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14. ABSTRACT Mouse models suggest that chronic stress promotes ovarian tumorigenesis, but the relationship between stress and ovarian cancer has never been evaluated in humans. In our analysis of self-reported stress and risk of ovarian cancer, we noted that phobic anxiety and social isolation were suggestively associated with increased risk of ovarian cancer (hazard ratios of 1.14 and 1.24, respectively). Depression was significantly associated with increased ovarian cancer risk (hazard ratio: 1.26), as was being widowed (hazard ratio: 1.38). Taken together, these data are consistent with animal data demonstrating the adverse impact of chronic stress on ovarian cancer risk.					
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INTRODUCTION

The objective of this Ovarian Cancer Academy award is to evaluate the role of psychosocial stress in ovarian cancer risk through multiple measures of stress. This study is being conducted in the Nurses' Health Studies (NHS and NHSII), two large prospective cohorts with about 1200 ovarian cancer cases between the two studies. In these two study populations, we have repeated questionnaires in which we have queried psychosocial stress, as well as pre-diagnostic blood specimens on 350 cases, and tissue blocks on 250 cases. The first specific aim of this application is to examine whether self-reported stress exposures (depressive symptoms, phobic anxiety, social support, job strain, care-giving stress) are associated with ovarian cancer risk. Also, in this aim, we will evaluate whether any associations are stronger for tumors which express the β_2 adrenergic receptors, as studies in mouse models have suggested that β_2 adrenergic receptor activation drives ovarian tumorigenesis. In the second aim, we will use metabolomic profiling of women with and without post-traumatic stress disorder (PTSD) to derive a signature of chronic stress and then apply that metabolomic stress signature to study women with and without ovarian cancer. As secondary aims, we will evaluate whether stress is more strongly associated with more aggressive tumors (defined by how quickly fatal the tumors are, and by likely tubal vs. ovarian origin) and will leverage the metabolomics data to query other potential pathways of interest, including lipid dysregulation.

KEYWORDS

Ovarian cancer, psychosocial stress, anxiety, depression, social support, metabolomics

ACCOMPLISHMENTS

The major goals of this project were 1) to evaluate whether self-reported psychosocial stress is associated with ovarian cancer, particularly for tumors that express the β_2 -adrenergic receptor (SOW task 1); 2) to develop a metabolomic signature of chronic stress (SOW task 2); 3) to evaluate whether the PTSD metabolomic signature described in Task 2 is associated with risk of ovarian cancer (SOW task 3); to evaluate whether metabolomic biomarkers of lipid dysregulation are associated with ovarian cancer risk (SOW task 4); and 5) career development (SOW task 5).

For task 1, tasks 1a-1e in the prior grant period. In the current grant period, Dr. Poole, her mentors, and several students and post-doctoral fellows have completed analyses of whether stress-related exposures as well as known ovarian cancer risk factors are differentially associated with tumors that express the β_2 -adrenergic receptor (task 1f). Dr. Poole has been working with a post-doctoral fellow, Dr. Tianyi Huang, on this analysis and manuscript preparation on this manuscript is underway (Task 1g; see Table 1). As hypothesized, many stress exposures (e.g., depression, phobic anxiety) seem to only be associated with increased risk of tumors that express the β_2 -adrenergic receptor, although the numbers are small and not all stress exposures seem to increase risk of β_2 -adrenergic receptor positive tumors. Additional analyses are ongoing. In addition, other manuscripts relating to task 1b are in various stages of preparation. A manuscript evaluating the association of depression with ovarian cancer risk has been accepted for publication in Gynecologic Oncology; the manuscript on phobic anxiety has been submitted to Psychosomatic Medicine; manuscript preparation for the analyses of social support is nearly complete; analyses of the associations of job strain and caregiver burden are underway (See preliminary results in Table 2). While longer hours of caregiving do not seem to be associated with ovarian cancer risk,

Table 1. Differences in stress exposure associations (RR; 95% CI) by tumor β_2 -adrenergic receptor expression			
	Tumor β_2 -adrenergic receptor expression		
	Positive	Negative	P-het
Depression	2.36 (0.87, 6.42)	1.14 (0.65, 2.01)	0.23
Phobic anxiety	2.60 (1.15, 5.87)	1.21 (0.84, 1.73)	0.09
Caregiver stress	0.97 (0.30, 3.07)	0.99 (0.52, 1.87)	0.03
High job demand	0.81 (0.23, 2.84)	0.85 (0.51, 1.40)	0.95
High job control	2.22 (0.62, 7.93)	1.11 (0.67, 1.83)	0.32
Relative risk (RR) and 95% confidence interval (CI) adjusting for age, known ovarian cancer risk factors, and cohort (NHS vs. NHSII)			

Table 2. Associations of caregiver burden and job strain on ovarian cancer risk.		
Stress measure	Comparison	RR (95% CI)
Caregiver burden	≥ 15 hours/week of caregiving vs. none	0.86 (0.67, 1.11)
Job strain	Job insecurity	1.28 (1.01, 1.61)

women with less secure jobs were at suggestively higher risk of ovarian cancer. For these analyses, Dr. Poole is mentoring a post-doctoral fellow (Claudia Trudel-Fitzgerald) and a doctoral student (Mollie Barnard), respectively. As noted in the prior progress report, completion of task 1 was somewhat delayed due to complications in the β 2-adrenergic receptor. However, due to the delays in task 1, we started task 3 earlier than expected.

