Germline loss-of-function *BRCA1* and *BRCA2* mutations and risk of *de novo* hematopoietic malignancies

Breast cancer susceptibility genes type one (*BRCA1*) and type two (*BRCA2*) encode tumor suppressor proteins involved in homologous recombination in response to DNA double-strand breaks.[1] Germline mutations resulting in loss of *BRCA1/2* function prevent cells from undergoing normal homologous recombination in the setting of double-strand breaks, leading to somatic DNA mutations that arise from alternative error-prone DNA repair mechanisms such as non-homologous end joining.[1] Germline loss-of-function mutations in *BRCA1* occur in about 0.07-0.09% of the population at birth, whereas *BRCA2* mutations occur in approximately 0.14-0.22%.[2,3] Development of hereditary breast cancer is strongly associated with these germline mutations, and the penetrance for breast cancer by the age of 80 is approximately 48% for carriers of *BRCA1* germline mutations and 74% for those with such alleles in *BRCA2*.[2,3] Similarly, the penetrance for ovarian cancer by the age of 80 is about 22% for carriers of deleterious germline variants in either *BRCA1* or *BRCA2*.[3]

The development of therapy-related myeloid neoplasms (t-MN), such as myelodysplastic syndrome and acute myeloid leukemia, as well as other hematopoietic malignancies (HM) is a well-recognized complication of the treatment of solid tumors, and they arise in approximately 2% of patients treated with cisplatin or olaparib.[4] Although some recent clinical trials of olaparib have reported lower rates of associated myelodysplastic syndrome/acute myeloid leukemia, data from the Federal Drug Administration pharmacovigilance program continue to suggest an increased risk.[5] Germline carriers of deleterious *BRCA1/2* variants treated with these agents are at a higher risk of developing a t-MN, and our group and others observe that about 20% of women who have been treated for breast cancer and subsequently develop a t-MN have deleterious germline variants in *BRCA1/2* or related genes.[6-8]

Double-strand break DNA repair pathways are also important to the pathogenesis of *de novo* myelodysplastic syndrome/acute myeloid leukemia and other HM. However, because most studies on germline risk for HM from germline *BRCA1/2* mutations have focused on t-MN, it is not known whether HM risk is conferred exclusively in the setting of therapy. Some previous studies did not find increased risks of *de novo* HM within patients carrying *BRCA* mutations; however, these cohorts were ascertained from patients and families primarily presenting with breast or ovarian cancers.[9] Despite this, there remains little work examining the role that *BRCA* mutations play in the subpopulation of patients and families who present with hereditary HM rather than solid organ malignancies. Therefore, we sought to determine the frequency and prevalence of germline *BRCA1/2* mutations in patients with *de novo* HM without a prior diagnosis of a solid organ malignancy and in the absence of prior cytotoxic treatment or radiotherapy. We identified patients at the University of Chicago diagnosed with a HM from February 2012 to October 2020, who were heterozygous for pathogenic (P) or likely pathogenic (LP) germline *BRCA1* or *BRCA2* variants. All of the patients had signed informed consent to research. We included patients with *de novo* HM as well as those with a t-MN, who served as a comparator group. Germline *BRCA1/2* testing criteria included a personal and family history of a HM as well as the National Comprehensive Cancer Network malignancy-specific guidelines for germline testing.[3] Testing for germline *BRCA1/2* variants was performed in a CLIA-certified clinical genomics laboratory using standard clinical protocols. Variants were interpreted as per American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines, with germline status of the *BRCA1/2* variant confirmed by DNA derived from cultured skin fibroblasts (*Online Supplementary Table S1*). The variants for the gnomAD control cohort were obtained through the web portal, for the gnomAD non-cancer population, version 3.1.2.[10] For the allele burden calculation, variants were considered damaging if they were known P, defined as having been deposited as P or LP into ClinVar, or were expected to result in clear loss-of-function by disrupting the protein product (e.g., large deletions, frameshifts). Variants with conflicting interpretations in ClinVar were included if the majority (>50%) of deposits were pathogenic. HM were assessed for acquired loss of heterozygosity (LoH) via clinical molecular profiling and next-generation sequencing as well as by clinical karyotyping/fluorescence *in situ* hybridization analysis for loss of chr17 (*BRCA1*) or chr13 (*BRCA2*), with copy number variations confirmed by chromosomal microarrays for those with available samples to avoid missing smaller chromosome rearrangements that could not be seen on clinical cytogenetic/fluorescence *in situ* hybridization analysis.

