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6. AUTHOR(S)
Noah D. Kauff, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Memorial Sloan-Kettering Cancer Center
New York, New York 10021

E-Mail: kauffn@mskcc.org

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13. ABSTRACT (Maximum 200 Words)
The principal investigator was funded via a Physician-Scientist Training Award to participate in a comprehensive training plan to foster the transition to independent clinical breast cancer researcher, This plan included 1) conduct of a prospective study examining modifiers of the efficacy of risk-reducing salpingo-oophorectomy for the prevention of breast and ovarian cancer in carriers of BRCA mutations; and 2) participation in coursework in research methodology, biostatistics, molecular biology, and ethics.

Progress from 5/1/2003 - 4/30/2004 includes: 1) Accrual at a greater than expected rate to the planned research study; 2) Participation in a clinical cancer research methods course with production of a new research proposal for the Gynecologic Oncology Group; 3) Co-authored manuscript examining prostate cancer risk of men with BRCA mutations; and 4) Conducted a pilot study suggesting that women from BRCA-negative hereditary breast cancer families are not at increased risk for ovarian cancer.

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Award Number: DAMD17-03-1-0375

TITLE: Modifiers of the Efficacy of Risk-Reducing Salpingo-Oophorectomy for the Prevention of Breast and Ovarian Cancer in Carriers of BRCA1 and BRCA2 Mutations

PRINCIPAL INVESTIGATOR: Noah D. Kauff, M.D.

CONTRACTING ORGANIZATION: Memorial Sloan-Kettering Cancer Center
New York, New York 10021

REPORT DATE: May 2004

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Introduction

The principle investigator was funded beginning on May 1, 2003 by the Department of Defense Breast Cancer Research Program via a Physician-Scientist Training Award (PTSA) to participate in a comprehensive training plan designed to assist the principal investigator in making the transition from junior faculty member to independent clinical breast cancer researcher. There were two chief components of the plan. The first component was the conduct of a prospective research study entitled, "Modifiers of the Efficacy of Risk-Reducing Salpingo-Oophorectomy for the Prevention of Breast and Ovarian Cancer in Carriers of *BRCA1* and *BRCA2* Mutations," under the direction and mentorship of Kenneth Offit, M.D., M.P.H. The second component of the comprehensive training plan was for the principal investigator to participate in formal coursework in research methodology, biostatistics, methods of molecular biology, and ethics of clinical research. This progress report will summarize progress and accomplishments made as well as difficulties and challenges encountered during the first year of this award that ran from May 1, 2003 through April 30, 2004.

1) Progress on Research Project Component of Award

The principal investigator in concert with a multidisciplinary team at Memorial Sloan-Kettering Cancer Center (MSKCC) reported the first prospective evaluation of the role of salpingo-oophorectomy in reducing the risk of both breast cancers and *BRCA*-related gynecologic (ovarian, fallopian tube, and primary peritoneal) cancers in carriers of *BRCA1* and *BRCA2* mutations. In that study, we demonstrated that risk-reducing salpingo-oophorectomy (RRSO) is associated with a decreased combined incidence of breast and *BRCA*-related gynecologic cancer. While these results were encouraging, there were important limitations in that preliminary data that need to be addressed before this surgical procedure becomes integrated into the routine management of all carriers of *BRCA* mutations.

First, it is not at all clear that all women with *BRCA* mutations share the same cancer risks. The current study will address the biologically plausible possibility that women with *BRCA2* mutations may not derive the same preventive benefit following oophorectomy as women with *BRCA1* mutations. Data pertaining to this issue may be important for the development of tailored risk-reduction strategies for women with *BRCA* mutations. Second, it is also not clear that surgery will necessary improve *mortality* due to breast or ovarian cancer. Prospective information addressing the actual effect of RRSO on subsequent cancer-specific mortality is critically needed in order that women with *BRCA* mutations can make informed decisions regarding the risks and benefits of preventive surgery. Third, determining the specific risk reduction conferred by RRSO for the prevention of specific types of cancer is an important unanswered question for many women with *BRCA* mutations considering the procedure. The only data currently available on this issue is retrospective with a potential for substantial bias.

In order to address some of these issues, with the assistance of the PSTA, we are conducting a prospective study to: 1) determine the degree of protection conferred by RRSO for the prevention of subsequent breast and *BRCA*-related gynecologic cancer in a) carriers of *BRCA1* mutations and b) carriers of *BRCA2* mutations; 2) determine the effect of RRSO on cancer-specific mortality in carriers of *BRCA1* and *BRCA2* mutations; and 3) determine the effect in carriers of *BRCA* mutations of RRSO on the incidence of a) subsequent breast cancer and b) subsequent *BRCA*-related gynecologic cancer.

Briefly we are ascertaining women with a *BRCA1* or a *BRCA2* mutation, greater than 35 years of age, who have not previously undergone bilateral oophorectomy, who have undergone genetic counseling at MSKCC from June 1, 2003 through May 30, 2007 and have consented to prospective follow-up. (Accrual for this study began June 1, 1995.) Uptake of RRSO or use of ovarian surveillance is being determined for all participants by annual questionnaire, telephone contact, and medical record review. Follow-up is planned through May 30, 2008. The time to cancer or time to cancer-specific mortality will be analyzed

for each of the specific aims using Kaplan-Meier analysis and a Cox proportion hazards model. Total estimated accrual through April 30, 2004 was 310 participants with ovarian tissue at risk and 238 participants with both breast and ovarian tissue at risk. To date accrual is exceeding expectations with 327 (105% of expected) participants with ovarian tissue at risk and 278 (117% of expected) participants with both breast and ovarian tissue at risk accrued through April 30, 2004.

Specific components of the statement of work for June 2003 – May 2004 relevant to the research component of the training award:

a) June 2003 - July 2003 - Training of Genetic Counselor (dedicated to the project) to obtain and enter follow-up information

   This was completed as scheduled. Yelena Kemel, M.S is a genetic counselor trained and funded for 50% of her effort via this award to obtain and enter follow-up information.

b) June 2003 - Sept 2003 - Review and revision of follow-up questionnaires

   This was completed as scheduled. The follow-up instrument used for this study was completely revised to capture: 1) detailed information regarding current cancer screening and prevention practices including risk-reducing surgical and chemo-preventive approaches; 2) information regarding any new cancers diagnosed in the participant since the participant's initial evaluation by Clinical Genetics; 3) information regarding any new cancer diagnosed in 1st or 2nd degree relatives since the participant's initial evaluation by Clinical Genetics; and 4) information designed to address reasons for adherence or non-adherence to screening recommendations. This questionnaire was piloted in the summer and fall of 2003 on a group of women from *BRCA*-negative hereditary breast cancer families who had consented to prospective follow-up. After changes were made as a result of this pilot use, additional modifications were made resulting in the final document that is included in appendix A.

c) Oct 2003 - Dec 2003 - Submission of revised questionnaires to MSKCC Institutional Review Board

   This was completed as scheduled with IRB approval of the revised documents obtained November 11, 2003.

d) April 2004 - May 2004 - 1st Interim Data Analysis

   This data analysis is currently in progress. In order to optimize our ability to follow-up both responders and non-responders in our cohort, the cohort is broken down into four groups based upon the quarter in which they received results. Annual follow is obtained for one of each of these four sub-cohorts each quarter. We have now collected data using our revised follow-up instrument for three of these four sub-cohorts. When data is received from the last sub-cohort this summer, we will conduct a preliminary analysis for each of our three specific aims.

2) Progress of Didactic Training Component of Award

Part of the time freed by the PSTA is being used by the Principal Investigator to participate in workshops offered by American Association for Cancer Research and the American Society of Clinical Oncology. The Principal Investigator participated in the first of these workshops, Methods in Clinical Cancer Research, in July 2003. This was 38.5 hour course designed to introduce clinical fellows and junior faculty the principles of good clinical trial design, expose early clinical scientists to the full spectrum of

challenges in clinical research, and develop well trained, experienced researchers whose expertise will foster better clinical trial design. As part of this workshop, the PI further developed a concept and wrote a protocol for a, "Prospective Cohort Study of Gynecologic Cancer Screening and Risk-Reducing Surgery in Women with Hereditary Non-Polyposis Colon Cancer Syndrome (HNPCC)" This protocol has been approved by the Gynecology Oncology Group for further development, and is currently on the priority protocol list of that cooperative group.

Part of the time freed by the PSTA is also to be used by the Principal Investigator to participate in formal coursework in the Clinical Epidemiology and Health Services Research Program at Weill Graduate School of Medical Sciences of Cornell University (WGSMS). These courses will include Introduction to Research Methodology and Statistical Analysis, Advanced Biostatistics, the regularly scheduled Research Methodology Colloquia, and Ethics of Clinical and Health Services Research. Although it was envisioned that participation in this coursework would occur last fall, due to the timing of notification of the award and changes in the offering dates of these courses, the PI was unable to participate in the courses as originally anticipated. In fulfillment of the requirements of the training award, the PI will be participating in these courses this upcoming summer and fall.

3) Progress of Other Training Partly Supported by This Award

A) Determination of Risk of Prostate Cancer in Male Carriers of *BRCA1* and *BRCA2* Mutations

The PI was a co-first author of a study led by Kenneth Offit, M.D., M.P.H. that showed that the risk for prostate cancer is significantly elevated in men who carry *BRCA2* mutations. This study confirmed than men with *BRCA2* mutations have a 4.8 fold increased risk of prostate cancer compared to the general population. This was published as a featured article in the May 1, 2004 edition of Clinical Cancer Research. (Reprint is attached in Appendix B.)

