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Environmental and Lifestyle Influences on Breast Cancer Risk: Clues from Women with Inherited Mutations in BRCA1 and BRCA2

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This project aims to identify potentially preventable environmental influences on breast and ovarian cancer by focusing on a population of women with genetically inherited predisposition to the disease. This is an extension of our ongoing research into the genetics of breast and ovarian cancer among Jewish women in the New York City area. The IDEA project centered on female relatives of breast cancer patients with confirmed mutations in BRCA1 or BRCA2. Each relative provided a blood sample for mutation testing and completed an extensive questionnaire addressing epidemiologic factors in breast cancer risk. Among participants, inherited mutations in BRCA1 and BRCA2 were more frequent in women with a younger breast cancer diagnosis and in women with a breast and/or ovarian cancer family history. Breast cancer risks increased over time among women with mutations, suggesting the influence of environmental factors. The experiences and exposures of women with mutations who did and did not develop breast or ovarian cancer were compared to identify factors that ameliorate or exacerbate risk in this high-risk group. These risk factors may be generalized to women without inherited vulnerability to breast or ovarian cancer, as inherited cancer is virtually indistinguishable, clinically and biologically, from its noninherited counterpart.
DAMD17-98-1-8257

FINAL REPORT

ENVIRONMENTAL AND LIFESTYLE INFLUENCES ON BREAST CANCER RISK: CLUES FROM WOMEN WITH INHERITED MUTATIONS IN BRCA1 AND BRCA2

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INTRODUCTION

Women with inherited disease-associated mutations in BRCA1 or BRCA2 have significantly elevated risks of breast cancer and of ovarian cancer. However, not all women with inherited BRCA1 or BRCA2 mutations develop breast or ovarian cancer, and among those who do, ages at cancer onset vary widely, even within the same family. If a woman with a BRCA1 or BRCA2 predisposing mutation remains free of breast and ovarian cancer for many years, it is possible that her status is due to chance, to modifying genes segregating in some families or to environmental factors that influence risk. In this project, we evaluate environmental and lifestyle factors that could influence the penetrance of mutations in BRCA1 and BRCA2. It is possible that risk factors identified among genetically predisposed women may be generalized to women who have not inherited vulnerability to breast or ovarian cancer, because clinically and biologically, inherited cancer is virtually indistinguishable from its far more common, non-inherited counterpart.

BODY OF REPORT

Task 1. Send letters to eligible relatives explaining the study and inviting them to pre-test counseling.

Task 2. Provide pre-test counseling to relatives, administer informed consent and release forms for hospital records, obtain completed epidemiologic questionnaires and send blood samples to the University of Washington for mutation analysis.

Task 3. Maintain a database of contacts for participants and for those who decline participation after pre-test counseling.

By the end of the granting period (August 31, 2001), the study completed the enrollment of eligible probands. The probands comprise 1021 incident breast cancer patients of Jewish ancestry diagnosed at any of 12 cancer centers in the greater New York area: Albert Einstein Medical Center, Beth Israel Medical Center, Columbia Presbyterian Medical Center, Hackensack University Medical Center, Greerich Hospital, Memorial Sloan-Kettering Cancer Center, New York University Medical Center, North Shore University Hospital, Stamford Hospital, Strang Cancer Prevention Center, White Plains Hospital Center and Englewood-Mount Sinai Medical Center.

Each patient eligible to participate was offered pre-test genetic counseling and testing for inherited predisposition due to any of three ancient BRCA1 and BRCA2 mutations (BRCA1 185delAG, BRCA1 5382insC, BRCA2 6174delT). Each eligible patient who chose to participate provided information about her family history of breast cancer, completed the Environmental Factors Questionnaire and provided a blood sample for DNA isolation. Our study coordinator,
board-certified Genetic Counselor Jessica Mandell, M.S., supervised completion of Tasks 1, 2 and 3 at each of the collaborating sites.

