Population Prevalence of First-Degree Family History of Breast and Ovarian Cancer in the United States: Implications for Genetic Testing[§]

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Abstract: *Background*: The U.S. Preventive Services Task Force (USPSTF) recommends that women whose family history is associated with an increased risk for deleterious mutations in BRCA1 or BRCA2 genes be referred for genetic counseling and evaluation.

Methods: Using data from the 2005 National Health Interview Survey, we examined the percentage of respondents in the U.S. population who report specific first-degree family history patterns and the percentage who reported they had received testing services.

Results: Overall, less than 1% of the general population (about 1.4 million persons) reported a family history of breast and ovarian cancers that would be appropriate for referral for genetic counseling and possible genetic testing for cancer susceptibility. Males comprised 40% of those with a positive specified family history. The number of persons who reported having had a genetic test for breast or ovarian cancer susceptibility was very small.

Conclusion: Very few of those eligible for testing actually report having been tested for breast or ovarian cancer susceptibility. Healthcare providers need opportunities to improve knowledge of genetics concepts and clear guidelines on the use of genetic cancer susceptibility tests.

Keywords: Breast cancer, family history, genetic testing, ovarian cancer.

INTRODUCTION

Carcinoma of the breast is the most common cancer in U.S. women (excluding skin cancer), and the second leading cause of cancer-related mortality. In 2008, it is estimated that 182,460 women will develop invasive breast cancer and 40,480 women will die of the disease [1]. Ovarian cancer is projected to account for 21,650 new cases and 15,520 deaths this year [1]. The etiology of breast and ovarian cancers is still poorly understood with known risk factors explaining only a small proportion of cases. Of women with breast cancer, approximately 5% to 10% have a mother or sister with breast cancer, and up to 20% have a family history that includes a first- or second-degree relative with breast cancer [2, 3]. Germline mutations in BRCA1 and BRCA2 have been associated with an increased risk for breast and/or ovarian cancers [4, 5].

Several characteristics are associated with an increased likelihood of BRCA mutations of clinical significance. These include breast cancer diagnosed at an early age, bilateral breast cancer, history of both breast and ovarian cancer, presence of breast cancer in one or more male family members, multiple cases of breast cancer in the family, both breast and ovarian cancer in the family, or one or more family members with two primary cases of breast and ovarian cancer [6, 7]. Genetic tests, commercially available since 1996, have been developed to identify individuals carrying a hereditary BRCA1/2 mutation that may be at increased risk for breast and/or ovarian cancers [6]. The U.S. Preventive Services Task Force (USPSTF) concluded that family history can be used to narrow the pool of people who could be considered for genetic testing and have specified that women who have specific family history patterns should be routinely referred for genetic counseling and evaluation [2].

Few population-based studies have examined the percentage of persons in the general population who have a positive family history of cancer, as defined by the USPSTF guidelines, that would make them eligible for genetic counseling and testing or the percentage of these eligible persons who have undergone genetic counseling and evaluation. Because women with specific family histories indicating that they are at increased risk should be routinely referred for genetic counseling and evaluations for testing for mutations in the BRCA breast and ovarian cancer susceptibility genes [8], we examined the percentage of respondents in the general U.S. population who report a first-degree family history of breast and/or ovarian cancer that falls into the specific USPSTF family history categories and the percentage who reported that they had subsequently received testing services. Assessments of the prevalence of first-degree family history of breast and ovarian cancer, that use high quality, population-based data can inform the monitoring of genetic testing

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for cancer susceptibility and contribute to public health efforts that rely upon assessments of family history to promote healthy behaviors [9, 10].

MATERIALS AND METHODOLOGY

The data used for analysis were obtained from the Cancer Control Module (CCTM) of the 2005 National Health Interview Survey (NHIS). The NHIS, which uses a multistage probability design, is an annual nationwide survey of approximately 38,000 households in the civilian, noninstitutionalized U.S. population. The CCTM was administered to a nationally representative sample of 31,428 adults. It assessed cancer-related health behaviors and screening as well as family history of cancer in first-degree relatives. Weights were used to adjust for differences in probability of selection, nonresponse, and post-stratification and to determine population-based estimates. The overall adult response rate in our sample was 69%.

