Hospital and Moffitt Cancer Center.
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.
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 to submit updated follow-up to the Data Coordinating Center at Moffitt Cancer Center. This included reviewing data available from all cohorts previously selected to participate and re-reviewing other cohorts in OC3 to make sure we were maximizing data collection related to updated use of aspirin and other analgesic medications. Data requests were formally submitted to the cohorts in Jan 2020 and at the time of this progress report, data had been received from 3 cohorts of the 11 cohorts. As part of subtask 2, we established a data capture and processing architecture as provided in the Quad chart (upper right-hand corner). Briefly, once individual cohorts have prepared their de-identified data (only OC3IDs are provided, no study identifier or exact dates are provided), the submit their data to the Moffitt Sharefile secure file transfer. Data coordinators at Moffitt then transfer the cohorts to Moffitt's secure local area network and the OC3 team at Moffitt reviews the data, generates and tabulates data reports for each variable and a group of 4 individuals (Britton Trabert, Mary Townsend, Lauren Hurwitz, and Yessica Martinez) work to together to develop harmonization code and mapping that are then implemented in OPAL and output is generated for the group to review. We have biweekly conference calls with a group of ~7 individuals to review data and discuss progress and troubleshoot any issues we are having. The data harmonization process so far is running smoothly and we have harmonized approximately 40 variables for 2 of the 3 submitted cohorts and are working towards completing the 3rd. We periodically follow-up with each cohort that has an outstanding data request and have timelines in terms of delivery for each. We anticipate that all data for aim 1 will be received by the 3rd quarter of CY21 and harmonization will be completed shortly thereafter, considering that we are harmonizing the data as it is received. We anticipate starting to conduct analyses in the 4th quarter of CY21 and have a draft manuscript by the end of the first quarter of CY22.
For major task 4 we (NCI, Drs. Trabert and Hurwitz) have completed study-specific analyses of frequent aspirin use and ovarian cancer risk by strata of defined effect modifiers in both OCAC and OC3 and have completed the first iteration of the meta-analysis. 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 have 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. We anticipate finalizing that manuscript and submitting it early in CY21.
For major task 5 we established an agreement with the University of Iowa (Dr. Charles Lynch) and have started to collect tumor tissue blocks for the TMA. Creation of the TMA is ongoing at Moffitt (site 2). The University of Iowa identified almost ~300 ovarian cancer tumor blocks from within the Iowa Women's Health Study that they can send to Moffitt's Tissue Core to create the TMA for Aim 3. We had budgeted for the collection of ~250 additional tumors, and given that we were able to obtain all of these from one site (Iowa Women's Health Study) we have revised the project to not solicit tumors from SS and WHI, since that would now be cost prohibitive. To complete subtask 1, Drs. Trabert and Lynch developed a study protocol for IRB review at the University of Iowa and received all necessary approvals to start work. Dr. Trabert reviewed data from all identified tumor blocks to verify their inclusion and worked out the transfer protocol and established a communication pipeline between Iowa and Moffitt's Tissue core that includes oversight by Drs. Trabert and Townsend. Progress on Subtask 2: The first shipment of tumor blocks was sent to Moffitt's Tissue Core and were being processed by the time this report was written. All tissue blocks will be selected and sent to Moffitt by May 2021 and the TMAs should be completed by summer. In the interim we made progress on subtask 3 by evaluating preliminary results from the molecular analysis of quality control TMA's made of NHS study samples and finalized the molecular markers that will be evaluated on each panel. The panel that will include COX and NFkB markers needs to be pilot tested and that protocol was developed and submitted for review to the Tissue core. We are currently planning to evaluate the test panel in March 2021 and be prepared to start running molecular assays by the 4th quarter of CY21.

What opportunities for training and professional development did the project provide?
How were the results disseminated to communities of interest?

Nothing to report

How were the results disseminated to communities of interest?

Nothing to report

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

Over the next reporting period we plan to finalize the updated data collection for the OC3 cohorts and complete data harmonization (Major task 3), to submit the manuscript for Major Task 4, and to complete the creation of the TMA and finalize the tumor tissue markers that will be measured on the TMA (Major task 5).

4. IMPACT: D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

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

Nothing to report

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:

Changes in approach and reasons for change

For Major Task 5, instead of utilizing the NCI laboratory for creation and quantification of the TMA we have decided to go with our back up laboratory (Moffitt Cancer Center). The NCI laboratory is in underwent a major geographic relocation (entire lab moved facilities March 2020-September 2020) and as such they would not have been able to make progress on our project in a timely fashion. Rather than suffer major delays and down time, we utilized our contingency laboratory and are making progress on major task 5 as a result of this change.

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:

None

Significant changes in use or care of vertebrate animals:

Not applicable

Significant changes in use of biohazards and/or select agents: Not applicable

6. PRODUCTS:

Publications, conference papers, and presentations:

Nothing to report

Journal publications:

Nothing to report

Books or other non-periodical, one-time publications:

Nothing to report

Other publications, conference papers, and presentations:

Website(s) or other Internet site(s):

Nothing to report

Technologies or techniques:

Nothing to report

Inventions, patent applications, and/or licenses:

Nothing to report

Other Products:

- *data or databases;* **follow-up data collection for 3 of 12 prospective cohorts was completed during this CY.**
- *physical collections;*

- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Name:	Britton Trabert
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0002-1539-6090
Nearest person month worked:	2.4 calendar months
Contribution to Project:	Project management
Funding Support:	NCI intramural research program

Name:	Shelley Tworoger
Project Role:	Site PI/Co PI
Researcher Identifier (e.g. ORCID ID):	0000-0002-6986-7046
Nearest person month worked:	0.72 calendar months
Contribution to Project:	Study site management, assistance with project management
Funding Support:	Dr. Tworoger's effort is being funded by this grant

Name:	Mary Townsend
Project Role:	Applied Research Scientist
Researcher Identifier (e.g. ORCID ID):	0000-0003-2452-4477
Nearest person month worked:	2.4 calendar months
Contribution to Project: Contribution to Project:	Coordinated receipt of tumor tissues with Moffitt lab, worked with bioinformatics team to identify data colletion/distribution flow, received and catalogued DUAs.
Funding Support:	Dr. Townsend's effort is being funded by this grant

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 9.06 calendar months and has changed as follows:
No longer active: 59067 (Shields, 0.72 calendar), R01 CA193965 (Terry, 1.08 calendar).

Additions to active support: 9JK02 (Tworoger, 2.4 calendar), W81XWH1910346 (Trabert, 0.72 calendar), Q81XWH1910307 (Kaaks, 0.24 calendar), U01CA200464 (Heine, Gillies, Schabath 0.12 calendar), OT123-407 (BMS 0.36 calendar), OC190330 (Tworoger, 0.6 calendar)

Changes to active support level of effort: W81XWH-17-1-0153 (Kubzansky, decreased from 0.6 to 0.3 calendar), P01 CA087969 (Eliassen, decreased from 2.4 to 1.92 calendar), P30 CA076292 (Cleveland, increased from 0.6 to 2.4 calendar).

What other organizations were involved as partners?
Organization Name: University of Iowa
Location of Organization: (if foreign location list country) Iowa City, Iowa
Partner's contribution to the project (identify one or more) Other. Contribution of tumor tissue from Iowa Women's Health Study to create Tumor Tissue Microarray

8. SPECIAL REPORTING REQUIREMENTS:

QUAD CHARTS:

Attached

9. APPENDICES:

None