For each proband identified with a BRCA1 or BRCA2 mutation, all adult relatives, regardless of cancer history, were offered the opportunity to participate in the project. Jessica Mandell provided pre-test genetic counseling for each of these relatives. Each relative who agreed to participate completed the Environmental Factors Questionnaire and provided a blood sample. Thus far, 340 living relatives from families with BRCA1 or BRCA2 mutations have been enrolled and genotyped. Based on family structure, genotypes from these 340 relatives also yielded information about 673 deceased relatives in mutation positive families. Analyses of relatives therefore include 1013 (340 + 673) relatives for whom BRCA1 and BRCA2 genotypes are known.

**Task 4. Genotype blood samples from participants for relevant mutations in BRCA1 and BRCA2.**

In our laboratory at the University of Washington, BRCA1 and BRCA2 were genotyped in each participant for three founder mutations known to be common in the Jewish population. Of our 1021 probands, 11 were enrolled at their special request despite not meeting our precise criteria for date of diagnosis and two withdrew without providing DNA. These 13 probands and their families are excluded from the analyses that follow. Frequencies of each mutation, by age of proband at diagnosis, are shown in Table 1.

**Table 1. Proportion of NYBCS probands with BRCA1 and BRCA2 mutations, by age at diagnosis of breast cancer.**

<table>
<thead>
<tr>
<th>Proband age at diagnosis of breast cancer</th>
<th>Number of probands</th>
<th>BRCA1 185delAG</th>
<th>BRCA1 5382insC</th>
<th>BRCA2 6174delT</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>33</td>
<td>0.15</td>
<td>0.12</td>
<td>0.09</td>
<td>0.36</td>
</tr>
<tr>
<td>35-39</td>
<td>72</td>
<td>0.11</td>
<td>0.13</td>
<td>0.11</td>
<td>0.35</td>
</tr>
<tr>
<td>40-44</td>
<td>135</td>
<td>0.08</td>
<td>0.01</td>
<td>0.07</td>
<td>0.16</td>
</tr>
<tr>
<td>45-49</td>
<td>187</td>
<td>0.05</td>
<td>0.01</td>
<td>0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>50-59</td>
<td>305</td>
<td>0.02</td>
<td>0.03</td>
<td>0.02</td>
<td>0.07</td>
</tr>
<tr>
<td>60+</td>
<td>276</td>
<td>0.004</td>
<td>0.004</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Total</td>
<td>1008*</td>
<td>0.042</td>
<td>0.024</td>
<td>0.037</td>
<td>0.102</td>
</tr>
</tbody>
</table>

*Of our 1021 probands, 11 were enrolled at their special request despite not meeting criteria for date of diagnosis; two others withdrew without providing DNA. These 13 probands were not included in this or subsequent tables.
In addition, pedigrees provided by each proband were used to assess whether the presence of a family history of breast and ovarian cancer was related to the likelihood of the proband carrying a founder BRCA mutation. The relationship between family history of cancer and the presence of mutations in the probands is shown in Table 2.

Table 2. Proportion of NYBCS probands with BRCA1 and BRCA2 mutations, by family history of breast or ovarian cancer.

<table>
<thead>
<tr>
<th>Family History*</th>
<th>Number of probands</th>
<th>BRCA1 185delAG</th>
<th>BRCA1 5382insC</th>
<th>BRCA2 6174delT</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1008</td>
<td>0.042</td>
<td>0.024</td>
<td>0.037</td>
<td>0.102</td>
</tr>
<tr>
<td>Breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother or Sister</td>
<td>315</td>
<td>0.06</td>
<td>0.03</td>
<td>0.05</td>
<td>0.14</td>
</tr>
<tr>
<td>Grandmother or Aunt</td>
<td>348</td>
<td>0.06</td>
<td>0.03</td>
<td>0.04</td>
<td>0.12</td>
</tr>
<tr>
<td>Any male relative</td>
<td>21</td>
<td>0.10</td>
<td>0</td>
<td>0.14</td>
<td>0.24</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother or Sister</td>
<td>50</td>
<td>0.20</td>
<td>0.08</td>
<td>0.04</td>
<td>0.32</td>
</tr>
<tr>
<td>Grandmother or Aunt</td>
<td>60</td>
<td>0.17</td>
<td>0.03</td>
<td>0.03</td>
<td>0.23</td>
</tr>
<tr>
<td>No breast/ovarian cancer in Mother or Sister</td>
<td>658</td>
<td>0.02</td>
<td>0.02</td>
<td>0.03</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*Probands may be in more than one category, depending on family history

Task 5. Report results of studies to patients as part of post-test genetic counseling.