B) Pilot Analysis of Risk of Ovarian Cancer in women from *BRCA*-negative hereditary breast cancer families

Using time freed up by the PSTA, the PI conducted a pilot study examining the incidence of breast and ovarian cancer in 171 women from *BRCA*-negative hereditary breast cancer families who were prospectively followed for a mean of 3.6 years. Observed rate of cancer was compared with that expected from the SEER database. In this analysis, as expected, new breast cancer cases were seen more frequently than would be predicted from population rates. Importantly, ovarian cancer was not seen more frequently than would be expected in the general population. If these preliminary results are confirmed, this information will have important implications for cancer screening in these kindreds. This data has been accepted for presentation at the 2004 Meeting of the American Society of Clinical Oncology. (Presentation is attached in Appendix C.)

Key Research Accomplishments

- Accrual at a greater than expected rate to the study, "Modifiers of the Efficacy of Risk-Reducing Salpingo-Oophorectomy for the Prevention of Breast and Ovarian Cancer in Carriers of *BRCA1* and *BRCA2* Mutations."

- Participation in AACR/ASCO course Methods in Clinical Cancer Research with production of a working draft of a protocol for the Gynecologic Oncology Group entitled, "Prospective Cohort Study of Gynecologic Cancer Screening and Risk-Reducing Surgery in Women with Hereditary Non-Polyposis Colon Cancer Syndrome (HNPCC)."

- Co-authored a study confirming that men with *BRCA2* mutations are at significantly increase risk of prostate cancer.

- Completed a pilot study suggesting that women from *BRCA*-negative hereditary breast cancer families are not at increased risk of ovarian cancer.

Reportable Outcomes

- Co-authored a study confirming that men with *BRCA2* mutations are at significantly increase risk of prostate cancer.[1]

- Completed a pilot study suggesting that women from *BRCA*-negative hereditary breast cancer families are not at increased risk of ovarian cancer.[2]

Conclusions

With the support of the PTSA, the principle investigator is participating in a comprehensive training plan designed to assist him in making the transition from junior faculty member to independent clinical breast cancer researcher. Additionally, time freed by the PTSA has allowed the principal investigator to pursue several productive avenues of research addressing cancer risks in individuals from inherited breast and ovarian cancer families. It is anticipated that continued support from the PTSA will continue to further the principal investigator's development and ability to become an effective and highly productive clinical breast cancer researcher.

References

[1] Kirchhoff T†, Kauff ND†, Mitra N, Nafa K, Huang H, Palmer C, Gulati T, Wadsworth E, Donat S, Robson ME, Ellis NA, Offit K. *BRCA* Mutations and Risk of Prostate Cancer in Ashkenazi Jews. Clinical Cancer Research 2004; 10: 2918-21.

[2] Kauff N, Cigler T, Hurley K, Huang H, Rapaport H, Wadsworth E, Robson M, Norton L, Barakat R, Offit K. Incidence of ovarian cancer in *BRCA*-negative hereditary breast cancer families. Accepted for presentation at the 40th Annual Meeting of the American Society of Clinical Oncology, New Orleans, LA, June 2004.

† T. Kirchoof and N. Kauff contributed equally to this report.

MEMORIAL SLOAN-KETTERING CANCER CENTER
Clinical Genetics Service
Female Follow-up Questionnaire

Important Note: The past several years have been an exciting time of progress in the research efforts of the Clinical Genetics Service. Your responses to our questionnaires have provided important information about risk of cancer in individuals with a family history of the disease, and also on the effects of various risk-reducing strategies. Articles based on these results have been published in the New England Journal of Medicine, Journal of Clinical Oncology, Cancer, and Journal of the National Cancer Institute. Summaries of this research are available on our web site at http://www.mskcc.org/mskcc/html/603.cfm

To take our work to the next level, we have identified several important clinical questions which require more detailed medical follow-up information to obtain a full answer. Therefore, we have created *a new, comprehensive medical follow-up questionnaire.* In some cases you may see questions that we have asked before, but with expanded options for responses. As much as possible, we have converted our questions to a "check box" format for easy, rapid responding. We also ask some new questions on topics related to screening, medication use, and new cancers in family members. Please fill out the enclosed questionnaire as completely as possible, thinking back to when you were **first** seen at Clinical Genetics. This will help us ensure that our records are both complete and up-to-date. Feel free to provide us with comments and feedback so that we can continue our efforts to provide state-of-the-art, scientifically sound genetic counseling services.

Clinical Genetics Service
Memorial Sloan-Kettering Cancer Center
1275 York Avenue-Box 295, New York, NY
Telephone: 212-434-5149 Fax: 212-434-5166

New Cancers Since Your Initial Clinical Genetics Visit

Name **(CGS to Fill in)**
Today's Date ____/____/____
Date of Birth____/____/____

1) Since you were seen at Clinical Genetics on **(CGS to Fill in)**, have you had any cancer diagnoses?

- ☐ Yes
- ☐ No **(If no, please skip to Question #8, *page 4*)**

2) If you have been diagnosed with cancer **since we last saw you**, please indicate the type of cancer, age, and date of the diagnosis.

Diagnosis 1:
- ☐ Breast
- ☐ Ovary or Fallopian Tube
- ☐ Colon
- ☐ Lung
- ☐ Melanoma
- ☐ Other, *(please specify)*:_____

Age of diagnosis: _____ Date diagnosis:____/____/____

☐ New Cancer ☐ Recurrence of Prior Cancer ☐ Not Sure

Diagnosis 2:
- ☐ Breast
- ☐ Ovary of Fallopian Tube
- ☐ Colon
- ☐ Lung
- ☐ Melanoma
- ☐ Other, *(please specify)*:_____

Age of diagnosis: _____ Date diagnosis:____/____/____

☐ New Cancer ☐ Recurrence of Prior Cancer ☐ Not Sure

Information on New Cancers Diagnosed Since Your Clinical Genetics Appointment

Since your initial Clinical Genetics visit, if you have been diagnosed with:

- **BREAST CANCER, please answer Question #3, *pages 1-2***
- **OVARIAN or FALLOPIAN TUBE CANCER, please answer Question #4, *page 2***
- **COLON or RECTAL CANCER, please answer Question #5, *page 3***
- Any **OTHER** type of cancer, **please answer Questions #6 and #7, *page 3***

3) New Breast Cancer

a) If you have been diagnosed with **Breast Cancer** since you were last seen at Clinical Genetics, how was the cancer detected?

- ☐ I felt a mass doing breast self-examination and my doctor ordered further tests.
- ☐ My doctor felt a mass during a clinical breast examination and ordered further tests.
- ☐ I had an abnormal screening mammogram (without symptoms) and my doctor ordered further tests.
- ☐ I had an abnormal screening breast ultrasound (without symptoms) and my doctor ordered further tests.
- ☐ I had an abnormal screening Breast MRI (without symptoms) and my doctor ordered further tests.
- ☐ I had both an abnormal screening mammogram AND breast ultrasound (without symptoms) and my doctor ordered further tests.
- ☐ I had both an abnormal screening mammogram AND breast MRI (without symptoms) and my doctor ordered further tests.
- ☐ Other, *(please specify)*: _____

b) If you have been diagnosed with **Breast Cancer** since you were last seen at Clinical Genetics, what side was the Breast Cancer on?

☐ Right ☐ Left ☐ Both Sides

c) If you have been diagnosed with **Breast Cancer** since you were last seen at Clinical Genetics, how was the cancer treated? *(Please indicate all that apply)*

- ☐ Mastectomy
- ☐ Lumpectomy
- ☐ Chemotherapy, *indicate regimen* _____
- ☐ Tamoxifen Date Started _____ Are you still taking? _____
  If No, Date Stopped _____
- ☐ Raloxifene Date Started _____ Are you still taking? _____
  If No, Date Stopped _____
- ☐ Aromatase Inhibitor (ie. Anastrozole (Arimidex™), Letrozole (Femara™))
  Specific Drug _____
  Date Started _____ Are you still taking? _____
  If No, Date Stopped _____
- ☐ Radiation therapy
- ☐ Other, *(please specify):* _____

d) If you have been diagnosed with **Breast Cancer** since you were last seen at Clinical Genetics, what was your menopausal status at the time of your diagnosis? *(Please check all that apply)*

- ☐ I was menstruating regularly every 3-6 weeks
- ☐ I was having irregular menstrual flows
- ☐ I had not had a menstrual cycle in the previous 2-6 months.
- ☐ I had not had a menstrual cycle in over 6 months
- ☐ I had previously undergone a natural menopause at age _____
- ☐ I had previously undergone a chemotherapy or radiation therapy induced menopause at age _____
- ☐ I had previously had my ovaries removed at age _____
- ☐ I had previously had my uterus removed at age _____

4) New Ovarian or Fallopian Tube Cancer

a) If you have been diagnosed with **Ovarian or Fallopian Tube Cancer** since you were last seen at Clinical Genetics, how was the cancer detected?