We identified 25 individuals with a diagnosis of a HM who also had deleterious germline *BRCA1* or *BRCA2* variants: 14 in *BRCA1*, and 11 in *BRCA2* (*Online Supplementary Table S1*). The patients' demographics and clinical findings are presented in Table 1, and the germline variants are detailed in *Online Supplementary Table S1*. The most common ethnic backgrounds were Western European (*BRCA1*; 7 [50%], *BRCA2*; 6 [55%]) and Ashkenazi Jewish (*BRCA1*; 4 [29%],

Table 1. Characteristics of patients carrying *BRCA1/2* mutations diagnosed with hematopoietic malignancies.

Patients' characteristics	*BRCA1*, N=14	*BRCA2*, N=11
Gender, N (%)[†]		
Female	10 (71)	7 (64)
Male	4 (29)	4 (36)
Ethnic background, N (%)		
Western European	7 (50)	6 (55)
Ashkenazi Jewish	4 (29)	1 (9)
Eastern European	2 (14)	1 (9)
Northern European	1 (7)	0 (0)
African American	0 (0)	1 (9)
Unknown	0 (0)	2 (18)
Age at first malignancy in yrs, median (range)[‡]	48.7 (20.1-74.6)	66.7 (36.6-74.4)
Age at first malignancy in yrs (HM *vs.* solid), median (range)		
HM as first diagnosis	49.5 (21.3-67.4)	47.3 (20.1-52.7)
Solid tumor as first diagnosis	63.4 (52.8-70.3)	66.9 (36.6-74.4)
Number of malignancies, N (%)		
1	3 (21)	6 (55)
2	8 (57)	4 (36)
3	3 (21)	1 (9)
Order of HM, N (%)		
HM diagnosed as first cancer	8 (57)	8 (73)
HM diagnosed after prior cancer	6 (43)	3 (27)
Type of malignancy, N (%)	N=28 total	N=17 total
Myeloid	11 (39)	6 (35)
Lymphoid	6 (21)	2 (12)
Multiple myeloma	0 (0)	4 (24)
Breast	7 (25)	1 (6)
Gynecological	2 (7)	0 (0)
Prostate	1 (4)	1 (6)
Colon	1 (4)	0 (0)
Melanoma	0 (0)	1 (6)
Thyroid	0 (0)	1 (6)
Bladder	0 (0)	1 (6)
Treatment received for solid malignancy, N (%)		
Chemotherapy	3 (21)	2 (18)
Radiation	2 (14)	2 (18)
Surgery	10 (71)	3 (27)
Treatment received for HM, N (%)		
Chemotherapy	14 (100)	11 (100)
Radiation	1 (7)	1 (9)
Autologous hematopoietic stem cell transplant	0 (0)	4 (36)
Allogeneic hematopoietic stem cell transplant	3 (21)	4 (27)

[†]χ^2 P=0.178 (NS) for gender difference between germline *BRCA1* and *BRCA2* mutation carriers. [‡]*t*-test P=0.014 for difference in age of first malignancy between germline *BRCA1* and *BRCA2* mutation carriers. yrs: years; HM: hematopoietic malignancy; NS: not statistically significant.