Results of our genetic testing were reported to all probands in the context of post-test genetic counseling at their original cancer centers. Results were reported to each participating relative in the context of post-test genetic counseling by Jessica Mandell, at a time and place convenient for the relative. Medical referrals for relatives with BRCA1 or BRCA2 mutations were arranged by Ms. Mandell through local cancer centers.

Task 6. Enter responses from questionnaires for use in analysis.

This task has been carried out by Ming Lee, biostatistics coordinator for the project at the University of Washington, for all 1021 probands and 340 relatives.
Task 7. Carry out statistical analyses of associations of epidemiologic risk factors and breast cancer incidence among mutation carriers and (for comparison) relatives not carrying mutations. These analyses are in progress by Dr. King and Dr. Lee.

The evaluation of environmental exposures among all relatives carrying a predisposing BRCA mutation examines gene-environment interaction. A powerful approach is to compare cumulative incidence of breast cancer by age among female mutation carriers with and without a specified risk factor. The project enrolled adequate participants to provide statistical power at beta = .8 for most comparisons. Data from 1008 probands and their families are being assessed for the following:

Lifetime risk of breast cancer, by mutation status
Lifetime risk of ovarian cancer, by mutation status
Association of weight and physical activity as a teenager with breast cancer incidence among women with mutations
Association of age at menarche, first birth and menopause with breast cancer incidence among women with mutations
Association of hormone replacement therapy with breast cancer incidence among women with mutations
Association of oral contraceptive use with breast cancer incidence among women with mutations
Association of breastfeeding with breast cancer incidence among women with mutations
Association of exposure to cigarette smoke (either smoking history or indirect exposure) with breast cancer incidence among women with mutations
Association of alcohol consumption with breast cancer incidence among women with mutations
Association of medical x-ray exposure and occupational exposure to radiation with breast cancer incidence among women with mutations
Association of occupational or household exposure to pesticides with breast cancer incidence among women with mutations

Analysis of the first 861 probands and their families was presented on October 5, 2000 as a special “late-breaking session” of the 50th Annual Meeting of the American Society of Human Genetics in Philadelphia, Pennsylvania. The abstract from this presentation was published in the American Journal of Human Genetics in January, 2001 (see Appendix 1). The following information summarizes these published results. This data was also presented on November 3, 2000 at the National Society of Genetic Counselors 19th Annual Education Conference in Atlanta, Georgia (see Appendix 2).
Breast and Ovarian Cancer Risk

For all women in families with mutations, the risks of developing breast and ovarian cancer were determined using life table methods. Only relatives with known mutations were included in this analysis. Risk of breast cancer was very high among mutation carriers: risk by age 40 was .19 (.16-.22), by age 50 was .35 (.31-.39), by age 60 was .53 (.48-.58), by age 70 was .68 (.63-.73) and by age 80 was .82 (.77-.87).

Separate analysis was performed on the three founder BRCA mutations to assess possible variation in breast cancer risk. There was no statistically significant difference in lifetime risk for breast cancer between the BRCA1 and BRCA2 mutations.

To assess possible self-selection of participants and hence possible bias in estimates of risk, analyses of lifetime breast cancer risks were carried out in three ways (proband were excluded from all analyses). (1) All female relatives with BRCA1 or BRCA2 mutations were evaluated. (2) All relatives except mothers were evaluated, to adjust for the possibility that patients with affected mothers were more likely to enter the study. (3) We evaluated only “low-incidence” families, that is, families without ovarian cancer and no more than one case of breast cancer in first or second degree relatives. All analyses revealed similar high penetrance of the BRCA1 and BRCA2 alleles.