- ☐ I had symptoms from the cancer (ie. bloating or abdominal fullness) and my doctor ordered further tests.
- ☐ I had an abnormal pelvic ultrasound (without symptoms) and my doctor ordered further tests.
- ☐ I had an abnormal CA-125 blood test (a tumor marker for ovarian cancer) (without symptoms) and my doctor ordered further tests.
- ☐ I had both an abnormal pelvic ultrasound AND CA-125 blood test (without symptoms) and my doctor ordered further tests.
- ☐ Other, *(please specify)*: _____

b) If you have been diagnosed with **Ovarian or Fallopian Tube Cancer** since you were last seen at Clinical Genetics, how was the cancer treated? *(Please indicate all that apply)*

- ☐ Surgery (hysterectomy and/or oophorectomy)
- ☐ Chemotherapy, *indicate regimen* _____
- ☐ Radiation therapy
- ☐ Other, *(please specify)*: _____

c) If you have been diagnosed with **Ovarian or Fallopian Tube Cancer** since you were last seen at Clinical Genetics, what was your menopausal state at the time of your diagnosis? *(Please check all that apply)*

- ☐ I was menstruating regularly every 3-6 weeks
- ☐ I was having irregular menstrual flows
- ☐ I had not had a menstrual cycle in the previous 2-6 months.
- ☐ I had not had a menstrual cycle in over 6 months
- ☐ I had previously undergone a natural menopause at age _____
- ☐ I had previously undergone a chemotherapy or radiation therapy induced menopause at age _____
- ☐ I had previously had my ovaries removed at age _____
- ☐ I had previously had my uterus removed at age _____

5) New Colon or Rectal Cancer

a) If you have been diagnosed with a **Colon or Rectal Cancer** since you were last seen at Clinical Genetics, how was the cancer detected?

- ☐ I noticed a mucous discharge and my doctor ordered further tests
- ☐ I noticed a change in bowel habits and my doctor ordered further tests.
- ☐ I had abdominal pain and/or bloating and my doctor ordered further tests.
- ☐ I noticed rectal bleeding and my doctor ordered further tests.
- ☐ My doctor detected blood in my stool during a rectal exam and ordered further tests.
- ☐ My doctor felt a mass in my rectum on a digital rectal exam and ordered further tests.
- ☐ I underwent a **screening** colonoscopy (an exam of my entire colon without having had any previous symptoms) and my doctor detected a cancer.
- ☐ I underwent a **screening** sigmoidoscopy (an exam of part of my colon without having had any previous symptoms) and my doctor detected a cancer.
- ☐ Other, *(please specify)*: _____

b) If you have been diagnosed with a **Colon or Rectal Cancer** since you were last seen at Clinical Genetics, how was the colorectal cancer treated? *(Please indicate all that apply)*

- ☐ Single colon surgery
- ☐ Multiple colon surgeries
- ☐ Chemotherapy, *please indicate regimen*:_____
- ☐ Radiation
- ☐ Other, *(please specify)*:_____

6) If you have been diagnosed with a **Lung Cancer, Melanoma or Any Other Cancer** since you were last seen at Clinical Genetics, how was the cancer **detected**? _____

7) How was this **Lung Cancer, Melanoma or Any Other Cancer** treated? _____

New Cancers in Relatives

8) Since you were last seen at Clinical Genetics, has any **Close Relative (Parent, Grand Parent, Brother, Sister, Child, Grand Child, Aunt, Uncle or First Cousin)** had a NEW cancer diagnosis?

- ❒ Yes **(If yes, please answer Question #9)**
- ❒ No **(If no, please skip to Question #10, *page 5)***

9) If a **Close Relative** was diagnosed with cancer since we last saw you, please indicate the type of relative, the type of cancer, and the age of the diagnosis.

	Relation			Type of Cancer	
Relative #1	❒ Mother ❒ Father ❒ Brother ❒ Sister ❒ Son ❒ Daughter ❒ Grandchild	❒ Maternal Grandmother ❒ Maternal Grandfather ❒ Paternal Grandmother ❒ Paternal Grandfather	❒ Maternal Aunt ❒ Maternal Uncle ❒ Paternal Aunt ❒ Paternal Uncle ❒ Maternal First Cousin ❒ Paternal First Cousin ❒ Other: _____	❒ Breast ❒ Ovary/Fallopian Tube ❒ Colon ❒ Prostate ❒ Lung ❒ Melanoma ❒ Uterus ❒ Other _____	Age of Diagnosis: _____ ❒ New Cancer ❒ Recurrence of Prior Cancer ❒ Not Sure
Relative #2	❒ Mother ❒ Father ❒ Brother ❒ Sister ❒ Son ❒ Daughter ❒ Grandchild	❒ Maternal Grandmother ❒ Maternal Grandfather ❒ Paternal Grandmother ❒ Paternal Grandfather	❒ Maternal Aunt ❒ Maternal Uncle ❒ Paternal Aunt ❒ Paternal Uncle ❒ Maternal First Cousin ❒ Paternal First Cousin ❒ Other: _____	❒ Breast ❒ Ovary/Fallopian Tube ❒ Colon ❒ Prostate ❒ Lung ❒ Melanoma ❒ Uterus ❒ Other _____	Age of Diagnosis: _____ ❒ New Cancer ❒ Recurrence of Prior Cancer ❒ Not Sure
Relative #3	❒ Mother ❒ Father ❒ Brother ❒ Sister ❒ Son ❒ Daughter ❒ Grandchild	❒ Maternal Grandmother ❒ Maternal Grandfather ❒ Paternal Grandmother ❒ Paternal Grandfather	❒ Maternal Aunt ❒ Maternal Uncle ❒ Paternal Aunt ❒ Paternal Uncle ❒ Maternal First Cousin ❒ Paternal First Cousin ❒ Other: _____	❒ Breast ❒ Ovary/Fallopian Tube ❒ Colon ❒ Prostate ❒ Lung ❒ Melanoma ❒ Uterus ❒ Other _____	Age of Diagnosis: _____ ❒ New Cancer ❒ Recurrence of Prior Cancer ❒ Not Sure
Relative #4	❒ Mother ❒ Father ❒ Brother ❒ Sister ❒ Son ❒ Daughter ❒ Grandchild	❒ Maternal Grandmother ❒ Maternal Grandfather ❒ Paternal Grandmother ❒ Paternal Grandfather	❒ Maternal Aunt ❒ Maternal Uncle ❒ Paternal Aunt ❒ Paternal Uncle ❒ Maternal First Cousin ❒ Paternal First Cousin ❒ Other: _____	❒ Breast ❒ Ovary/Fallopian Tube ❒ Colon ❒ Prostate ❒ Lung ❒ Melanoma ❒ Uterus ❒ Other _____	Age of Diagnosis: _____ ❒ New Cancer ❒ Recurrence of Prior Cancer ❒ Not Sure

10) Medication Questions

Please complete the following chart. Questions on the top row refer to the specific medications listed in the left-most column.

	Since being seen at Clinical Genetics, have you started taking or are you still taking this medication on a regular basis (more than one time per week)?	**Why were you or are you taking this medication?** *(Check all that apply)*	**If you are taking the medication, how likely is it that you will continue taking it in the next 6 months?**	**If you have never taken the medication, are you considering taking the medication in the future?**
a) Hormone Replacement with estrogen or progesterone (ie. Premarin, Prempro, Estrace, Provera, etc.)	❒ yes ❒ no Type *(specify brand):* _____ Date started ___/___/____ Date ended ___/___/____ ❒ Still taking	❒ Hot flashes or night sweats ❒ Vaginal dryness ❒ Prevention or treatment of osteoporosis ❒ Prevention of heart disease ❒ Prevention of dementia ❒ Other: _____	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely ❒ 6 = If my doctor tells me to
b) Oral Contraceptives	❒ yes ❒ no Date started ___/___/____ Date ended ___/___/____ ❒ Still taking	❒ Prevention of pregnancy ❒ Regulation of menstrual cycle ❒ Painful or heavy menses ❒ Prevention of ovarian cancer ❒ Other: _____	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely ❒ 6 = If my doctor tells me to
c) Tamoxifen (Nolvadex™)	❒ yes ❒ no Date started ___/___/____ Date ended ___/___/____ ❒ Still taking	❒ Treatment of breast cancer ❒ Prevention of breast cancer ❒ Prevention or treatment of osteoporosis ❒ Other: _____	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely ❒ 6 = If my doctor tells me to
d) Raloxifene (Evista™)	❒ yes ❒ no Date started ___/___/____ Date ended ___/___/____ ❒ Still taking	❒ Treatment of breast cancer ❒ Prevention of breast cancer ❒ Prevention or treatment of osteoporosis ❒ Other _____	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely ❒ 6 = If my doctor tells me to
e) Anti-inflammatory medications (ie. Aspirin, Aleve, Motrin, Naprosyn, Ibuprofren, Celebrex, Vioxx etc.)	❒ yes ❒ no Type *(specify brand):* _____ Date started ___/___/____ Date ended ___/___/____ ❒ Still taking	❒ Arthritis ❒ Prevention of colon cancer ❒ Prevention of heart disease ❒ Painful or heavy menses ❒ Other: _____	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely ❒ 6 = If my doctor tells me to

Breast Cancer Screening

11) Have you EVER had a mastectomy (surgical removal of one or both breasts) either before or after being seen at Clinical Genetics?

- ☐ No
- ☐ Yes, I have had a unilateral mastectomy (removal of ONE breast).
- ☐ Yes, I have had a bilateral mastectomy (removal of BOTH breasts) **If yes, please skip to Question #18, *page 11***

12) Mammograms

a) How many mammograms have you had **in the last year**?
☐ Never had a mammogram ☐ None in the last year ☐ One ☐ Two ☐ Three or more

b) When was your **last** mammogram?
- ☐ Never had a mammogram
- ☐ In the last six months
- ☐ Between six months and one year ago
- ☐ Between one and two years ago
- ☐ More than two years ago

c) What was the reason for your **last** mammogram?
- ☐ Never had a mammogram
- ☐ Routine screening or check-up
- ☐ Lump in your breast
- ☐ Pain in your breast
- ☐ Other, *(please specify)*:_____

d) **Since being seen by Clinical Genetics**, have you had an **abnormal Mammogram** that required follow-up mammograms, X-rays, ultrasounds, CT scans, MRIs, biopsies, or surgery?