Respondents were asked if any first-degree relatives (father, mother, sister, brother, daughter, or son) had breast or ovarian cancer and if the relative with cancer was younger than age 50 when diagnosed. Specific questions were:

- Biological father ever have cancer? What kind of cancer? Father <50 when diagnosed with breast cancer?
- Biological mother ever have cancer? What kind of cancer? Mother <50 when diagnosed with breast cancer? Mother <50 when diagnosed with ovarian cancer?
- Number of full brothers who ever had cancer? What kind of cancer? Number of brothers <50 when diagnosed with breast cancer?
- Number of full sisters who ever had cancer? What kind of cancer? Number of sisters <50 when diagnosed with breast cancer?
- Number of full sons who ever had cancer? What kind of cancer? Number of sons <50 when diagnosed with breast cancer?
- Number of full daughters who ever had cancer? What kind of cancer? Number of daughters <50 when diagnosed with breast cancer?

The USPSTF recently recommended that women whose family history is associated with an increased risk for deleterious mutations in BRCA1 or BRCA2 genes be referred for genetic counseling and evaluation for BRCA testing. Both maternal and paternal family histories are important [2]. For non-Ashkenazi Jewish women, these specific family history patterns are defined by the USPSTF as:

- two first-degree relatives with breast cancer, 1 of whom received the diagnosis at age 50 years or younger;
- a combination of 3 or more first- or second-degree relatives with breast cancer regardless of age at diagnosis;
- a combination of both breast and ovarian cancer among first- and second-degree relatives;
- a first-degree relative with bilateral breast cancer;
- a combination of 2 or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis;
- a first- or second-degree relative with both breast and ovarian cancer at any age; and
- a history of breast cancer in a male relative [2].

Because the clinical guidelines pertain to those currently unaffected by breast or ovarian cancer, data from 442 individuals who reported having breast cancer and 81 who reported having ovarian cancer were excluded from the analysis, leaving data from 30,915 respondents to be analyzed. SUDAAN 9 was used to determine the number of respondents that reported each family history pattern and, using appropriate weights, to estimate the proportion of the general population represented by this subpopulation. We also determined the number of respondents who reported having a genetic test for breast or ovarian cancer susceptibility and estimated the proportion of the general population represented.

RESULTS

The number of respondents who reported each specific family history pattern, along with their estimated proportion in the general population, is reported in Table **1**. Overall, less than 1% (about 1.4 million persons) of the general population reported a family history of breast and ovarian cancers that would indicate routine referral to a genetic counseling program and possible genetic testing for susceptibility. A family history of two first-degree relatives, with one relative diagnosed prior to age 50, was reported most often and comprised nearly 0.39% of the general population. Cases of both breast and ovarian cancer in a family were reported next often (0.22%), and breast and ovarian cancer in the same relative was reported next often at 0.14%. The remaining family history patterns combined comprised 0.13% of the general population. When stratified by age (<40 years, 40-59 years, 60+ years), female respondents with a family history were more likely to be 60 + years for most family history types (data not shown). This finding is most likely because respondents of older age have older relatives who are more susceptible to cancer. This age gradient was not observed for men.

Men comprised 40% (79/219) of those with a positive specified family history after weighting. This observation was consistent across most patterns of family history. An equivalent number of men and women reported a family history of male breast cancer.

Genetic testing was reported rarely among those who reported an eligible family history (data not shown). Overall, less than 2% (n=4) of those eligible reported having had a genetic test. These respondents fell into three family history patterns—two first-degree relatives with breast cancer with one younger than age 50 at diagnosis, breast and ovarian cancer in a first- or second-degree relative, and breast and ovarian cancer in the same relative at any age at diagnosis. Population estimates based on these few individuals would be highly unstable and, thus, are not reported. However, these data indicate that the number of people who have an eligible family history and subsequently participate in genetic testing for cancer susceptibility is quite small.

