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TITLE: Use of Exogenous Progestins and Risk of in Situ and Invasive Breast Cancer

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INTRODUCTION:

Given the large number of women exposed to progestins through either contraceptives or menopausal hormone therapies, clarifying the etiologic role of progestin in relation to breast cancer is of public health importance. This study's two projects will further our understanding of the potential risk of breast cancer associated with progestin use. Project 1 involves the enrollment of 225 *in situ* breast cancer cases 20-44 years of age. Project 2 is a case-control study of women 55-74 years of age that will enroll 325 controls and 975 breast cancer cases (325 each of three different histologic types of breast cancer). Both projects involve a detailed in-person interview and review and testing of tumor samples for various tumor markers. Project 1 will evaluate the hypothesis that DMPA use, particularly current use and use prior to a first full-term pregnancy, is associated with an increased risk of *in situ* breast cancer. Given that lobular and ductal-lobular carcinomas are more hormonally responsive than ductal tumors, Project 2 will test the hypothesis that hormonally related risk factors for breast cancer will be more strongly associated with tumors with a lobular component than they will be with pure ductal carcinomas.

BODY:

Task 1. Develop Interview Instrument, Other Study Materials, and Tracking System, Months 1-3:

- a. I will lead the development of the structured interview instruments for both projects. In the development of the questionnaire for Project 1 I will utilize a variety of available historical forms that have been extensively field tested and perfected. The questionnaire for Project 2 will be largely based on the questionnaire we used in our completed study of lobular cancer that this project will build on. Both questionnaires will ascertain information on exposures that occurred prior to each subject's "Reference Date" (the date of diagnosis for cases and a comparable assigned date for controls) including: use of hormones, reproductive history, family history of cancer, medical history, anthropometric characteristics, and demographic information.

Status: Drafts of questionnaires are completed, but are pending human subjects approval from DOD.

- b. Several other materials will be prepared for these projects including: approach letters to potentially eligible cases and controls; an interview consent form; a HIPAA compliant authorization to access personal health information; tumor tissue (cases only), medical records, and pharmacy records release forms; and a blood specimen donation consent form.

Status: Drafts of all of these documents are completed, but all are pending human subjects approval from DOD.

- c. Study personnel, including the study manager and interviewers, will be trained on the specific procedures to be used in these projects.

Status: The study manager has been trained and has worked closely with the PI to develop all study materials and assist in the preparation of submissions for DOD human subjects review. Interviewers have not yet been trained given that DOD human subjects approval of study documents is still pending, and a projected date for when final DOD human subjects approval will be obtained, and consequently when participant recruitment can begin, has not been provided by DOD.

- d. Institutional Review Board approval, both locally and from the U.S. Army, will be sought for both studies' protocol and documents.

Status: Local IRB approval has been obtained. We have experienced an extremely lengthy and unanticipated delay in receiving IRB approval from DOD. We have responded in a very timely way to all requests from the DOD IRB (all within two weeks, and most within one week), and have sought updates on the status of our application regularly. Once we learned that the DOD IRB process is such a lengthy one, we elected to first only pursue approval for Project 2 given that this project is much more involved and is where the majority of funding for this grant is allocated. This decision was made so that Project 2 could get approved as quickly as possible since we would not be hindered by needing to respond to requests related to both projects at the same time. It does now appear that the protocol for Project 2 will be considered a minimal risk activity and that we are close to receiving final approval. However, no approximate date for final approval has yet been specified by the DOD IRB. Once approval for Project 2 is obtained, we will begin the process to obtain approval for Project 1. Given the similarities between the two projects, we do hope that this will be a much more efficient process since we can use all that we have learned through obtaining approval for Project 2.

- e. We will modify the computerized tracking systems we currently use in our other studies to fit the specific needs of these projects. These systems will allow for up-to-date tracking of study progress and retrieval of information on any aspect of the study as needed. For Project 2 these systems are largely already in place given that it will build on a recently completed study.

Status: Complete. The tracking systems are in place and are ready to be utilized once DOD IRB approval is obtained.

Task 2. Finalize Subject Eligibility Criteria, Months 1-3

- a. The population base for both of these studies will be the three-county Seattle/Tacoma metropolitan area in Washington State. All subjects must have been residents of one of these three counties at their reference date.

Status: Complete, pending final DOD IRB approval.

- b. For Project 1, women must be premenopausal and 20-44 years of age at their reference date. For Project 2, women must be postmenopausal and 55-74 years of age at their reference date.

Status: Complete, pending final DOD IRB approval.

- c. Women with a prior history of invasive or *in situ* breast cancer will be excluded.