☐ Yes ☐ No

e) If you have had an **abnormal Mammogram** that required follow-up **since being seen by Clinical Genetics**,

When did this abnormal result occur? (mm/yr) ___/_____

What was the abnormal result?
- ☐ Mass
- ☐ Calcification
- ☐ Cyst
- ☐ Other, *(please specify)*:_____
- ☐ Don't Know / Not Sure

What was done?
- ☐ Repeat Mammogram
- ☐ Ultrasound
- ☐ MRI
- ☐ Other, *(please specify)*:_____
- ☐ Needle Aspiration
- ☐ Stereotatic Biopsy
- ☐ Biopsy in Operating Room

Was a Cancer diagnosed? ☐ Yes ☐ No

f) If your last mammogram was not just routine screening or check-up, when was your last mammogram that was just for routine screening or check-up?
- ☐ Never had a screening mammogram
- ☐ In the last six months
- ☐ Between six months and one year ago
- ☐ Between one and two years ago
- ☐ More than two years ago

13) Breast MRI

a) How many Breast MRIs have you had **in the last year**?
☐ Never had a Breast MRI ☐ None in the last year ☐ One ☐ Two ☐ Three or more

b) When was your **last** Breast MRI?

- ☐ Never had a Breast MRI
- ☐ In the last six months
- ☐ Between six months and one year ago
- ☐ Between one and two years ago
- ☐ More than two years ago

c) What was the reason for your **last** Breast MRI?

- ☐ Never had a Breast MRI
- ☐ Routine screening or check-up
- ☐ Lump in your breast
- ☐ Pain in your breast
- ☐ Other, *(please specify)*:_____

d) **Since being seen by Clinical Genetics**, have you had an **abnormal Breast MRI** that required follow-up mammograms. X-rays, ultrasounds, CT scans, MRIs, biopsies, or surgery?

☐ Yes ☐ No

e) If you have had an **abnormal Breast MRI** that required follow-up **since being seen by Clinical Genetics**,

When did this abnormal result occur? (mm/yr) ___/_____

What was the abnormal result?

- ☐ Mass
- ☐ Calcification
- ☐ Cyst
- ☐ Other, *(please specify)*:_____
- ☐ Don't Know / Not Sure

What was done?

- ☐ Repeat MRI
- ☐ Mammogram
- ☐ Ultrasound
- ☐ Other, *(please specify)*:_____
- ☐ Needle Aspiration
- ☐ Stereotatic Biopsy
- ☐ Biopsy in Operating Room

Was a Cancer diagnosed? ☐ Yes ☐ No

f) If your last Breast MRI was not just routine screening or check-up, when was your last Breast MRI that was just for routine screening or check-up?

- ☐ Never had a screening Breast MRI
- ☐ In the last six months
- ☐ Between six months and year ago
- ☐ Between one and two years ago
- ☐ More than two years ago

14) Breast Ultrasound

a) How many Breast Ultrasounds have you had **in the last year**?

☐ Never had a Breast Ultrasound ☐ None in the last year ☐ One ☐ Two ☐ Three or more

b) When was your **last** Breast Ultrasound?

- ☐ Never had a Breast Ultrasound
- ☐ In the last six months
- ☐ Between six months and one year ago
- ☐ Between one and two years ago
- ☐ More than two years ago

c) What was the reason for your **last** Breast Ultrasound?

- ☐ Never had a Breast Ultrasound
- ☐ Routine screening or check-up
- ☐ Lump in your breast
- ☐ Pain in your breast
- ☐ Other, *(please specify)*:_____

d) **Since being seen by Clinical Genetics**, have you had an **abnormal Breast Ultrasound** that required follow-up mammograms, X-rays, ultrasounds, CT scans, MRIs, biopsies, or surgery?

☐ Yes ☐ No

e) If you have had an **abnormal Breast Ultrasound** that required follow-up **since being seen by Clinical Genetics,**

When did this abnormal result occur? (mm/yr) ___/_____

What was the abnormal result? ☐ Mass ☐ Calcification ☐ Cyst ☐ Other, *(please specify)*:_____ ☐ Don't Know / Not Sure

What was done? ☐ Repeat Ultrasound ☐ Mammogram ☐ MRI ☐ Other, *(please specify)*:_____ ☐ Needle Aspiration ☐ Stereotatic Biopsy ☐ Biopsy in Operating Room

Was a Cancer diagnosed? ☐ Yes ☐ No

f) If your last Breast Ultrasound was not just routine screening or check-up, when was your last Breast Ultrasound that was just for routine screening or check-up?

☐ Never had a screening Breast Ultrasound
☐ In the last six months
☐ Between six months and year ago
☐ Between one and two years ago
☐ More than two years ago

15) Clinical Breast Examinations (Examination by a physician)

a) How many Clinical Breast Exams have you had **in the last year**?

☐ Never had a Clinical Breast Exam
☐ None in the last year ☐ One ☐ Two ☐ Three ☐ Four or more

b) When was your **last** Clinical Breast Exam?

☐ Never had a Clinical Breast Exam
☐ In the last three months
☐ Between three and six months ago
☐ Between six months and one year ago
☐ Between one and two years ago
☐ More than two years ago

c) What was the reason for your **last** Clinical Breast Exam?

☐ Never had a Clinical Breast Exam
☐ Routine screening or check-up
☐ Lump in your breast
☐ Pain in your breast
☐ Other, *(please specify)*:_____

d) **Since being seen by Clinical Genetics**, have you had an **abnormal Clinical Breast Exam** that required follow-up mammograms, X-rays, ultrasounds, CT scans, MRIs, biopsies, or surgery?

☐ Yes ☐ No

e) If you have had an **abnormal Clinical Breast Exam** that required follow-up **since being seen by Clinical Genetics,**

When did this abnormal result occur? (mm/yr) ___/_____

What was the abnormal result? ☐ Mass ☐ Nipple Discharge ☐ Skin Change ☐ Other, *(please specify)*:_____ ☐ Don't Know / Not Sure

What was done? ☐ Mammogram ☐ Ultrasound ☐ MRI ☐ Other, *(please specify)*:_____ ☐ Needle Aspiration ☐ Stereotatic Biopsy ☐ Biopsy in Operating Room

Was a Cancer diagnosed? ☐ Yes ☐ No

f) If your last Clinical Breast Exam was not just routine screening or check-up, when was your last Clinical Breast Exam that was just a routine screening or check-up?

- ☐ Never had a Clinical Breast Exam
- ☐ In the last three months
- ☐ Between three and six months ago
- ☐ Between six months and one year ago
- ☐ Between one and two years ago
- ☐ More than two years ago

16) Self Breast Examination

a) How often have you done Self Breast Examinations **in the last year**?

- ☐ I am not doing Breast Self Exams
- ☐ More than Once a Month
- ☐ Every Month
- ☐ Every Other Month
- ☐ Every Three Months
- ☐ Every Four Months
- ☐ Every Six Months

b) When did you **last** do Self Breast Examination?

- ☐ I do not perform Self Breast Exams
- ☐ In the last month
- ☐ Between one and three months ago
- ☐ Between three and six months ago
- ☐ Between six months and one year ago
- ☐ More than one year ago

c) **Since being seen by Clinical Genetics**, have you found an abnormality on **Self Breast Examination** that required examination by a physician, follow-up mammograms, X-rays, ultrasounds, CT scans, MRIs, biopsies, or surgery?

☐ Yes ☐ No

d) If you have had an **abnormal Self Breast Examination** that required follow-up **since being seen by Clinical Genetics,**

When did this abnormal result occur? (mm/yr)___/_____

What was the abnormal result?

- ☐ Mass
- ☐ Nipple Discharge
- ☐ Skin Change
- ☐ Other, *(please specify)*:_____
- ☐ Don't Know / Not Sure

What was done?

- ☐ Physician Examination
- ☐ Mammogram
- ☐ Ultrasound
- ☐ MRI
- ☐ Needle Aspiration
- ☐ Stereotatic Biopsy
- ☐ Biopsy in Operating Room
- ☐ Other, *(please specify)*:_____

Was a Cancer diagnosed? ☐ Yes ☐ No

17) Future Plans for Breast Cancer Screening

Please fill in the chart below. Questions in the top row refer to specific screening modalities in the left-most column.

	When are you planning to have your next test?	How likely are you to have the test by that time?
a) Mammogram	❒ in the next three months ❒ in the next six months ❒ in the next year ❒ I'm planning on having a mammogram, but I'm not sure when. ❒ I'll have a mammogram when my doctor wants me to. ❒ I'm not sure when to go for my next mammogram. ❒ I'm undecided whether I'll have another mammogram. ❒ I've decided not to have another mammogram.	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely
b) Breast MRI	❒ in the next three months ❒ in the next six months ❒ in the next year ❒ I'm planning on having a breast MRI, but I'm not sure when. ❒ I'll have a breast MRI when my doctor wants me to. ❒ I'm not sure when to go for my next breast MRI. ❒ I'm undecided whether I'll have another breast MRI. ❒ I've decided not to have another breast MRI.	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely
c) Breast Ultrasound	❒ in the next three months ❒ in the next six months ❒ in the next year ❒ I'm planning on having a breast ultrasound, but I'm not sure when. ❒ I'll have a breast ultrasound when my doctor wants me to. ❒ I'm not sure when to go for my next breast ultrasound. ❒ I'm undecided whether I'll have another breast ultrasound. ❒ I've decided not to have another breast ultrasound.	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely
d) Clinical Breast Examination (examination by a physician)	❒ in the next three months ❒ in the next six months ❒ in the next year ❒ I'm planning on having a clinical breast exam, but I'm not sure when. ❒ I'll have a clinical breast exam when my doctor wants me to. ❒ I'm not sure when to go for my next clinical breast exam. ❒ I'm undecided whether I'll have another clinical breast exam. ❒ I've decided not to have another clinical breast exam.	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely
e) Self Breast Examination	❒ in the next month ❒ in the next three months ❒ in the next six months ❒ in the next year ❒ I'm planning on doing a self breast exam, but I'm not sure when. ❒ I'll do a self breast exam when my doctor wants me to. ❒ I'm not sure when to do my next self breast exam. ❒ I'm undecided whether I'll do another self breast exam. ❒ I've decided not to do another self breast exam.	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely

Prophylactic Breast Surgery Information

18) Have you EVER had one or both breasts removed prophylactically, (for risk reduction, not for treatment of cancer)?