Birth cohort of mutation carriers with breast cancer was used to evaluate the presence of modifying factors on cancer risk. Breast cancer risk increased significantly by birth cohort (P<.01): carriers born before 1940 had a 17% risk by age 45 and 38% risk by age 55 where carriers born after 1940 had risks of 47% and 69% at these ages. Higher age-specific risks among the younger cohort suggest that exposures to environmental and lifestyle factors may modify breast cancer risk as the prevalence of modifying factors has changed over time.

Risk of ovarian cancer increased with age among BRCA mutation carriers, particularly after age 40, suggesting a generally later age of onset than for the development of breast cancer. For relatives with BRCA1 mutations, ovarian cancer risk by age 40 was .01 (.00-.02), by age 50 was .20 (.16-.24), by age 60 was .40 (.34-.46) by age 70 was .47 (.41-.53) and by age 80 was .55 (.47-.62). For relatives with BRCA2 mutations, ovarian cancer risk was significantly lower (P=.02): by age 40, .02 (.00-.05); by age 50, .03 (.00-.05); by age 60, .09 (.03-.15); by age 70, .16 (.07-.24); and by age 80, .28 (.14-.41). Ovarian cancer risk did not vary by birth cohort.

Environmental Factors

Impacts of modifying factors on breast cancer risk were evaluated by Cox regression. Among the group of women with BRCA mutations, being of normal weight at menarche (RH=0.4,
P=.02) and being physically active in sports as a teenager (RH=0.6, P=.07) provided a protective effect on breast cancer development as an adult.

Mutation carriers who developed breast cancer after menopause and who used hormone replacement therapy showed a slightly higher risk of breast cancer (RH=1.3, P=.03). Risk was not influenced by age at menarche, age at first pregnancy, use of oral contraceptives, smoking, alcohol consumption, household or occupational exposure to radiation or chemicals, or genotype at the RAD51 promoter.

KEY RESEARCH ACCOMPLISHMENTS

- 1021 incident breast cancer patients of Jewish ancestry enrolled in our study, received genetic counseling, completed the Environmental Factors questionnaire and were genotyped for the three ancient Jewish BRCA1 and BRCA2 mutations. Proband enrollment has been completed.

- Genotypes have been reported back to all participants requesting this information in the context of post-test counseling.

- Among our probands, 103 carry one of the three ancient BRCA mutations.

- 340 relatives from these 103 families with BRCA1 or BRCA2 mutations have been enrolled and genotyped, yielding genetic information for a total of 1013 relatives, including those genotyped directly and their deceased parents and other relatives.

- Data from the first 861 probands and families has been analyzed to determine the risks of breast and ovarian cancer due to inherited BRCA1 and BRCA2 mutations and how these risks are modified by lifestyle and environmental factors. Risk of breast cancer was very high among mutation carriers: risk by age 40 was .19 (.16-.22), by age 60 was .53 (.48-.58) and by age 80 was .82 (.77-.87). Risks did not differ for BRCA1 vs. BRCA2 mutations. Risk of breast cancer among women with mutations is also increasing with time, suggesting the influence of environmental factors. Risk of ovarian cancer among women with mutations was high, particularly after age 40 and among women with BRCA1 mutations.

- Environmental Factors Questionnaires of probands and their relatives have been collected and are being encoded for statistical analysis. Software for statistical analysis has been developed. Modifying risk factors for 1008 participants are currently being evaluated using Cox regression.
REPORTABLE OUTCOMES

Reportable outcomes generated from the study, as of August 31, 2001:


Presentation at the National Society of Genetic Counselors 19th Annual Education Meeting in Atlanta, Georgia on November 3, 2000; abstract printed in meeting agenda

