Hereditary Cancer-Associated Mutations in Women Diagnosed with Two Primary Cancers: An Opportunity to Identify Hereditary Cancer Syndromes after the First Cancer Diagnosis

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Key Words
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Abstract
Objectives: Patients with hereditary cancer syndromes are at high risk for a second primary cancer. Early identification of these patients after an initial cancer diagnosis is the key to implementing cancer risk-reducing strategies. Methods: A commercial laboratory database was searched for women with a history of both breast and ovarian or colorectal and endometrial cancer who underwent genetic testing for hereditary breast and ovarian cancer (HBOC) or Lynch syndrome (LS). Results: Among women with both breast and ovarian cancer, 22.4% (2,237/9,982) had a BRCA1 or BRCA2 mutation. Among women with both colorectal and ovarian cancer, 28.1% (264/941) had a mutation associated with LS. In 66.6% of BRCA1 or BRCA2 mutation carriers and in 58.3% of LS mutation carriers, >5 years passed between the cancer diagnoses. Of patients with HBOC and LS, 56 and 65.2%, respectively, met the National Comprehensive Cancer Network guidelines for hereditary cancer testing after their initial diagnosis based on their personal cancer history alone.

Conclusions: A substantial number of women tested for LS or HBOC after being diagnosed with two successive primary cancers were diagnosed with a hereditary cancer syndrome. In many cases, the time interval between the diagnoses was long enough to allow for the implementation of surveillance and/or prophylactic measures.

Introduction

Approximately 5–10% of all cancers occur in patients with hereditary cancer syndromes, over 50 of which have been described [1]. Two of the most common hereditary cancer syndromes are hereditary breast and ovarian cancer (HBOC) and Lynch syndrome (LS; also known as hereditary nonpolyposis colorectal cancer). Patients with hereditary cancer syndromes are at risk for additional malignancies following their first diagnosis [1], and, therefore, the identification of these patients is important in order to minimize their risk for a second cancer diagnosis.

It is estimated that 5–10% of all breast and ovarian cancers result from heritable mutations [2]. HBOC is caused by the most commonly inherited mutations, namely those in the breast cancer, early-onset 1 (BRCA1) and 2
(BRCA2) genes [1]. Patients with HBOC are frequently diagnosed with ovarian cancer, with up to 10% of all ovarian cancers resulting from mutations in BRCA1 or BRCA2 [3, 4]. Furthermore, there is an elevated risk for pancreatic cancer, prostate cancer, and melanoma [5, 6].

The risk for breast cancer in BRCA1 or BRCA2 mutation carriers is up to 87% at 70 years of age [7], while the risk for nonmutation carriers is only 8% [8]. Patients with HBOC are often diagnosed at a younger age than those with sporadic breast cancer, with the average age at diagnosis being 52 years of age [9, 10]. The average age of patients diagnosed with sporadic breast and ovarian cancer is 61 and 63 years of age in the general population, respectively [11].

LS results primarily from mutations in DNA mismatch repair genes, including MLH1, MSH2, MSH6, and PMS2 [12]. It accounts for 2–4% of all cases of colorectal cancer [13, 14] and for the majority of inherited endometrial cancers [15–17]. Several studies have indicated that women with LS may have an equal risk for colorectal and endometrial cancer and that patients may present first with either cancer [18–20]. These patients are also at an elevated risk for ovarian, gastric, hepatobiliary tract, and ureter cancer, as well as sebaceous adenoma or carcinoma [21, 22]. The lifetime risk for colorectal or endometrial cancer in the general population is 2 and 1.5% [23], respectively, as compared to 82% [19] and 71% [24] in patients with LS. Patients with LS are also more often diagnosed with cancer at an earlier age than those with sporadic colorectal or endometrial cancer. The average age of onset for colorectal cancer in patients with LS is 58 years [11], while the average age of onset for sporadic colorectal or endometrial cancer in those patients is 69 and 62 years, respectively [11].