- ☐ No **(If no, please skip to Question #20, *page 12*)**
- ☐ Yes

a) I have had a prophylactic mastectomy (surgical removal of one or both breasts to prevent cancer)
☐ Left Breast ☐ Right Breast ☐ Both Breasts

b) When did you have prophylactic mastectomy? Date: ___/___/____
- ☐ Before being seen at Clinical Genetics
- ☐ After being seen at Clinical Genetics
- ☐ Don't remember / Not Sure

c) At the time of the prophylactic mastectomy:
- ☐ I had a reconstruction with saline implants
- ☐ I had a reconstruction with silicone implants
- ☐ I had a reconstruction with a TRAM flap
- ☐ I had a reconstruction with a Latissimus Dorsi flap
- ☐ I had another kind of reconstruction (*please specify*) _____
- ☐ I did not have reconstruction

How many nights did you spend in the hospital ☐ 0 ☐ 1 ☐ 2 ☐ Other ___

Were there any complications? ☐ Yes ☐ No
What kind? _____

19) Satisfaction with Prophylactic Mastectomy

What is your level of satisfaction with your decision to undergo prophylactic mastectomy?
- ☐ Very dissatisfied
- ☐ Dissatisfied
- ☐ Neither satisfied or dissatisfied
- ☐ Satisfied
- ☐ Very satisfied

20) Future Plans for Breast Cancer Risk Reduction

(If you still have ONE or BOTH breasts, please select one of the choices below, A-G, that best describes your plans for risk reduction. Otherwise, please skip to Question #21)

- ☐ **A)** I am not planning to have prophylactic mastectomy.
- ☐ **B)** I have not given prophylactic mastectomy much thought.
- ☐ **C)** I have scheduled a prophylactic mastectomy on: Date: ___/___/____
  - ☐ Left Breast ☐ Right Breast ☐ Both Breasts
- ☐ **D)** I plan to have a prophylactic mastectomy:
  - ☐ in the next three months
  - ☐ in the next six months
  - ☐ in the next year
- ☐ **E)** I plan to have a prophylactic mastectomy after:
  - ☐ I reach the age of _____
  - ☐ I finish childbearing (in about _____ years)
  - ☐ Other event *(please specify)*:_____ (in about _____years)
- ☐ **F)** I would plan to have a prophylactic mastectomy, BUT ONLY:
  - ☐ If I develop breast cancer in one breast
  - ☐ If my doctor tells me I should
  - ☐ Other reason, *(please specify)*:_____
- ☐ **G)** I am considering having a prophylactic mastectomy but I have no definite plans. I am considering mastectomy:
  - ☐ Extremely strongly
  - ☐ Strongly
  - ☐ Moderately
  - ☐ Slightly

Ovarian Cancer Screening

21) Have you EVER had an oophorectomy (surgical removal of one or both ovaries) either before or after being seen at Clinical Genetics?

- ☐ No
- ☐ Yes, I have had one ovary removed for treatment or risk reduction
- ☐ Yes, I have had both ovaries removed for treatment or risk reduction. **(If yes, please skip to Question #25, *page 15)***

22) Transvaginal Ultrasound

a) How many transvaginal ultrasounds have you had **in the last year**?
☐ Never had a transvaginal ultrasound ☐ None in the last year ☐ One ☐ Two ☐ Three or more

b) When was your **last** transvaginal ultrasound?
- ☐ Never had a transvaginal ultrasound
- ☐ In the last six months
- ☐ Between six months and one year ago
- ☐ Between one and two years
- ☐ More than two years ago

c) What was the reason for your **last** ultrasound? *(Check all that apply)*
- ☐ Never had a transvaginal ultrasound
- ☐ Routine screening or check-up
- ☐ Pain in your belly
- ☐ Bloating/constipation/other discomfort
- ☐ Abnormal vaginal bleeding
- ☐ High number on a blood test (CA-125)
- ☐ Repeat test because previous abnormal ultrasound
- ☐ Fertility treatment
- ☐ Physician felt a mass during a pelvic exam
- ☐ Other, *(please specify)*:_____

d) **Since being seen by Clinical Genetics,** have you had an **abnormal transvaginal** ultrasound that required follow-up x-rays, ultrasounds, CT scan, MRI or surgery?

❒ Yes ❒ No

e) If you have had an abnormal Transvaginal Ultrasound **since being seen by Clinical Genetics,**

When did this abnormal result occur? (mm/yr) ___/_____

What was the abnormal result?
❒ Ovarian Cyst
❒ Ovarian Mass
❒ Calcifications
❒ Fibroids
❒ Thickened Lining of the Uterus
❒ Other, *(please specify)*:_____
❒ Don't Know/Not Sure

What was done?
❒ Repeat Ultrasound
❒ MRI
❒ CA-125 Blood test
❒ CT Scan
❒ Endometrial Biopsy in the Office
❒ D & C
❒ Hysteroscopy
❒ Other, *(please specify)*:_____
❒ Laparoscopy with removal of ❒ zero ❒ one or ❒ two ovaries
❒ Hysterectomy with removal of ❒ zero ❒ one or ❒ two ovaries

Was a Cancer diagnosed? ❒ Yes ❒ No

f) If your last transvaginal ultrasound was not just a routine screening or check-up, when was your last ultrasound that was just for routine screening or check-up?
❒ Never had a transvaginal ultrasound for routine screening or check-up
❒ In the last six months
❒ Between six months and one year
❒ Between one and two years
❒ More than two years ago

23) CA-125 Blood Tests

a) Have many CA-125 Blood Tests have you had **in the last year**?
❒ Never heard of a CA-125 blood test
❒ Never had a CA-125 blood test
❒ None in the last year
❒ One
❒ Two
❒ Three or more

b) When was your **last** CA-125 Blood Test?
❒ Never had a CA-125 Blood Test
❒ In the last six months
❒ Between six months and one year ago
❒ Between one and two years
❒ More than two years ago

c) What was the reason for your **last** CA-125 Blood Test? *(Check all that apply)*
❒ Never had a CA-125 Blood Test
❒ Routine screening or check-up
❒ Pain in your belly
❒ Bloating/constipation/other discomfort
❒ Physician felt a mass during a pelvic exam
❒ Repeat test because of prior abnormal CA-125
❒ Abnormal ultrasound
❒ Other, *(please specify)*:_____

d) **Since being seen by Clinical Genetics** have you had an **abnormal CA-125 Blood Test** that required follow-up x-rays, ultrasounds, CT scan, MRI or surgery?

❒ Yes ❒ No

e) If you have had an abnormal CA-125 Blood Test **since being seen by Clinical Genetics,**
When did this abnormal result occur? (mm/yr) ___/_____

What was done? ❒ Repeat CA125 Blood test ❒ Endometrial Biopsy in the Office
❒ Ultrasound ❒ D & C
❒ MRI ❒ Hysteroscopy
❒ CT Scan ❒ Other, *(please specify)*:_____
❒ Laparoscopy with removal of ❒ zero ❒ one or ❒ two ovaries
❒ Hysterectomy with removal of ❒ zero ❒ one or ❒ two ovaries

Was a Cancer diagnosed? ❒ Yes ❒ No

f) If your last CA-125 Blood Test was not just a routine screening or check-up, when was your last CA-125 Blood test that was just a routine screening or check-up?

❒ Never had a CA-125 Blood Test for routine screening or check-up
❒ In the last six months ❒ Between six months and one year
❒ Between one and two years ❒ More than two years ago

24) Future Plans for Ovarian Cancer Screening

Please fill in the chart below. Questions in the top row refer to specific screening modalities in the left-most column.

	When are you planning to have your next test?	**How likely are you to have the test by that time?**
a) Transvaginal Ultrasound	❒ in the next three months ❒ in the next six months ❒ in the next year ❒ I'm planning on having a transvaginal ultrasound, but I'm not sure when. ❒ I'll have a transvaginal ultrasound when my doctor sends me for one. ❒ I'm not sure when to go for my next transvaginal ultrasound. ❒ I'm undecided whether I'll have another transvaginal ultrasound. ❒ I've decided not to have another transvaginal ultrasound.	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely
b) CA-125 Blood Test	❒ in the next three months ❒ in the next six months ❒ in the next year ❒ I'm planning on having a CA-125 Blood Test, but I'm not sure when. ❒ I'll have a CA-125 Blood Test when my doctor sends me for one. ❒ I'm not sure when to go for my next CA-125 Blood Test. ❒ I'm undecided whether I'll have another CA-125 Blood Test. ❒ I've decided not to have another CA-125 Blood Test.	❒ 1 = Not at all ❒ 2 = A little bit ❒ 3 = Moderately ❒ 4 = Very ❒ 5 = Extremely

Prophylactic Oophorectomy Information

25) Have you ever had one or both ovaries removed prophylactically, (for risk reduction, not for treatment of cancer)?