Status: Complete, pending final DOD IRB approval.

Task 3. Case Identification, Months 3-50

- a. For Project 1, cases are premenopausal women 20-44 years of age diagnosed with *in situ* breast cancer from January 1, 2005 to June 30, 2009. For Project 2, cases are postmenopausal women 55-74 years of age diagnosed with invasive lobular, ductal-lobular, or ductal breast carcinoma from April 1, 2004 to December 31, 2008.

Status: Cannot begin until DOD IRB approval is obtained.

- b. All cases will be ascertained through the Cancer Surveillance System (CSS), a population-based cancer registry covering 13 counties in western Washington State. It is a participant in the NCI SEER Program.

Status: Cannot begin until DOD IRB approval is obtained.

- c. For Project 1, based on recent data, a minimum of 63 eligible *in situ* cases per year are expected during each of the proposed 4.5 years of case ascertainment for an estimated total of 280 eligible cases. For Project 2, based on recent data, a minimum of 90 eligible lobular cases and 90 eligible ductal-lobular cases per year are expected during each of the proposed 4.5 years of case ascertainment for an estimated total of 405 eligible cases of each type. Since ductal carcinoma is more common than both lobular and ductal-lobular carcinoma, an age-matched random sample of ductal cases will be selected for enrollment in this study.

Status: Cannot begin until DOD IRB approval is obtained.

- d. From our prior experience with breast cancer studies, we anticipate that at least 80-85% will agree to be interviewed. Hence, a minimum of 225 of the eligible 280 cases eligible for Project 1, and 325 of the 405 eligible cases in each of the histology groups for Project 2 would agree to participate.

Status: Cannot begin until DOD IRB approval is obtained.

- e. Twice each month CSS files identifying newly diagnosed potentially eligible cases of breast cancer will be downloaded to our personal computers and reviewed by the study manager.

Status: Cannot begin until DOD IRB approval is obtained.

- f. The physicians of all eligible cases will receive a letter requesting permission to interview their patient.

Status: Cannot begin until DOD IRB approval is obtained.

- g. The cooperation of area physicians is crucial to the success of studies such as the one proposed. The physician response rates achieved by this research unit have consistently been high (greater than 99%).

Status: Cannot begin until DOD IRB approval is obtained.

Task 4. Control Identification, Months 3-50

- a. General population controls with no prior history of breast cancer who are 20-44 years of age (Project 1) and 55-74 years of age (Project 2) will be identified through random digit dialing (RDD). However, all of the work related to controls for Project 1, including identification, approach, and data collection will be funded by the parent R01 (NCI) grant, and not by the Era of Hope Scholar Award.

Status: Cannot begin until DOD IRB approval is obtained.

- b. We will use a system that automates the administration, execution, and tracking of the RDD process.

Status: Cannot begin until DOD IRB approval is obtained.

- c. This control identification procedure has been used successfully for prior and on-going studies in our research group. For example, in a recent breast cancer case-control study our interview response rate (number interviewed/number eligible) among women 35-44 was 88% for controls and 90% for cases.

Status: Cannot begin until DOD IRB approval is obtained.

Task 5. Approach to Study Subjects, Months 4-53

- a. Cases and controls will be approached about each of these studies through a letter describing the study's purpose and procedures, and advising them that an interviewer will call soon.

Status: Cannot begin until DOD IRB approval is obtained.

- b. Within one week of the initial mailing, a trained interviewer will call the subject to answer any questions, verify eligibility, and schedule the interview. Then a letter confirming the appointment will be sent to subjects.

Status: Cannot begin until DOD IRB approval is obtained.

- c. We will attempt to complete all interviews in the woman's home. If this is not possible, the interviewer will arrange to have the interview take place in a location agreeable to the subject.

Status: Cannot begin until DOD IRB approval is obtained.

- d. In our past studies we have been able to interview 60% of subjects willing to participate within three months of initial contact, and 93% within six months.

Status: Cannot begin until DOD IRB approval is obtained.

Task 6. Conduct of Interviews, Months 4-55

- a. For Project 1, 225 *in situ* cases will be interviewed. For Project 2, 325 lobular cases, 325 ductal-lobular cases, 325 ductal cases, and 325 controls will be interviewed. These sample sizes were selected to provide both studies with adequate statistical power to evaluate each of their specific aims.

Status: Cannot begin until DOD IRB approval is obtained.

- b. At the time of the interview a consent form will first be reviewed and then signed by both the study subject and the interviewer.

Status: Cannot begin until DOD IRB approval is obtained.

- c. The interview will then be conducted.

Status: Cannot begin until DOD IRB approval is obtained.