BRCA2; 1 [9%]). Contrary to the prevailing notion that individuals with P/LP *BRCA1/2* variants develop t-MN exclusively, eight (57%) of *BRCA1*-mutated and eight (73%) of *BRCA2*-mutated patients developed a HM as their first cancer. Several of these patients developed two (*BRCA1*: 8 [57%], *BRCA2*: 4 [36%]) or more than two (*BRCA1*: 3 [21%], *BRCA2*: 1 [9%]) independent malignancies, which included a range of diagnoses, both commonly associated (e.g., breast and prostate cancer) and not commonly associated (e.g., colon cancer) with *BRCA1/2* mutations. An allele burden represents a calculation of the relative frequency at which a mutated allele is found in a population with a phenotype of interest (e.g., HM) *versus* a control population (e.g., healthy gnomAD controls). Comparing the allele burden of probands with P or loss-of-function germline *BRCA* mutations who had a *de novo* HM diagnosis within the cohort of all patients with clinical panel-based testing for germline predisposition to a diagnosed HM over the

same time period within the overall University of Chicago cohort *versus* a non-cancer control population (gnomAD v.3.1.2, non-cancer), there is enrichment for P or loss-of-function *BRCA1* (OR=8.61, 95% CI: 4.00-18.51, *P*<0.0001) and *BRCA2* (OR=4.65, 95% CI: 2.29-9.43, *P*<0.0001) alleles (Table 2).

In the germline *BRCA1*-mutated patient cohort (n=14), eight developed a HM, either myeloid or lymphoid, as their first cancer diagnosis (Figure 1A). Subtypes included: chronic myeloid leukemia (n=1), myelodysplastic syndrome (n=1), systemic mastocytosis (n=1), Hodgkin lymphoma (n=1), acute lymphoblastic leukemia (n=1), diffuse large B-cell lymphoma (n=1), chronic lymphocytic leukemia (n=1), and follicular lymphoma (n=1). The average age at diagnosis of the first HM was 49.5 years (range, 21.3-67.4 years), compared to 63.4 years (range, 52.8-70.3 years) for the patients with deleterious germline *BRCA1* variants who developed a solid tumor malignancy first. Among the eight who developed a HM first, five went on to develop secondary solid malignancies, including breast (n=3), prostate (n=1), and colon (n=1) cancer, with two of these patients then developing a tertiary t-MN. The other six developed a solid tumor as their first cancer (Figure 1B). Subtypes included breast (n=4), ovarian (n=1), and Fallopian tube (n=1). All six of these patients went on to develop a secondary t-MN, with one patient developing a tertiary lymphoid neoplasm. Treatment received included: chemotherapy (17/33 treatment events, 52%), radiation (3/33 treatment events, 9%), allogeneic hematopoietic stem cell transplantation (3/33 treatment events, 9%), and surgery (3/33 treatment events, 9%). Within the overall University of Chicago cohort with clinical cancer predisposition testing and a HM, patients with deleterious germline *BRCA1* variants constituted 1.6% (17/1074) of overall HM diagnoses, 2% (11/544) of myeloid diagnoses, 1.6% (6/371) of lymphoid diagnoses, and no multiple myeloma diagnoses. In the *BRCA2* patient cohort (n=11), eight individuals developed a HM, either myeloid or lymphoid/multiple myeloma, as their first cancer diagnosis (Figure 1C). Subtypes included multiple myeloma (n=4), acute myeloid leukemia (n=3), and chronic lymphoytic leukemia (n=1). The average age of a HM diagnosis as the first cancer was 47.3 years (range, 20.1-52.7 years) *versus* 66.9 years (range, 36.6-74.4 years) for patients who developed a solid organ malignancy first. Among the eight patients who developed a HM as a first diagnosis, one subsequently developed prostate cancer and one developed therapy-related acute lymphocytic leukemia. The other three *BRCA2* patients developed a solid organ malignancy as their first cancer, including breast cancer (n=1), melanoma (n=1), and bladder cancer (n=1). The one patient with melanoma subsequently developed thyroid cancer, which was treated with radiation. All three of these patients eventually developed a t-MN. The treatments received in the *BRCA2* cohort included chemotherapy (13/26 treatment events, 50%), radiation (3/26 treatment events, 12%), autologous stem cell transplantation (4/26 treatment events, 15%), allogeneic stem cell transplantation (3/26 treatment events, 12%) and surgery (7/26 treatment events, 27%). Within the overall University of Chicago cohort with clinical cancer predisposition testing and a HM, patients with deleterious germline *BRCA2* variants accounted for 1.1% (12/1074) of overall HM, 1.1% (6/544) of myeloid diagnoses, 0.5% (2/371) of lymphoid diagnoses, and 1.8% (4/218) of multiple myeloma diagnoses.