❒ No **(If no, please skip to Question #27, *page 16*)**
❒ Yes

a) I have had a prophylactic oophorectomy
❒ Left Ovary ❒ Right Ovary ❒ Both Ovaries

This surgery was done: ❒ Laparoscopically ❒ Open Surgery

b) When did you have prophylactic oophorectomy? Date: ___/___/____
❒ Before being seen at Clinical Genetics
❒ After being seen at Clinical Genetics
❒ Don't remember / Not Sure

c) At the time of the removal of the ovaries:
❒ My Uterus was Removed
❒ My Uterus was Left In
❒ My Uterus had been previously removed

How many nights did you spend in the hospital ❒ 0 ❒ 1 ❒ 2 ❒ Other _____

Were there any complications? ❒ Yes ❒ No
What kind? _____

d) At the time of my prophylactic oophorectomy:
❒ I was menstruating regularly every 3-6 weeks
❒ I was having irregular menstrual flows
❒ I had not had a menstrual cycle in the previous 2-6 months.
❒ I had not had a menstrual cycle in over 6 months
❒ I had previously undergone a natural menopause at age _____
❒ I had previously undergone a chemotherapy or radiation therapy induced menopause at age _____
❒ I had previously had my uterus removed at age _____

26) Satisfaction with Prophylactic Oophorectomy

What is your level of satisfaction with your decision to undergo prophylactic oophorectomy?
❒ Very dissatisfied
❒ Dissatisfied
❒ Neither satisfied or dissatisfied
❒ Satisfied
❒ Very satisfied

27) Future Plans for Ovarian Cancer Risk Reduction

(If you still have ONE or BOTH ovaries, please select one of the choices below, A-G, that best describes your plans for risk reduction. Otherwise, please skip to Question #28)

- ❒ **A)** I am not planning to have prophylactic oophorectomy.
- ❒ **B)** I have not given prophylactic oophorectomy much thought.
- ❒ **C)** I have scheduled a prophylactic oophorectomy on: Date: ___/___/____
  - ❒ Left Ovary ❒ Right Ovary ❒ Both Ovaries
- ❒ **D)** I plan to have a prophylactic oophorectomy
  - ❒ in the next three months
  - ❒ in the next six months
  - ❒ in the next year
- ❒ **E)** I plan to have a prophylactic oophorectomy after:
  - ❒ I reach the age of _____
  - ❒ I finish childbearing (in about _____ years)
  - ❒ Other event, *(please specify)*:_____ (in about _____years)
- ❒ **F)** I would plan to have a prophylactic oophorectomy, BUT ONLY:
  - ❒ If I develop breast cancer
  - ❒ If my doctor tells me I should
  - ❒ Other reason, *(please specify)*:_____
- ❒ **G)** I am considering having a prophylactic oophorectomy but I have no definite plans. I am considering oophorectomy:
  - ❒ Extremely strongly
  - ❒ Strongly
  - ❒ Moderately
  - ❒ Slightly

28) Menstrual Status

Please describe your **current** menstrual status:

- ❒ I am menstruating regularly every three-six weeks
- ❒ I am having irregular menstrual flows
- ❒ I have not had a menstrual cycle in the previous two-six months.
- ❒ I have not had a menstrual cycle in over six months
- ❒ I have undergone a natural menopause at age _____
- ❒ I have undergone a chemotherapy or radiation therapy induced menopause at age _____
- ❒ I have had a prophylactic oophorectomy as noted above
- ❒ I have had my ovaries removed because of abnormalities on screening as noted above.
- ❒ I have had my ovaries removed for other reasons at age _____
- ❒ I have had my uterus removed for other reasons at age _____

29) Colon Cancer Screening

a) How many Colonoscopies have you had in the **last Five years**?
❒ Never had a colonoscopy ❒ None ❒ One ❒ Two ❒ Three or more

b) When was your **last** Colonoscopy?
❒ Never had a Colonoscopy
❒ In the last year
❒ Between one and two years ago
❒ Between two and five years
❒ More than five years ago

c) What was the reason for your **last** Colonoscopy? *(Check all that apply)*
❒ Never had a Colonoscopy
❒ Routine screening or check-up
❒ Pain in your belly
❒ Bloating/constipation/other discomfort
❒ Doctor felt a mass during a rectal exam
❒ Rectal Bleeding
❒ The doctor found blood in your stool
❒ Other, *(please specify)*:_____

d) **Since being seen by Clinical Genetics,** have you had an **abnormal Colonoscopy**?

❒ Yes ❒ No

e) If you have had an abnormal Colonoscopy **since being seen by Clinical Genetics**,

When did this abnormal result occur? (mm/yr) ___/_____

What was done? ❒ Repeat Colonoscopy
❒ Barium Enema
❒ CT Scan
❒ MRI
❒ Virtual Coloscopy
❒ Laparoscopy
❒ Exploratory Surgery
❒ Other, *(please specify)*:_____

Was a Cancer diagnosed? ❒ Yes ❒ No

f) If your last Colonoscopy was not just a routine screening or check-up, when was your last Colonoscopy that was just for routine screening or check-up?
❒ Never had a Colonoscopy
❒ In the last year
❒ Between one and two years ago
❒ More than two years ago but less than five years ago
❒ More than five years ago

g) When are you planning to have your next Colonoscopy?
❒ In the next three months
❒ In the next six months
❒ In the next year
❒ In the next two to five years
❒ I'm planning on having a Colonoscopy, but I'm not sure when.
❒ I'll have a Colonoscopy when my doctor sends me for one.
❒ I'm not sure when to go for my next Colonoscopy.
❒ I'm undecided whether I'll have another Colonoscopy.
❒ I've decided not to have another Colonoscopy.

h) How likely are you to have a Colonoscopy by that time?

1	2	3	4	5
Not at all	A little bit	Moderately	Very	Extremely

Additional Comments:

Thank you for taking the time to answer this questionnaire. Your participation is greatly appreciated. If you have any questions please feel free to contact the Clinical Genetics Service at (212) 434-5149.

Featured Article

BRCA Mutations and Risk of Prostate Cancer in Ashkenazi Jews

Tomas Kirchhoff,[1] Noah D. Kauff,[1] Nandita Mitra,[2] Kedoudja Nafa,[1] Helen Huang,[1] Crystal Palmer,[1] Tony Gulati,[1] Eve Wadsworth,[1] Sheri Donat,[3] Mark E. Robson,[1] Nathan A. Ellis,[1] and Kenneth Offit[1]

[1]Clinical Genetics Service, Department of Medicine, [2]Department of Epidemiology and Biostatistics, and [3]Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York

Abstract

Purpose: **The Breast Cancer Linkage Consortium and other family-based ascertainments have suggested that male carriers of *BRCA* mutations are at increased risk of prostate cancer. Several series looking at the frequency of *BRCA* mutations in unselected patients with prostate cancer have not confirmed this finding. To clarify this issue, we conducted a large case-control study.**

Experimental Design: **Blood specimens from 251 unselected Ashkenazi men with prostate cancer were screened for the presence of one of the three common Ashkenazi founder mutations in *BRCA1* and *BRCA2*. The incidence of founder mutations was compared with the incidence of founder mutations in 1472 male Ashkenazi volunteers without prostate cancer using logistic regression analysis after adjusting for age.**

Results: **Thirteen (5.2%) cases had a deleterious mutation in *BRCA1* or *BRCA2* compared with 28 (1.9%) controls. After adjusting for age, the presence of a *BRCA1* or *BRCA2* mutation was associated with the development of prostate cancer (odds ratio, 3.41; 95% confidence interval, 1.64–7.06; $P = 0.001$). When results were stratified by gene, *BRCA2* mutation carriers demonstrated an increased risk of prostate cancer (odds ratio, 4.78; 95% confidence interval, 1.87–12.25; $P = 0.001$), whereas the risk in *BRCA1* mutation carriers was not significantly increased.**

Conclusions: ***BRCA2*** **mutations are more likely to be found in unselected individuals with prostate cancer than age-matched controls. These results support the hypothesis that deleterious mutations in *BRCA2* are associated with an increased risk of prostate cancer.**

Introduction

Early reports from the Breast Cancer Linkage Consortium and other family-based ascertainments suggested that families with deleterious mutations in *BRCA1* and *BRCA2* had an increased number of prostate cancers compared with families without known inherited predisposition (1–5). Biological support for this association was provided by Gao *et al.* (6), who demonstrated loss of heterozygosity at the *BRCA1* locus in hereditary prostate cancer cases. In an attempt to confirm these findings, several groups have looked at the incidence of deleterious *BRCA1* and *BRCA2* mutations in unselected series of patients with prostate cancer (7–11). The majority of these series have been performed in Ashkenazi populations because of the high frequency of three founder mutations in *BRCA1* and *BRCA2* in this group. Most series of unselected patients have concluded that deleterious *BRCA* mutations contribute little, if anything, to the incidence of prostate cancer in the Ashkenazi population. In the only series of unselected patients suggesting a weak association of *BRCA* mutations with prostate cancer risk, the effect was limited to *BRCA1* mutation carriers (11). However, this finding was not confirmed in two recent family-based ascertainments limited to *BRCA1* mutation carriers (12, 13). To better elucidate the impact of deleterious *BRCA1* and *BRCA2* mutations on prostate cancer risk, we conducted a large case-control study comparing the incidence of deleterious *BRCA1* and *BRCA2* founder mutations in unselected Ashkenazi prostate cancer patients and compared this with the frequency of *BRCA1* and *BRCA2* founder mutations in a well-characterized control population.