Patients with hereditary cancer syndromes are at a much higher risk for being diagnosed with a second cancer than the general population. Such cancers can be synchronous or metachronous and in the same organ or in a distant organ. The risk for contralateral breast cancer in BRCA1 or BRCA2 mutation carriers is up to 64% at 70 years of age [25], compared with 2–11% for the general population [26]. Furthermore, the 10-year risk for contralateral breast cancer after a first diagnosis is 43.4% in BRCA1 mutation carriers [27] and an estimated 6% in the general population [28]. Patients diagnosed with cancer at a young age, as commonly occurs in HBOC, are at the highest risk for developing contralateral breast cancer [3, 29]. In addition to the risk for contralateral breast cancer, BRCA1 or BRCA2 mutation carriers also have an elevated risk for ovarian cancer [3, 4]. A large study estimated that, in patients with HBOC, the risk for developing ovarian cancer following primary breast cancer is between 6.8 and 12.7%, depending on mutation status, with BRCA1 carriers having the highest risk [30].

Patients with LS are also at risk for second primary cancer. A study in women diagnosed with two primary cancers found that 49% presented first with colorectal cancer and 51% with endometrial cancer [18]. In women presenting with colorectal cancer, the 20-year risk for endometrial cancer may be as high as 48% [31].

The current National Comprehensive Cancer Network (NCCN) guidelines recommend molecular genetic testing in individuals with a personal and/or family history consistent with HBOC or LS [3, 32]. With regard to personal cancer history, it is recommended that all patients with ovarian cancer should be tested for BRCA1 or BRCA2 mutations, in addition to those diagnosed with breast cancer before the age of 45 [3]. Genetic testing for LS is suggested for patients diagnosed with colorectal cancer or endometrial cancer before the age of 50 [32].

Newly developed risk assessment algorithms that are able to calculate the likelihood of hereditary cancer based on personal and family history are currently in use [33]. Starting in 2014, NCCN guidelines recommend screening for LS in patients scoring ≥5% risk on mutation models such as the PREMM1,2,6, which evaluates the risk for carrying a mutation in MLH1, MSH2, and MSH6 [32, 33].

This retrospective analysis focused on women diagnosed with at least two primary cancers who were tested for hereditary cancer mutations in order to determine the prevalence of mutation carriers and to examine the time interval between the two diagnoses. In addition, the number of women who would meet the current NCCN guidelines for genetic testing after their first cancer diagnosis was determined.

Materials and Methods

To collect patient records, a commercial laboratory database was queried for women with a personal history of both breast and ovarian cancer (HBOC query) or both colorectal and endometrial cancer (LS query) who underwent genetic testing. Patient information was obtained from the health care provider on the test order form. Information from test request forms included personal and family history, type of cancer, and age at cancer diagnoses. All patients included in the HBOC query were tested between September 2006 and October 2013 and had full sequencing of BRCA1 and BRCA2, and some patients also had large rearrangement testing of BRCA1 and BRCA2. The LS query included all patients who had full sequencing of MSH6 in addition to full sequencing and large rearrangement testing of MLH1 and MSH2 between May 2008 and
Some patients also had large rearrangement testing of MSH6 and EPCAM as well as full sequencing and large rearrangement testing of PMS2. Candidates were excluded from this retrospective study if they (1) were tested only for the Ashkenazi Jewish founder mutations in BRCA1 or BRCA2, (2) had single-gene testing for LS or HBOC, or (3) were tested for a previously identified familial HBOC or LS mutation. Patients with a second breast cancer or a second colorectal cancer were not queried due to the difficulty of distinguishing between a second primary cancer and a recurrence.

Mutation prevalence was established and patients carrying HBOC- or LS-associated mutations were stratified based on age at earliest cancer diagnosis. The time that elapsed between the first and the second diagnosis was established. The percentage of patients who would have met the 2012 or 2013 NCCN testing guidelines after the initial cancer diagnosis was also determined using patient cancer history. Patient family cancer history was not included in this analysis.

Results

HBOC Query

This analysis identified 9,982 patients diagnosed with both primary breast and ovarian cancer and 2,237 women (22.4%) with a mutation in either BRCA1 or BRCA2 or in both BRCA1 and BRCA2 (fig. 1). The majority had mutations in BRCA1 (fig. 2). Patients presenting with a first malignancy between 30 and 39 years of age were most likely to carry a mutation in BRCA1 or BRCA2 (35.8%), followed by those diagnosed between 40 and 49 years of age (30.6%; table 1).