Table 1. Population Estimates of Family History Types Recommended for Routine Counseling for Genetic Testing, NHIS, 2005

Family History Type[1,2]	Females n	Males n	Sample n	Weighted Population Estimate[3]	Weighted Pop. (%)	Weighted 95% CI
2 first-degree relatives with breast cancer, 1 <50 years at diagnosis	76	42	118	835,790	0.39	0.32, 0.48
Breast and ovarian cancer in first- or second-degree relatives	53	25	78	476,297	0.22	0.17, 0.29
Breast and ovarian cancer in same relative, any age at diagnosis	31	15	46	299,523	0.14	0.10, 0.19
3+ first- or second-degree relatives with breast cancer, any age at diagnosis; 2+ first- or second-degree relatives with ovarian cancer, any age at diagnosis; and Breast cancer in male relative	29	18	47	286,596	0.13	0.10, 0.19
Total[4]	140	79	219	1,439,766	0.67	0.58, 0.78

[1]Includes male respondents.
[2]Family history as defined by USPSTF, although second-degree relatives not ascertained in these data. Bilateral breast cancer not assessed.
[3] Weighted to the 2000 U.S. standard population.
[4] Some respondents fall into more than one category of family history.

DISCUSSION

The estimates for the population prevalence of having at least one first-degree relative with breast or ovarian cancer based on 2005 NHIS data are 7.3% for breast and 1.6% for ovarian cancer (data not shown); these figures represent 15.7 million and 3.3 million people in the general population with family histories of breast and ovarian cancer, respectively. These estimates are in agreement with recently published data from the 2000 NHIS that reported the population prevalence of a family history of breast cancer as 7.7% and a family history of ovarian cancer as 1.8% [11]. This report presents an estimate of the number of persons in the general population who report a family history of breast and/or ovarian cancers that make them suitable for referral for routine counseling for genetic testing for susceptibility to breast and ovarian cancers. More than 1.4 million people in the United States report such a family history as specified by the USPSTF.

Although the clinical guidelines for the USPSTF recommendation focus on women, our analysis showed that significant numbers of men report family history patterns that also make them eligible for referral for routine counseling. The information from men's family histories can be of great consequence because this information may be critical for discerning possible cancer risk among their daughters [12, 13]. In addition mens' knowledge of their genetic status is important because there is evidence of increased risk of breast cancer to themselves [14] as well as increased risk of other cancers, including prostate, among BRCA2 carriers [15-18].

The findings in this report are subject to at least three limitations. First, only first-degree relatives could be assessed in these data. No information on second-degree relatives was collected. Second, bilateral breast cancer could not be assessed because the data do not allow for reporting of multiple primaries of the same cancer type. As a result of both of these limitations, we were able to only partially assess the prevalence of USPSTF family history categories. The estimates presented in this study therefore underestimate the population-based prevalence of family history patterns eligible for routine referral for genetic counseling and further evaluation. Indeed, the USPSTF estimates that 2% of adult US women have such family histories [2]. However, a recently published study found that 7.5% of a population-based sample of women, ascertained for first- *and* second-degree family history of breast and ovarian cancer, met USPSTF criteria for the indicted family histories [19]. Finally, family history is subject to recall bias. However, self-reported family history of breast cancer has been found to be relatively accurate [20-22], although there is often underestimation of cancer in second-degree relatives [22, 23] and in relatives from the father's side of the family [24]. Family history of ovarian cancer is not always reported accurately [20].

CONCLUSION

Few studies have gauged intent to pursue genetic testing in samples from the general population. An inverse relationship between family history and interest in testing has been reported in a primary care population [25]. Conversely, having any family history was associated with interest in testing among a group of women due for a mammogram [26]. However, interest does not always correlate with participation in testing. Prior studies have identified potential barriers to genetic testing for cancer susceptibility including worry, apprehension about possible test results, concern over the potential for genetic discrimination, loss of health insurance, or stigmatization or cost of testing [27, 28].

In the present study, very few of those eligible for testing actually reported having been tested for breast or ovarian cancer susceptibility. Overall, the uptake rate in our sample for genetic testing among those with an eligible family history was 4/219, or 1.8%. We were unable to determine if the low rate of uptake reflects disinterest in testing among respondents or rather lack of referral by physicians. However a national sample of U.S. physicians indicated that many physicians, particularly primary care physicians, feel inadequately qualified to counsel patients on genetic issues [29, 30]. As a result, many persons with an eligible family history of breast and/or ovarian cancer may have been denied appropriate follow-up for routine genetic counseling and testing. Physicians and other healthcare providers need to be supported with opportunities to improve knowledge of genetics concepts and provided clear guidelines on the use of genetic cancer susceptibility tests.

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