CONCLUSIONS

Among probands in this study, inherited founder mutations in BRCA1 and BRCA2 are more frequent in women with younger ages at breast cancer diagnosis and in women with a family history of breast and/or ovarian cancer. Lifetime risks of breast cancer due to BRCA mutations are high: by age 40, .19 (.16-.22); by age 60, .53 (.48-.58); and by age 80, .82 (.77-.87). Risks do not differ for BRCA1 vs. BRCA2 mutations. Lifetime risk of ovarian cancer among women with mutations are high, particularly after age 40 and among women with BRCA1 mutations. Risks of breast cancer are increasing with time among women with mutations, as among women generally, suggesting an influence of environmental modifying factors on breast cancer risk. Identifying these factors may be relevant to all women, as inherited cancer is virtually indistinguishable, clinically and biologically, from its non-inherited counterpart. In addition, modifying environmental factors may explain the variation in inherited breast cancer risk profiles across populations. Evaluation of the impact on breast cancer risk of environmental effects is ongoing.
REFERENCES


BIBLIOGRAPHY


LIST OF PERSONNEL

Kelly Owens, PhD, 1998-2001
Postdoctoral Research Geneticist

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Postdoctoral Research Geneticist

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Genetic Counselor

Ksenia Peters, MS, 1999-2001
Genetic Counselor

Nancy Hanson, MS, 2001
Genetic Counselor

Tiffany Dovey, Erica May, Alisha Miller, Stephanie Snook, Jenni Ross
Undergraduate assistants
Breast and ovarian cancer risks among women with BRCA1 and BRCA2 mutations in the New York Breast Cancer Study (NYBCS). The NYBCS Collaborative Group.

Introduction: The goals of the New York Breast Cancer Study are to determine risks of breast and ovarian cancer due to inherited mutations in BRCA1 and BRCA2 and how those risks are modified by other factors.

Study Design: Participants in the NYBCS are incident cases of primary invasive breast cancer, regardless of age at diagnosis or family history (FH), who were diagnosed at any of 11 cancer centers in the New York City area and who identified their ancestry as Jewish. After genetic counseling and informed consent, each participant provided a blood sample, FH, and questionnaire information. Sequencing for BRCA1 185delAG, BRCA1 5382insC, and BRCA2 6174delT was carried out at the Univ. of Washington, Seattle, using protocols certified by CLIA and NY State Department of Health. For each proband with a mutation, family members were genotyped. Genotypes of deceased relatives were determined from surviving relatives or from biopsy specimens. Risks of breast and ovarian cancer were determined using case-control methods. Only relatives of known mutation status were included in the analyses. Modifications of risks by other factors were evaluated by Cox regression. Because prevalences of many nongeneic risks factors have changed over time, all Cox regressions were adjusted for birth cohort.

Results: 816 probands and their families participated in the study. To evaluate possible ascertainment bias, FH of all respondents was compared to FH of a sample of eligible participants who declined participation. 23% of participants vs. 29% of refusal had a mother with breast cancer; 54% of participants vs. 76% of refusal had a maternal relative with breast cancer; 3% of participants vs. 0% refusal had a mother with ovarian cancer. Eligible women declined participation most frequently cited insurance discrimination as the reason.

Mutation prevalence. 10.2% of probands carried one of the 3 ancient mutations: 4.2% BRCA1 185delAG, 2.5% BRCA1 5382insC, 3.3% BRCA2 6174delT. Affected mothers and sisters of wildtype probands were also genotyped; no additional mutations were detected at these 3 sites. As expected, mutation prevalence was associated with age at diagnosis and FH: 45% of probands dx<35; 1.7% or probands dx ≥35; 33% of probands with FH of ovarian cancer; 25% of probands with FH of male breast cancer; 21% of probands with + relatives with breast cancer but no ovarian cancer; 7% of probands with no FH of breast or ovarian cancer.

Risks of breast cancer among female relatives with mutations (excluding probands). Risk of breast cancer by age 40 was .19 (.15-.22), by age 50 was .35 (.31-.39), by age 60 was .53 (.48-.56), by age 70 was .68 (.63-.73), and by age 80 was .82 (.77-.87); risks did not differ for BRCA1 vs. BRCA2 mutations. If mothers were excluded from analysis, risks to remaining female relatives with mutations were the same as those above. Among apparently "low-risk" families (0-1 case of breast cancer and no ovarian cancer among 1st or 2nd relatives), risk to relatives with mutations by age 50 was .36 (.30-.42) and by age 80 was .76 (.66-.86).