In task 2, Dr. Poole completed task 2a in the prior grant period, as noted on the prior progress report. Metabolomics assays for task 2b are nearly complete in Dr. Clish's lab; Dr. Poole anticipates receiving results by the end of November, 2015. For task 3, ovarian cancer cases and controls have been selected, aliquoted and sent to Dr. Clish's lab (Task 3a) and he has begun metabolomics assays (Task 3b). Of note for tasks 2, 3, and 4, Dr. Clish recently added another platform that measures free fatty acids. Using departmental support for this additional platform, Dr. Poole has added this new platform to the assays to be completed. While this will be considerably more data, Dr. Poole and her mentors believe that it will be a stronger resource both to develop the signature of chronic stress as well as for completing task 4.

Task 4 has not yet begun.

For task 5 (career development), With regards to task 5b, Dr. Poole meets weekly with Dr. Tworoger (her Academy mentor) and monthly with Dr. Kubzansky (a co-mentor on this project). She will begin meeting with Dr. Quackenbush once the metabolomics results for task 2 have been received (expected by end of November 2015). For task 5c, Dr. Poole leads bi-weekly meetings of our internal Ovarian Cancer Analysis Group (OCAG) with her mentor, Dr. Tworoger, as well as with Dr. Katie Terry, a fellow Ovarian Cancer Academy Early Career Investigator. Dr. Poole has also attended the regular bi-monthly meetings of the stress and cancer working group. For task 5d, Dr. Poole attended the Dana Farber/Harvard Cancer Center (DF/HCC) annual breast and gynecologic cancer retreat in March, 2015, the annual meeting of the Ovarian Cancer Association Consortium in April, 2015, the Society for Epidemiologic Research (SER) annual meeting in June, 2015, and the DoD Ovarian Cancer Academy meeting in August 2015.

In addition to the career development tasks outlined in the statement of work, Dr. Poole was promoted to Assistant Professor in January 2015. She was named as Metabolomics Coordinator for the Harvard Cohorts (including the Nurses' Health Studies) and developed and directs the Channing Division of Network Medicine (CDNM)'s Junior Faculty group, which meets bi-weekly to discuss career challenges, present grant aims and receive feedback, and invites outside speakers to provide career advice. Dr. Poole is also a peer mentor to three post-doctoral fellows working in the CDNM. As the Metabolomics Coordinator, Dr. Poole has been working with Dr. Peter Kraft, a biostatistician and full professor at Harvard TH Chan School of Public Health (HSPH), to develop a quality control algorithm for future investigators using metabolomics data. This training will not only benefit the CDNM, but is serving as training to prepare her to accomplish Tasks 2-4 on her SOW.

Results from the ongoing research in the role of stress in ovarian cancer have been communicated to the scientific community in various ways. Dr. Huang presented a poster on depression and ovarian cancer at the SER annual meeting; Dr. Trudel-Fitzgerald (a post-doctoral fellow at HSPH) has presented on job strain and ovarian cancer at various scientific meetings; Ms. Barnard (a doctoral student and HSPH) will present a poster on caregiver burden at the upcoming AACR-Rivkin special conference on ovarian cancer (October 2015). Dr. Poole gave an oral presentation at the 2015 DF/HCC breast and gynecologic cancer retreat in March 2015.

In the next reporting period, Dr. Poole will work with her mentors to develop the metabolomic signature of stress (SOW task 2) and to apply it in the nested case-control study of ovarian cancer (SOW task 3). She will submit all manuscripts planned for SOW tasks 1 and 2, working with students and post-doctoral fellows to complete these projects.

IMPACT

The major impact of this project to date is the evidence that self-reported psychosocial stress seems to be related to developing ovarian cancer, the first demonstration of this in humans. While this adds to the evidence that stress management is important for long-term health, validation in other studies is required. The upcoming work on metabolomics will help elucidate the biologic underpinnings linking stress to ovarian cancer risk.

CHANGES/PROBLEMS

Nothing to Report

PRODUCTS

Publications, conference papers, and presentations

Journal publications.

- Tianyi Huang, Elizabeth Poole; Olivia Okereke; Laura Kubzansky; Heather Eliassen; Anil Sood; Molin Wang; Shelley Tworoger. Depression and Risk of Epithelial Ovarian Cancer: Results from Two Large Prospective Cohort Studies. Accepted for publication in Gynecologic Oncology.

Other publications, conference papers, and presentations.

- Elizabeth Poole. Stress as a potentially modifiable risk factor for ovarian cancer. Oral abstract presentation at the Dana Farber / Harvard Cancer Center Breast-Gynecologic Symposium, Boston, MA, March, 2015.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	Elizabeth Poole
Project role:	PI
Research Identifier	ORCID: 0000-0002-4680-4587
Nearest person month worked	7
Contribution to Project	PI – coordinated all analyses and assays
Funding Support	

Name:	Shelley Tworoger
Project role:	Mentor/co-investigator
Research Identifier	ORCID: 0000-0002-6986-7046
Nearest person month worked	1
Contribution to Project	Project mentor – provided guidance and feedback on all tasks; met weekly with Dr. Poole
Funding Support	

Name:	Tianyi Huang
Project role:	Post-doctoral fellow
Research Identifier	ORCID: 0000-0001-8420-9167
Nearest person month worked	1
Contribution to Project	Performed analyses of β 2-adrenergic receptor
Funding Support	US National Cancer Institute

Name:	Claudia Trudel-Fitzgerald
Project role:	Post-doctoral fellow
Research Identifier	ORCID: 0000-0001-9989-4259
Nearest person month worked	1
Contribution to Project	Performed analyses of job strain and risk of ovarian cancer
Funding Support	Canadian National Cancer Institute

Name:	Mollie Barnard
Project role:	Doctoral student
Research Identifier	N/A
Nearest person month worked	1
Contribution to Project	Performed analyses of caregiver burden and risk of ovarian cancer
Funding Support	US National Cancer Institute

No changes in active support to be reported.

No other organizations were involved as partners.