Patients and Methods

DNA was extracted from lymphocytes of blood specimens from 251 individuals of Ashkenazi Jewish ancestry diagnosed with adenocarcinoma of the prostate who received care at the outpatient urology clinic at Memorial Sloan-Kettering Cancer Center from April 2000 to September 2002. The samples were unselected for age or family history. Clinical and pathological records were reviewed to confirm the diagnosis of prostate cancer in all subjects. Once pathological diagnosis of prostate cancer was confirmed, the age of diagnosis was recorded, and all other identifying links were destroyed. The study design and anonymization method were approved by the Memorial Sloan-Kettering Cancer Center Institutional Review Board.

DNA from case samples was analyzed for the three common Ashkenazi founder mutations in *BRCA1* and *BRCA2* (185delAG and 5182insC in *BRCA1* and 6174delT in *BRCA2*) as described previously (14). Briefly, DNA was purified using the QiaAmp Blood DNA midi kit (Qiagen, Valencia, CA). DNA specimens were then analyzed for the presence of the Ashkenazi founder mutations using the following fluorescent-labeled primers flanking the mutation loci: *BRCA1*, 185delAG forward (5′-

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Note: T. Kirchhoff and N. Kauff contributed equally to this work.
Requests for reprints: Kenneth Offit, Clinical Genetics Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 192, New York, NY 10021. Phone: (212) 434-5150; Fax: (212) 434-5165; E-mail: offitk@mskcc.org.

Table 1 Frequency of *BRCA1* and *BRCA2* mutations in cases and controls

	Cases (n = 251)		Controls (n = 1472)				
Mutation	N (%)	Mean age of mutation carriers (range) (yrs)	N (%)	Mean age of mutation carriers (range) (yrs)	Age-adjusted odds ratio	95% CI[a]	P
BRCA1	5 (2.0%)	68.4 (65–71)	12 (0.8%)	57.1 (33–78)	2.20	0.72–6.70	0.16
BRCA2	8 (3.2%)	64.0 (48–78)	16 (1.1%)	46.5 (29–65)	4.78	1.87–12.25	0.001
BRCA1 or *BRCA2*	13 (5.2%)	65.7	28 (1.9%)	51.0	3.41	1.64–7.06	0.001

[a] CI, confidence interval.

CATTAATGCTATGCAGAAAAT) and 185delAG reverse (5′-CTTACTAGACATGTCTTTTCTTCCC) and 5382insC forward (5′-GTCCAAAGCGAGCAAGAGAATCTC) and 5382insC reverse (5′-GAATTCGAGACGGGAATCCAA); and *BRCA2*, 6174delT forward (TACTTGTGGGATTTTTAGCCAAGC) and 6174delT reverse (5′-GTGAGCTGGTCTGAATGTTCGTTA). PCR products were analyzed by RFLP, using modified sites (ACRES) for restriction enzymes *Taq*I (185delAG), *Dde*I (538insC), and *Bst*XI [6174delT (15)]. Carriers were recognized by the comparison of test digest with digests of PCR analyses of previously verified *BRCA1*/2 carriers.

We then compared the incidence of founder mutations in cases with a control group that included 1472 Ashkenazi Jewish male volunteers without prostate cancer identified as part of the Washington Ashkenazi Jewish Study who had previously undergone genotyping for the three Ashkenazi founder mutations (3). The authors of this study kindly provided the primary data files after excluding cases with a prior diagnosis of prostate cancer. The odds ratio for prostate cancer in cases compared with controls was estimated using a logistic regression model, after adjusting for age by treating it as an additional covariate in the model (16). For stratified analyses, χ^2 tests of association and Fisher's exact tests were conducted. Exact confidence intervals were computed for odds ratios. SAS version 8.2 (SAS Institute Inc., Cary, NC) was used for all analyses.

Results

Genotyping revealed that 13 of 251 cases (5%) were carriers of either a *BRCA1* or *BRCA2* mutation. Among the 13 carriers, 4 carriers had *BRCA1* 185delAG (1.6%), 1 carrier had *BRCA1* 5382insC (0.4%), and 8 carriers had *BRCA2* 6174delT (3.1%). Of the 1472 controls, 28 (1.9%) had either a *BRCA1* or *BRCA2* mutation: 9 (0.6%) had *BRCA1* 185delAG mutation; 3 (0.2%) had *BRCA1* 5382insC mutation; and 16 (1%) had a *BRCA2* 6174delT mutation.

Logistic regression analysis demonstrated that, after adjusting for age, the presence of an Ashkenazi founder mutation in *BRCA1* or *BRCA2* had a significant association with prostate cancer risk (odds ratio, 3.41; 95% confidence interval, 1.64–7.06; P = 0.001). In the multivariate model, age was also a significant predictor of prostate cancer risk ($P < 0.001$). When results were stratified by gene, *BRCA2* mutations were associated with an increased risk of prostate cancer (odds ratio, 4.78; 95% confidence interval, 1.87–12.25; P = 0.001). *BRCA1* mutation carriers also appeared to have an increased risk of prostate cancer, but the association was not statistically significant (odds ratio, 2.20; 95% confidence interval, 0.72–6.70; P = 0.16; Table 1).

Discussion

In the Ashkenazi Jewish population, the three founder mutations in *BRCA1* and *BRCA2* account for the vast majority of inherited breast and ovarian cancer families (17, 18). Despite evidence from several groups (2, 4) that prostate cancer was overrepresented in hereditary breast cancer families linked to *BRCA2* (Table 2), no series of unselected Ashkenazi Jewish men with prostate cancer prior to the current series has been able to confirm this association (Table 3). For *BRCA1*-linked kindreds, the prior family-based series have shown either a higher (1), lower (12), or average (13) risk of prostate cancer (Table 2). In unselected series examining the impact of *BRCA1* mutations on prostate cancer risk, four series did not demonstrate an association (7–10), and one population-based series observed a modest elevation in prostate cancer risk (95% confidence interval, 1.05–6.04; Ref. 11; Table 3). In contrast to these results, our study showed a significantly increased risk of prostate cancer in *BRCA2* but not *BRCA1* mutation carriers.

Several studies have suggested that *BRCA* mutations are predominately associated with an increased rate of early-onset prostate cancer (13, 19, 20). When our results were stratified by age, we were able to confirm that presence of a *BRCA* mutation was associated with a significantly increased risk for prostate after the age of 60 years (odds ratio, 3.71; 95% confidence interval, 1.25–11.65; P = 0.01), but not for prostate cancer before the age of 60 years (odds ratio, 3.03; 95% confidence interval, 0.56–10.72; P = 0.10). However, this analysis was limited by the very small number of men in the series (n = 3) less than 60 years old with prostate cancer and a *BRCA* mutation.

Whereas our finding of increased *BRCA2*-associated risk for prostate cancer is consistent with predictions based on family-based ascertainments, one of the reasons that our results may differ from prior unselected series is that these studies were not powered to discern different risks in *BRCA1 versus BRCA2* mutation carriers. Four of these series were limited to fewer than 200 cases. In one large series from Israel, the frequency of *BRCA2* mutations in prostate cancer cases (1.5%) was less than half the 3.1% frequency seen in our series. This difference may be due to the inclusion of only incident cases in the Israeli series, whereas we included both incident and prevalent cases. It is possible that a survival bias in our series resulted from a *BRCA2* mutation-associated survival advantage for patients with pros-

Table 2 Association of prostate cancer with *BRCA1* or *BRCA2* mutations: family-based ascertainments

Genes/Study	Ascertainment	Analysis method	Relative risk	95% Confidence interval
BRCA1				
Ford *et al.*, 1994 (1)	33 families with evidence of linkage to *BRCA1*	Prostate cancer incidence compared with population-specific rates	3.33	1.78–6.20
Brose *et al.*, 2002 (12)	147 families with a *BRCA1* mutation seen in a risk evaluation clinic	Prostate cancer incidence compared with population-specific rates	0.39	0.09–0.68
Thompson *et al.*, 2002 (13)	699 families with a documented *BRCA1* mutation	Prostate cancer incidence compared with population-specific rates	1.07	0.75–1.54
BRCA2				
BCLC[a] 1999 (2)	173 families selected for linkage analysis with a demonstrated *BRCA2* mutation	Prostate cancer incidence compared with population-specific rates	4.65	3.48–6.22
Sigurdsson *et al.*, 1997 (4)	16 families in which a woman with breast cancer was demonstrated to have the Icelandic founder mutation 999del5 in *BRCA2*	Prostate cancer incidence in first-degree relatives of case patients compared with population-specific incidence	4.6	1.9–8.8
BRCA1 and *BRCA2*				
Warner *et al.*, 1999 (5)	48 Ashkenazi Jewish breast cancer patients with a founder mutation in *BRCA1* or *BRCA2*	Prostate cancer incidence in 1st degree relatives compared with incidence in 1st degree relatives of healthy controls	3.36	1.49–7.56

[a] BCLC, Breast Cancer Linkage Consortium.

tate cancer, leading to an over representation of the 6174delT allele in our largely prevalent cohort. Such an effect, as has been observed in *BRCA*-associated ovarian cancer (21–23), requires confirmation through prospective studies.