Analysis of *BRCA1/2* within solid tumors arising in individuals with deleterious germline variants show LoH in 90% of *BRCA1*-associated breast cancer and 54% of *BRCA2*-associated breast tumors, functionally implicating the importance of the germline *BRCA* gene in tumor development.[11] We therefore tested for *BRCA1/2* LoH within leukemic cells

Table 2. Allele burden calculation for loss-of-function *BRCA1/2* variants and occurrence of primary *de novo* hematopoietic malignancies.

Probands with P/LoF† germline *BRCA* mutations with clinical panel testing for a first HM diagnosis		P/LoF† germline *BRCA* variants in a non-cancer gnomAD control population (v3.1.2)	Allele burden calculation		
			OR	95% CI	*P*
BRCA1	7 total variants‡	112 total variants	8.61	4.00-18.51	<0.0001
	1,074 total tests	147,895 total alleles*			
BRCA2	8 total variants	237 total variants¶	4.65	2.29-9.43	<0.0001
	1,074 total tests	147,870 total alleles*			
Total	15 total variants	-	-	-	-
	1,074 total tests	-			

†Pathogenicity was assessed as per ClinVar deposit, conflicting reports included if majority deposits were pathogenic or likely pathogenic; if no ClinVar deposition, clear loss-of-function protein damaging insertions or deletions were included. ‡One patient excluded due to non-proband status/research initiated testing. *Represents the average of total allele numbers reported per variant. ¶Excludes the *BRCA2* p.Lys3326Ter variant reported as benign in ClinVar. P: pathogenic; LoF: loss-of-function; HM: hematopoietic malignancy; gnomAD: Genome Aggregation Database; OR: odds ratio; CI: confidence interval.