Breast cancer risk increased significantly by birth cohort (P<.01): among mutation carriers born before 1940, risk by age 45 was .17 and by age 55 was .38, whereas for those born after 1940, risk by age 45 was .47 and by age 55 was .69.

Risks of ovarian cancer. For relatives with BRCA1 mutations, ovarian cancer risk by age 40 was .01 (.00-.02), by age 50 was .20 (.16-.24), by age 60 was .40 (.34-.46), by age 70 was .47 (.41-.53), and by age 80 was .55 (.47-.62). For relatives with BRCA2 mutations, ovarian cancer risks were significantly lower (P=.02): by age 40, .02 (.00-.05); by age 50, .03 (.00-.05); by age 60, .09 (.03-.15); by age 70, .16 (.07-.24); and by age 80, .28 (.14-.41). Risk of ovarian cancer did not vary by birth cohort.

Modification or risk. No extrinsic factor completely precluded breast cancer among women with mutations, but some experiences led to older (or younger) distributions of ages at breast cancer onset. Protective factors included being of normal weight, rather than overweight, at menarche (RH=0.4, P=.02) and being active in sports as a teenager (RH=0.6, P=.07). Among this group of women with mutations, risk was not influenced by age at menarche, age at first pregnancy, oral contraceptive use, smoking, alcohol consumption (within the modest levels of this population), household or occupational exposure to radiation or chemicals, or genotype at the RAD51 promoter. Among mutation carriers who reached menopause before developing breast cancer, use of hormone replacement therapy slightly exacerbated risk (RH=1.3, P=.03). Prophylactic mastectomy and oophorectomy and tamoxifen use are the focus of other studies and were not evaluated here.

Conclusions: Risks of breast cancer among women with BRCA1 or BRCA2 mutations are increasing with time, as are risks of breast cancer among women generally. This trend suggests that environmental influences are important and may explain variation in inherited breast cancer risk profiles across populations. BRCA1 and BRCA2 families with low cancer incidence are explained by Mendelian chance, not by differences in risks among mutation carriers. Ovarian cancer risks are high, particularly after age 40 and among women with BRCA1 mutations.

J. Mandell, M.C. King, J. Marks, and The New York Breast Cancer Study Consortium
Sarah Lawrence College, Bronxville, New York

Despite high risks, not all women with inherited BRCA1 or BRCA2 mutations develop breast or ovarian cancer, and among those who do, age at cancer onset varies, even in the same family. Environmental exposures, life experiences and variation at other genes may be responsible for these differences in risk. Since 1995, Dr. Mary-Claire King from the University of Washington in Seattle and Sarah Lawrence College in New York have conducted the New York Breast Cancer Study, a multi-center epidemiological project investigating the genetic and environmental causes of breast/ovarian cancer in the Jewish population. For the first time, the study publicly reports results. Through 12 collaborating hospitals, over 800 Jewish women in the New York area with invasive breast cancer have received genetic counseling and testing for the three founder BRCA mutations (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2) and completed our detailed lifestyle and medical/family history questionnaire. Approximately 10% of probands, or 80 families, carry a founder BRCA mutation. Each carrier family has subsequently been enrolled and tested by the study, comprising 265 relatives across the United States and internationally. From this research data we will present the actual risk of breast/ovarian cancer by age in women with founder BRCA mutations; differences in environmental factors for women with mutations who develop breast/ovarian cancer vs. women with mutations who remain cancer free; the incidence of other cancers in carrier families; other BRCA mutations carried by women diagnosed with breast cancer having strong cancer family histories; reactions to the cancer genetic counseling process; and medical care decisions influenced by genetic test results. By integrating genetic counseling, epidemiology and molecular genetics, the goal of the study is to determine the genetic and environmental factors important in controlling breast/ovarian cancer and apply what is learned from New York families to the general population of American women.