Another possible bias in our series could have occurred because the Washington Ashkenazi study was not population based but rather was composed of volunteers somewhat enriched for familial cancer history. If the frequency of founder mutations in unaffected individuals in the Washington Ashkenazi Study was different than the population frequency in Ashkenazi individuals in the greater New York area, this could have resulted in an over- or underestimation of the impact of *BRCA* mutations on prostate cancer risk. We believe this is unlikely because the founder mutation frequency seen in the Washington Ashkenazi Study is consistent with other large series of Ashkenazi individuals from both the greater New York area and other regions of the United States (24, 25).

Different methodologies were used for genotyping cases and controls. This theoretically could have introduced a bias in favor of a significant finding if the genotyping method for cases was more sensitive than the method used for controls. We believe this is unlikely, however, because the restriction site analysis used to genotype the cases and the allele-specific oligonucleotide assay used to genotype the controls have both been

Table 3 Incidence of founder *BRCA1* or *BRCA2* mutations in unselected series of Jewish patients with prostate cancer

Authors	*N*	Comparison group	Frequency of *BRCA* mutations in cases	Association of *BRCA* mutation and prostate cancer risk
Lehrer *et al.*, 1998 (7)[a]	60	268 Ashkenazi Jewish women with sporadic breast cancer	0 (0%) *BRCA1* 0 (0%) *BRCA2*	No
Nastiuk *et al.*, 1999 (8)[a]	83	Reported population incidence	1 (1.2%) *BRCA1* 2 (2.4%) *BRCA2*	No
Hubert *et al.*, 1999 (9)[a]	87	87 Ashkenazi Jewish men without prostate cancer	2 (2.3%) *BRCA1* 1 (1.1%) *BRCA2*	No
Vazina *et al.*, 2000 (10)	174	Reported population incidence	4 (2.3%) *BRCA1* 1 (0.6%) *BRCA2*	No
Giusti *et al.*, 2003 (11)	940	472 Ashkenazi Jewish men without prostate cancer	16 (1.7%) *BRCA1* 14 (1.5%) *BRCA2*	*BRCA1*-No[b] *BRCA2*-No

[a] Analysis limited to 185delAG mutation in *BRCA1* and 6174delT mutation in *BRCA2*.

[b] When control population was combined with 872 controls from the United States, presence of the 185delAG mutation in *BRCA1* was associated with an increased risk of prostate cancer. (odds ratio, 2.52; 95% confidence interval, 1.05–6.04).

shown in other studies to have a sensitivity for detecting the Ashkenazi founder mutations comparable with that of sequencing (22, 26, 27).

These results provide evidence that deleterious mutations in *BRCA2* are associated with an increased risk of prostate cancer. Current recommendations for male carriers of *BRCA* mutations include prostate cancer screening with digital rectal examination and serum prostate-specific antigen level annually beginning at age 50 years (28). Whereas there was no significantly increased risk for early-onset prostate cancer in this series, this finding requires confirmation in a larger cohort. Additional family-based studies may also help clarify the relative penetrance of *BRCA2* mutations for prostate cancer. Additionally, because a substantial proportion of familial prostate cancer is not linked to mutations in *BRCA1* and *BRCA2*, the search for other major prostate cancer predisposition genes will remain a high priority.

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Incidence of Ovarian Cancer in *BRCA*-Negative Hereditary Breast Cancer Families

Noah D. Kauff[1,4], Tessa Cigler[1], Karen E. Hurley[1,3], Helen Huang[1], Hannah Rapaport[1], Eve Wadsworth[1], Mark E. Robson[1,2], Larry Norton[2], Richard R. Barakat[4], Kenneth Offit[1]

[1]Clinical Genetics Service and [2]Breast Cancer Medicine Service, Department of Medicine, [3]Department of Psychiatry and Behavioral Sciences, and [4]Gynecology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

BACKGROUND: Mutations in *BRCA1* and *BRCA2* account for the majority of hereditary breast/ovarian cancer (HBOC) and half of hereditary breast cancer (HBC). Sequence analysis, however, is known to be incompletely sensitive for detecting *BRCA* mutations associated with HBOC/HBC. Because of this, many centers recommend consideration of ovarian cancer risk-reduction strategies in *BRCA*-negative individuals with a strong family history of breast cancer. Limited data is available regarding the actual risk of ovarian cancer in these individuals.

METHODS: Pedigrees from all women who underwent *BRCA* mutation testing at the Clinical Genetics Service at MSKCC from 8/1/96 through 7/31/02 and consented to prospective follow-up were reviewed. 285 individuals who 1) had no deleterious *BRCA* mutation on either founder mutation testing or full sequencing; and 2) whose family history included ≥3 breast cancers in a single lineage with one being diagnosed at ≤50 were identified and sent a structured questionnaire asking about occurrence of new cancer. Number of cancers expected was calculated from the SEER database for 1975–2000 and the Connecticut Tumor Registry Study of Multiple Primary Cancers. Observed versus expected cancers were compared using the Exact Poisson Test.

RESULTS: 171 (60%) individuals returned a questionnaire. At baseline, 77% had a personal history of breast cancer and a mean of 4.2 breast cancers in the kindred. 22 kindreds also had ≥1 individual with ovarian cancer. During a mean 3.6 years follow-up, a single fallopian tube cancer was reported in an individual with a *BRCA1* variant of uncertain significance. When the 11 patients with such variants were excluded, 8 breast, 4 non-melanoma skin, and one each of lymphoma, CML, uterine sarcoma and thyroid cancer were reported during 567 women years of follow-up. Breast cancer was seen significantly more than expected (8 vs 3.9 cases; p = 0.045). No ovarian cancers were observed vs 0.25 expected (p=0.78).

CONCLUSIONS: Individuals from HBC kindreds without a demonstrable *BRCA* mutation did not have an increased risk of ovarian cancer. If confirmed, these findings may have important implications for cancer screening in such kindreds.

Introduction

- Mutations in *BRCA1* and *BRCA2* account for greater than 95% of hereditary breast and ovarian cancer families and approximately 50% of site specific hereditary breast families.[1,2]
- Sequenced based mutation detection approaches, however, will only detect deleterious BRCA mutations in approximately 63–85% of families whose cancer predisposition demonstrate linkage to either the *BRCA1* or *BRCA2* loci.[3,4]
- Because of incomplete sensitivity of *BRCA* mutation testing, many centers recommend consideration of ovarian cancer screening or other risk-reduction strategies for women from hereditary breast cancer families who have not had a deleterious mutation identified.
- In order to clarify this issue, we undertook a pilot study to prospectively evaluate the incidence of both breast and ovarian cancer in a large series of women from hereditary breast cancer families in which no deleterious *BRCA1* or *BRCA2* mutation was identified.

Methods

- Pedigrees from all women who underwent *BRCA* mutation testing from 8/1/1996 through 7/31/02 and consented to prospective follow-up were reviewed.
- Probands were eligible for analysis if:
  - Proband did not have a personal history of ovarian cancer.
  - Family history included ≥3 breast cancers in a single lineage with at least one of the breast cancer occurring prior to 50 years of age.
  - No deleterious mutation was identified on full sequence analysis of both *BRCA1* and *BRCA2*. For patients without any non-Ashkenazi heritage, negative testing for the three common founder mutations was sufficient.
- 285 individuals that met eligibility criteria were sent a structured questionnaire that ascertained incidence of new cancers. Expected number of cancers was calculated from the Seer database for 1975–2000 and the Connecticut Tumor Registry Study of Multiple Primary Cancers.
- Observed vs. expected numbers of cancers were compared using the Exact Poisson Test.

Results

- 171 (60%) individual returned a questionnaire. Demographics of the study cohort are outlined in Table 1.

Table 1. Cohort Demographics

	n = 171
Mean Age at Results (range)	51.0 (21.7–87.5)
Mean Follow-up in Months (range)	42.9 (14.4–81.4)
Personal History of Breast Cancer	131 (76.6%)
Mean Number of Breast Cancers in Kindred (range)	4.2 (3–9)
Kindreds with Ovarian Cancer in Lineage	22 (12.9%)
Kindreds with Variant of Uncertain Significance	11 (6.4%)

New Cancers

- A single fallopian tube cancer was diagnosed in a woman with a *BRCA1* variant of uncertain significance 36 months after receiving results.
- When the 11 patient with variants of uncertain significance were excluded, 8 breast cancers, 4 non-melanoma skin cancers, and one each of endometrial stromal sarcoma, CML, lymphoma and thyroid cancer was reported during 567 women years of follow-up.

Incidence of Ob… vs. Expected Ca…

- Incidence of breast and ovarian cancer observed vs. expected from SEER
  - 8 cases of breast cancer observed vs. 1.37 expected ($p < 0.001$)
  - 0 cases of ovarian/fallopian tube cancer vs. 0.14 expected ($p = 0.87$)
- After correcting for the increased expected incidence of second cancers using data from the Connecticut Tumor Registry Study of Multiple Primary Cancers:
  - 8 cases of breast cancer observed vs. 3.9 expected ($p = 0.045$)
  - 0 cases of ovarian cancer observed vs. 0.25 expected ($p = 0.78$)
- Limiting the analysis to the 140 families with site specific breast cancer (no ovarian cancer in the lineage):
  - 7 cases of breast cancer observed vs. 3.33 expected ($p = 0.05$)
  - 0 cases of ovarian cancer observed vs. 0.21 expected ($p = 0.81$)

Conclusions

- In this pilot analysis, individuals from *BRCA*-negative hereditary breast cancer families did not have an increased risk of ovarian cancer.
- Even after accounting for increased risk conferred by a personal history of breast cancer, *BRCA*-negative members of hereditary breast cancer families have an increased risk of breast cancer compared to population derived rates.
- If these results are confirmed in larger studies, these findings may have important implications for cancer screening in such kindreds.

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