- d. HIPAA compliant authorizations to collect personal health information will be sought including:
- i. A tumor tissue release so that specimens can be ascertained and tested for a variety of molecular markers in the Porter lab;
 - ii. A medical records release so we can review medical records from locations where subjects have been prescribed contraceptives;
 - iii. A pharmacy records release that gives us permission to contact their usual pharmacies to verify and supplement reported medication use.

Status: Cannot begin until DOD IRB approval is obtained.

- e. All subjects will be asked to donate three tubes of blood. Subjects who refuse will be asked if they are willing to provide us with an oral tissue sample using commercial mouthwash. All blood and oral specimens will be transported to the Fred Hutchinson Cancer Research Center (FHCRC) Specimen Processing Laboratory within 24-hours of collection for processing and storage.

Status: Cannot begin until DOD IRB approval is obtained.

- f. Interviewers will edit each interview within 3 days of their completion. Next, one of our staff members who has extensive editing experience will edit and code the completed questionnaires. Lastly, the study manager will conduct a final edit of all questionnaires and determine which subjects need to be recontacted so that missing or incomplete data can be collected.

Status: Cannot begin until DOD IRB approval is obtained.

- g. Telephone validation interviews on a randomly selected 10% of interviewed women will be conducted within one month of the date that original interviews were completed to determine if the answers to selected questions are comparable to those given during the interview.

Status: Cannot begin until DOD IRB approval is obtained.

Task 7. Tissue Collection, Pathology Review and Laboratory Testing of Tumor Specimens, Months 4-55

- a. We will request that histology slides, tissue blocks, and pathology reports from the breast cancer cases we enroll be sent to the Porter lab at FHCRC from regional pathology laboratories.

Status: Cannot begin until DOD IRB approval is obtained.

- b. Based on our previous studies, we anticipate that at least 95% of subjects will consent to release their tissue. We have considerable experience in the acquisition of tumor blocks, and we anticipate that we will be able to collect tumor tissue for at least 75% of all cases.

Status: Cannot begin until DOD IRB approval is obtained.

- c. Whenever possible a single representative block is selected for all laboratory studies. In summary, we will:
- i. Conduct pathology reviews on all tumors;
 - ii. Assay expression of ER α , ER β , PR, and e-cadherin using immunohistochemistry (IHC) on conventional slides;

- iii. Harvest tissue cores from selected tissue blocks for construction of tissue microarrays (TMA). Biomarkers most relevant to the relationship between DMPA and breast cancer risk at the time TMA construction is complete will be evaluated on these slides. These TMA slides will also provide a valuable resource for future studies since they allow for high throughput testing of additional markers and offer maximum flexibility for studying new markers as they emerge and develop.

Status: Cannot begin until DOD IRB approval is obtained.

Task 8. Data Analysis and Manuscript Preparation, Months 51-60

- a. For Project 1, unconditional logistic regression will be used to compute odds ratios (and 95% confidence intervals) that characterize the relationship between DMPA use and *in situ* breast cancer risk. For Project 2, polytomous logistic regression will be used to compute odds ratios (and 95% confidence intervals) that characterize the relationship between hormone therapy use and risk of the three histologic types of breast cancer of interest in the same statistical model.

Status: Not scheduled to begin until month 51, though start date will likely be delayed because DOD IRB approval has not yet been obtained.

- b. Systematic assessment of the effect of potential confounders (including body mass index, body weight, parity, reproductive factors, and oral contraceptive use) on the estimates obtained will be performed.

Status: Not scheduled to begin until month 51, though start date will likely be delayed because DOD IRB approval has not yet been obtained.

- c. Two approaches will be used to assess effect modification. First, we will simply stratify our logistic regression analyses by the effect modifier of interest so that risks specific to each stratum of the potential effect modifier can be calculated. Second, we will include an interaction term between the exposure of interest and the effect modifier so that the statistical significance of the observed interaction (effect modification) can be determined.

Status: Not scheduled to begin until month 51, though start date will likely be delayed because DOD IRB approval has not yet been obtained.

- d. I will lead the preparation of the multiple anticipated manuscripts that will describe the results of these two projects.

Status: Not scheduled to begin until month 51, though start date will likely be delayed because DOD IRB approval has not yet been obtained.

KEY RESEARCH ACCOMPLISHMENTS:

None, participant enrollment has not begun because human subjects approval from DOD has not yet been obtained.

REPORTABLE OUTCOMES:

None.

CONCLUSION:

None.

REFERENCES:

None.

APPENDICES:

None; human subjects approval of study documents, including study questionnaires, has not yet been obtained from DOD.

SUPPORTING DATA:

None.