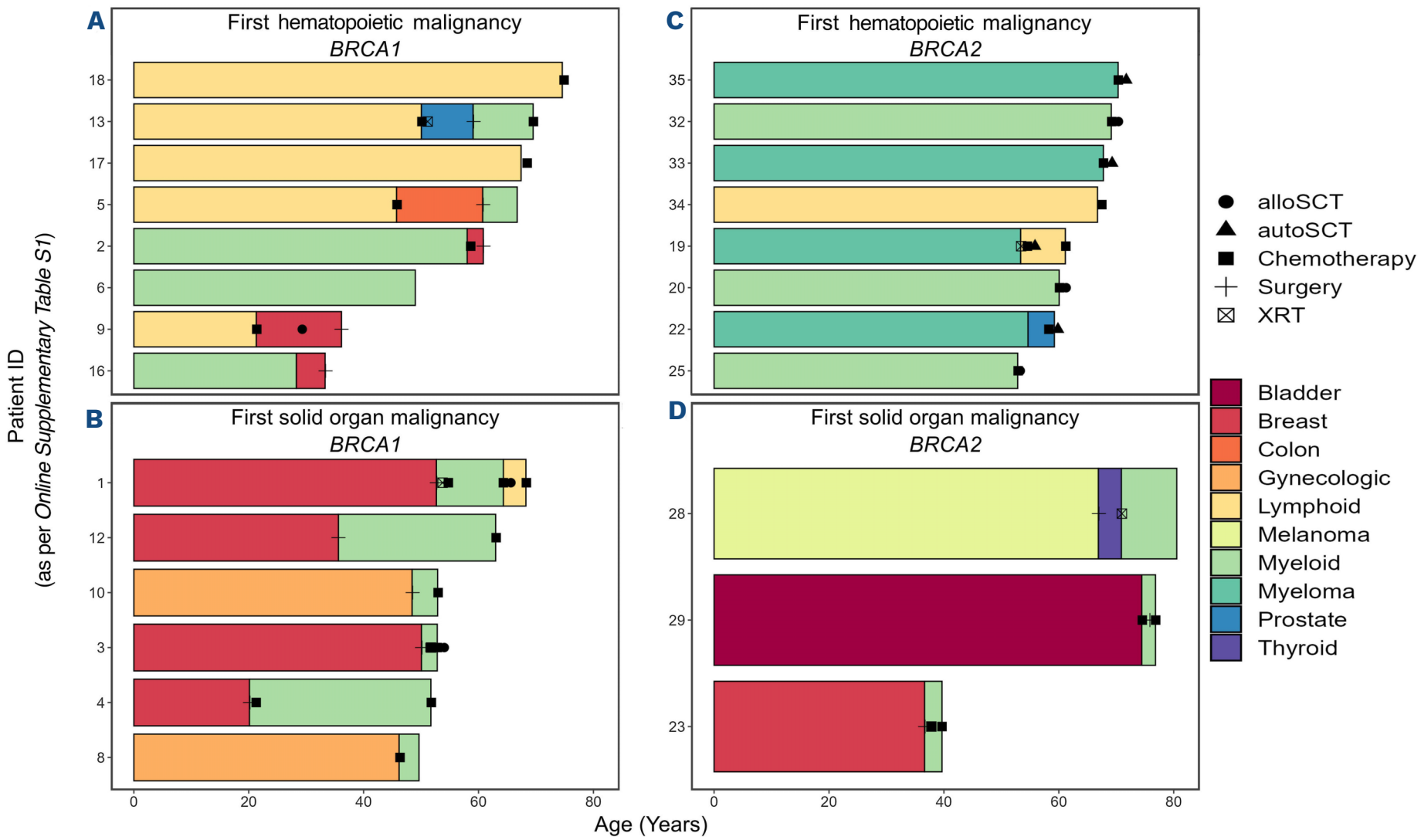

Figure 1. Time course of malignancies in patients with loss-of-function germline *BRCA1/2* variants. The swimmer plot depicts each patient in a distinct row, with the age of diagnosis of the malignancy indicated at the end of each block and the color denoting the type of malignancy. Symbols between intervals denote treatments: chemotherapy, autologous (auto) or allogeneic (allo) hematopoietic stem cell transplant (SCT), surgery, and radiation (XRT). (A) Half of germline *BRCA1* mutation carriers had a first diagnosis of hematopoietic malignancies, comprising myeloid (chronic myeloid leukemia [N=1], myelodysplastic syndrome [N=1], and systemic mastocytosis [N=1]) and lymphoid (Hodgkin lymphoma [N=1], acute lymphocytic leukemia [N=1], and non-Hodgkin lymphoma [N=3]) malignancies. (B) Among the six patients with a germline *BRCA1* mutation who developed a solid organ malignancy first, all developed a subsequent therapy-related myeloid neoplasm, with one developing a tertiary lymphoid neoplasm. (C) Among the germline *BRCA2*-mutated patients, eight developed a hematopoietic malignancy first: multiple myeloma (N=4), acute myeloid leukemia (N=3), and chronic lymphocytic leukemia (N=1). One patient subsequently developed prostate cancer and one a therapy-related acute lymphocytic leukemia. (D) Three of the *BRCA2*-mutated patients developed solid organ malignancies first: melanoma (N=1), bladder (N=1), and breast (N=1), all of whom subsequently developed therapy-related myeloid neoplasms.

(*Online Supplementary Table S1*). Among patients with germline *BRCA1* mutations and material evaluable for LoH, 13% (1/8) had evidence of LoH, with a chr17 deletion. Among similar patients with germline *BRCA2* mutations, 33% (2/6) had evidence of LoH, with one showing loss of chr13 and one having a somatic *BRCA2* mutation with a variant allele frequency of 27%. Overall, among germline *BRCA1/2* mutation carriers, we observed a 23% rate of LoH.