Of the BRCA1 or BRCA2 mutation carriers, 67.5% were diagnosed first with breast cancer, 20.5% were diagnosed first with ovarian cancer, and 7.2% were diagnosed concurrently with both breast and ovarian cancer. Nearly 60% of BRCA1 or BRCA2 mutation carriers (1,323 of 2,237 patients) were diagnosed with either breast or ovarian cancer before the age of 50. Furthermore, over 50% of BRCA1 or BRCA2 patients with sentinel breast cancer were diagnosed before the age of 45 (794 of 1,510 pa-
Patients). 21.4% of patients presented with a second cancer within 5 years of the first diagnosis. For 66.6% of patients with HBOC, more than 5 years passed between the first and the second diagnosis (table 2).

LS Query
This query identified 941 patients with both colorectal and endometrial cancer, 264 (28.1%) of whom had a mutation in MLH1, MSH2, MSH6, PMS2, or MSH2 and EPCAM (fig. 3). The distribution of these mutations is shown in figure 4. Nearly half of all patients diagnosed with a first primary cancer between 40 and 49 years of age carried a hereditary LS-associated mutation (121 of 259; table 3).

Within the LS cohort, 69.7% of patients were diagnosed with colorectal or endometrial cancer before the age of 50 (184 of 264). The presenting cancer was colorectal in 38.3% of patients and endometrial in 47.7% of patients, and 9.5% were diagnosed concurrently with colorectal and endometrial cancer (fig. 4). Of patients presenting with colorectal cancer, 80.2% (81 of 101) were diagnosed before the age of 50. More than 5 years passed between the first and the second diagnosis in 58.3% of patients (table 4), while 27.7% of patients were diagnosed with a second cancer within 5 years of the original diagnosis.

Table 1. Age breakdown of patients with both breast and ovarian cancer by age at first cancer diagnosis

| Age at first diagnosis | Breast and ovarian cancer |
|------------------------|---------------------------|
|                        | patient count, n | BRCA-positive patients, n | positive rate, % |
| 0–9                    | 3               | 0                         | 0               |
| 10–19                  | 47              | 3                         | 6.4             |
| 20–29                  | 428             | 84                        | 19.6            |
| 30–39                  | 1,211           | 433                       | 35.8            |
| 40–49                  | 2,627           | 803                       | 30.6            |
| 50–59                  | 2,747           | 610                       | 22.2            |
| 60–69                  | 1,756           | 211                       | 12              |
| 70–79                  | 717             | 55                        | 7.7             |
| 80–89                  | 150             | 1                         | 0.7             |
| ≥90                    | 2               | 1                         | 50              |
| Not specifiedb         | 294             | 36                        | 12.2            |
| Total                  | 9,982           | 2,237                     | 22.4            |

a Artificially high positive rate due to small sample size.
b No age indicated for at least one cancer diagnosis.

Table 2. Interval between the first and the second cancer diagnosis in patients with HBOC

| Time between first and second diagnosis, years | Frequency, n (%) |
|-----------------------------------------------|------------------|
| 1                                             | 84 (3.8)         |
| 2–5                                           | 395 (17.7)       |
| 6–10                                          | 486 (21.7)       |
| 11–15                                         | 384 (17.2)       |
| 16–20                                         | 297 (13.3)       |
| >20                                           | 323 (14.4)       |
| Not specifieda                                | 106 (4.7)        |
| Synchronous diagnosis                        | 162 (7.2)        |
| Total                                         | 2,237            |

a No age indicated for at least one cancer diagnosis.
Comparison with Current Guidelines

Based on the current NCCN guidelines, 56% of the patients identified with mutations in BRCA1 or BRCA2 who were diagnosed with both breast and ovarian cancer would have met the criteria for genetic testing after their first cancer based on either the presence of ovarian or breast cancer before the age of 45 (35.5% diagnosed with breast cancer before the age of 45, and 20.5% diagnosed with ovarian cancer at any age). Considering the overall population of patients with both breast and ovarian cancer, 12.5% had a mutation and met the criteria after the first cancer diagnosis. Of the patients identified as LS mutation carriers, 65.2% would have met the current NCCN criteria for genetic testing based on the age of diagnosis of the initial cancer diagnosis (30.7% diagnosed with colorectal cancer and 34.5% with endometrial cancer before the age of 50). For this cohort of women with colorectal and endometrial cancer, 18.3% had an LS mutation and met the NCCN criteria for testing after their initial cancer diagnosis.

