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

Genetic testing · Neoplasms · Second primary cancer · Hereditary breast and ovarian cancer syndrome · Colorectal neoplasms · Hereditary nonpolyposis · Neoplastic syndromes

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.

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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 $\geq 5\%$ risk on mutation models such as the PREMM_{1,2,6}, 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

Fig. 1. Incidence of breast and ovarian cancer in patients with HBOC. Patients with *BRCA1/2* mutations were segregated based on the first cancer diagnosis. Patients presenting with breast cancer were further stratified based on age at diagnosis. dx = Diagnosis. ^a No age indicated for at least one cancer diagnosis.

October 2013. 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).

Fig. 2. Mutation distribution in patients with HBOC. Patients diagnosed with breast and ovarian cancer underwent genetic testing for mutations in *BRCA1* and *BRCA2*.

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-

Fig. 3. Incidence of colorectal and endometrial cancer in patients with LS. Patients with LS-associated mutations were segregated based on the first cancer diagnosis. Patients presenting with either colorectal cancer or endometrial cancer were further stratified based on age at diagnosis. dx = Diagnosis. ^a No age indicated for at least one cancer 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 ^a
Not specified ^b	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.

tients). 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

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 specified ^a	106 (4.7)
Synchronous diagnosis	162 (7.2)
Total	2,237

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

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.

Fig. 4. Mutation distribution in LS mutation carriers with two cancers. Patients diagnosed with colorectal and endometrial cancer underwent genetic testing for mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *MSH2/EPCAM*.

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

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 specified ^a	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 specified ^a	12 (4.5)
Synchronous diagnosis	25 (9.5)
Total	264

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

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

take measures to either reduce their risk for a second cancer or increase the likelihood of early detection of a second malignancy. The interval times between the first and the second cancer diagnosis in this study suggest that there is time to initiate surveillance or prophylactic measures.

Many of the women in the present analysis were diagnosed with breast cancer after the age of 45 but they may still have qualified for testing based on family history or triple negative status. It is especially important to survey women with HBOC after a breast cancer diagnosis because many of them will survive their breast cancer but remain at risk for ovarian cancer, which has a higher mortality rate. Furthermore, current screening protocols for ovarian cancer, including transvaginal ultrasound and monitoring of serum CA-125 concentration, lack sensitivity and specificity and do not reduce the overall risk for mortality [34]. Bilateral salpingo-oophorectomy has been well established as a successful method for the prevention of ovarian and fallopian tube cancers in *BRCA1* and *BRCA2* carriers. In addition to significantly reducing the risk for ovarian cancer [35], preventive oophorectomy may also reduce the risk for breast cancer by up to 56% in *BRCA1* mutation carriers and 46% in *BRCA2* carriers [36]. Patients with HBOC often undergo bilateral mastectomy as treatment for their breast cancer as it significantly reduces the risk for a second breast cancer [37]. This cohort also demonstrates a group of patients who could have benefited from prophylactic mastectomy after an ovarian cancer diagnosis as they survived ovarian cancer for a period of time that also put them at risk for breast cancer.

Surveillance and prophylactic surgery are the standard of care in patients with LS as they may reduce the associated morbidity and mortality [38, 39]. Regular colonoscopic screening every 1–3 years may decrease the risk for colorectal cancer by over 60% [38]. It is important that screening takes place at more frequent intervals in patients with LS because the progression to carcinoma is much more rapid, occurring in <5 years, while sporadic cancer usually develops over a period of 5–10 years [1, 40]. Results from the current study reinforce the importance of regular colonoscopic screening as 47.7% of patients in this study presented first with endometrial cancer, making them vulnerable to a later diagnosis of colorectal cancer. Furthermore, it reinforces the role of gynecologists and gynecologic oncologists in supporting genetic testing for patients with endometrial cancer, as nearly half of all patients with LS present first with a gynecologic cancer.

In this study, at least 5 years passed between the first and the second diagnosis in the majority of patients with a hereditary cancer syndrome. Of note, a 5-year remission is a common oncology mark after which a patient is considered cancer-free. The data presented here suggest that patients with hereditary cancer syndromes are still vulnerable to a second diagnosis after the 5-year mark. As noted above, this allows time to employ risk-reducing strategies, including increased surveillance or prophylactic surgery.

As all patient information was gathered from the test request form, the current study is reliant on the ordering physician for correct information regarding personal history, age of onset, and diagnosis. Family history was not factored into the analysis, which limited the number of patients who met the NCCN guidelines after their first cancer. Taking a conservative approach and excluding these patients suggests that the rate of second primary cancer in patients with HBOC or LS in clinical practice may actually be higher than reported in this study.

Despite the establishment of recommended guidelines for genetic testing by the NCCN and the American Society of Clinical Oncologists (ASCO), in many 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].

In conclusion, the results presented here reinforce the importance of identifying patients who are at risk for having hereditary cancer syndromes. In certain cas-

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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Disclosure Statement

All authors are salaried employees of Myriad Genetic Laboratories, Inc.

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