These findings suggest that deleterious germline *BRCA1/2* variants are seen frequently in patients with *de novo* HM, and it is possible that they may confer risk for *de novo* HM, outside of the context of previous exposure to cytotoxic chemotherapy or radiation. As with other germline mutations, it is important to remember that deleterious germline *BRCA1/2* alleles are present in all cells of the body, and consequently, homologous recombination activity is defective globally. Hematopoietic cells may be particularly vulnerable to defective DNA repair mechanisms as they must divide continually throughout an individual's lifetime, and, thus, are more vulnerable to genotoxic stress. Further, overactivity of non-homologous end joining relative to homologous recombination promotes the development of leukemogenic hematopoietic stem and progenitor cells. In keeping with this, mice lacking *Brca1* in the hematopoietic compartment develop bone marrow failure and HM after stress erythropoiesis.[12] Mutations in other components of BRCA adjacent pathways, particularly the *FANC* gene family known to be defective in Fanconi anemia, are also well described as conferring risk for the development of spontaneous myeloid malignancies and other HM.[13] One novel finding in our study was the unexpected prevalence of lymphoid malignancies, particularly multiple myeloma in patients with deleterious germline *BRCA2* variants, given that mutations in *FANC* and other genes related to homologous

recombination tend to have hematopoietic manifestations related to myeloid malignancies and bone marrow failure. However, accumulation of chromosomal abnormalities and gene mutations is also fundamental to the pathogenesis of lymphoid neoplasms, and one report linked germline *BRCA2* mutations to a risk for non-Hodgkin lymphoma in adolescents and young adults, and a mouse model of truncating *Brca2* mutations was shown to develop thymic lymphomas.[14,15]

Our study represents a retrospective, single-center patient cohort, and the attendant possibility of ascertainment or referral bias in our patient database must be considered when interpreting these findings. In addition, differences in population composition between our cohort and the gnomAD comparison cohort (e.g., a higher proportion of Ashkenazi Jewish patients in our cohort) may also represent a confounding factor. Differences in upstream variant calling and curation between our local testing and gnomAD could be another confounder. However, we would note that similar allele burden testing approaches using public data such as gnomAD are an accepted approach in the literature and have been applied to other disorders. Among a handful of previous smaller studies that have addressed the question of *de novo* HM development in *BRCA* mutation carriers, some have demonstrated an increased risk.[15-17]

An appreciable number, though not all, of the patients in our cohort demonstrated LoH at the second *BRCA1/2* allele through either chromosomal loss or a damaging somatic mutation. However, only about half of *BRCA2* germline carriers with breast cancer will have LoH, suggesting that LoH may not be found in the tumor tissue of all patients with *BRCA1/2*-associated malignancies. Although it is possible that in patients with HM in the absence of LoH, the germline *BRCA1/2* mutation is merely a bystander, we note that other solid organ malignancies (e.g., *BRCA*-associated pancreatic cancer) also display variable degrees of LoH, making the exact role of LoH in the pathogenesis of *BRCA*-associated malignancies controversial.[18] Further, HM are often epigenetically-driven diseases, and there are multiple studies demonstrating promoter hypermethylation and epigenetic silencing of *BRCA1* and *BRCA2* in HM, particularly in myeloid malignancies.[19,20] We were unable to assess for epigenetic loss of *BRCA1/2* in our cohort, but future studies should assess whether this is a prominent mechanism of LoH in patients with HM and germline *BRCA1/2* mutations.

Although some larger cohorts have suggested that there is no increased risk for HM in carriers of *BRCA* mutations,[9] these studies primarily ascertained patients being tested for a known personal or family history of breast or ovarian cancer, possibly pre-selecting for a specific disease phenotype, utilized self-reported family histories, and are susceptible to misclassification bias. Although our work suggests the possibility of an association between germline *BRCA* mutations and *de novo* HM development, larger future studies focused on populations specifically ascertained with a question of a familial predisposition to HM will be needed to establish definitively the causality and magnitude of risk of developing *de novo* HM with these alleles.

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Contributions

RJS, ASA, and LAG reviewed and analyzed the clinical data and wrote and edited the manuscript. PW analyzed the molecular profiling data of all patients. AML and AG reviewed clinical cytogenetics and FISH analysis and also performed and analyzed chromosomal microarrays on all available patients' material. RJS and ASA generated the Tables and Figure.

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Data-sharing statement

Clinical sequencing data are available upon request.

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