Discussion

This retrospective analysis demonstrates that a substantial number of women who present with a second primary breast, ovarian, colorectal, or endometrial cancer carry a genetic mutation associated with a heritable cancer syndrome. Furthermore, patients who met the current NCCN guidelines for HBOC [3] or LS [32] genetic testing after their initial cancer diagnosis make up a large portion of all patients within these cohorts. Of 9,982 patients with breast and ovarian cancer tested for BRCA1 or BRCA2, 12.5% had a mutation and met the current NCCN criteria after their first cancer diagnosis. Of 941 patients with endometrial and colorectal cancer tested for LS, 18.3% had a mutation and met the current NCCN criteria after their first cancer diagnosis. This study highlights the importance of identifying appropriate patients for genetic testing, as they may be able to...

**Table 3. Age breakdown of patients with both colorectal and endometrial cancer by age at first cancer diagnosis**

| Age at first diagnosis | Colorectal and endometrial cancer patient count, n | LS-positive patients, n | Positive rate, % |
|-----------------------|--------------------------------------------------|------------------------|-----------------|
| 10–19                 | 4                                                | 1                      | 25              |
| 20–29                 | 55                                               | 16                     | 29.1            |
| 30–39                 | 133                                              | 46                     | 34.6            |
| 40–49                 | 259                                              | 121                    | 46.7            |
| 50–59                 | 261                                              | 63                     | 24.1            |
| 60–69                 | 140                                              | 9                      | 6.4             |
| 70–79                 | 57                                               | 3                      | 5.3             |
| 80–89                 | 10                                               | 0                      | 0               |
| Not specifieda        | 22                                               | 5                      | 22.7            |
| Total                 | 941                                              | 264                    | 28.1            |

*a No age indicated for at least one cancer diagnosis.

**Table 4. Interval between first and second cancer diagnoses in patients with LS**

| Years between first and second diagnoses | Frequency, n (%) |
|-----------------------------------------|------------------|
| 1                                       | 20 (7.6)         |
| 2–5                                     | 53 (20.1)        |
| 6–10                                    | 57 (21.6)        |
| 11–15                                   | 52 (19.7)        |
| 16–20                                   | 23 (8.7)         |
| >20                                     | 22 (8.3)         |
| Not specifieda                          | 12 (4.5)         |
| Synchronous diagnosis                   | 25 (9.5)         |
| Total                                   | 264              |

*a No age indicated for at least one cancer diagnosis.
In conclusion, the results presented here reinforce the importance of identifying patients who are at risk for having hereditary cancer syndromes. In certain cases, patients are not tested due to a lack of awareness of hereditary cancer syndromes or a perceived difficulty of referral for genetic testing. Early identification of patients with hereditary cancer syndromes benefits all involved with the care and treatment of these patients. As recommended by the ASCO, taking a thorough cancer family history at the first oncology visit is the first step in identifying at-risk patients [41, 42]. A recent study evaluating the ASCO Quality Oncology Practice Initiative demonstrated that physicians participating in the program consistently obtain some first- and second-degree family histories from their patients, although a complete family cancer history is collected in less than 40% of patients. While 25.6% of patients were referred for genetic testing following an evaluation of the family history, only about 50% of patients were correctly identified as candidates for genetic testing [42]. The ASCO expert statement on the collection and use of a cancer family history for oncology providers highlights the importance of identifying patients with hereditary cancer syndromes so their risk for a second primary cancer can be taken into account during the development of a management plan [41].

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es, increased surveillance may lead to the early identification of a second cancer. When surveillance is not appropriate or effective, as in ovarian cancer, prophylactic surgery following the first cancer may significantly reduce the risk for a second cancer. As genetic testing is part of the standard of care with support of the NCCN guidelines, there is an opportunity to develop best practices to ensure that all patients who meet the guidelines are offered testing to identify additional at-risk patients.

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