Received: 17 January 2020 | Revised: 21 May 2020 | Accepted: 22 May 2020

DOI: 10.1002/mgg3.1359

ORIGINAL ARTICLE

Molecular Genetics & Genomic Medicine Open Access WILEY

Comparison of suspected Lynch syndrome patients carrying *BRCA* and *BRCA*-like variants with Lynch syndrome probands: Phenotypic characteristics and pedigree analyses

Yun Xu[1,2] | **Cong Li**[1,2] | **Zhimin Wang**[3] | **Fangqi Liu**[1] | **Ye Xu**[1,2]

[1]Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

[2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

[3]Department of Genetics, Shanghai-MOST Key Laboratory of Health and Disease Genomics, Chinese National Human Genome Center and Shanghai Academy of Science & Technology, Shanghai, China

Correspondence
Ye Xu, Department of Colorectal Surgery, Fudan University Shanghai Cancer Center Dong'an Road, 270, Shanghai 200032, PR China.
Email: yexu@shmu.edu.cn

Fangqi Liu, Department of Colorectal Surgery, Fudan University Shanghai Cancer Center Dong'an Road, 270, Shanghai 200032, PR China.
Email: liufq021@163.com

Funding information
National Natural Science Foundation of China, Grant/Award Number: 81472620; Development Foundation for Shanghai Talents, Grant/Award Number: 2017120; Shanghai National Natural Science Foundation, Grant/Award Number: 16ZR1406700

Abstract

Background: Colorectal cancer (CRC) patients diagnosed with Lynch syndrome (LS) are recommended genetic testing. Increasing numbers of germline variants involved in homologous recombination have been identified in suspected LS patients. This study compared phenotypic the characteristics of suspected LS patients carrying *BRCA* and *BRCA*-like variants with those of LS patients.

Methods: Forty-two patients carrying pathogenic variants of DNA mismatch repair (*MMR*) genes (*MMR* group), 9 carrying *BRCA* variants, and 11 carrying *BRCA*-like variants (*BRCA/BRCA*-like group) who met LS clinical criteria were enrolled in this study. Clinical characteristics, pedigrees, and survival rates were compared and *BRCA* variants were analyzed.

Results: The earliest CRC-onset age and tumor differentiation were higher in the *BRCA/BRCA*-like group than in the *MMR* group. Metachronous CRCs were more numerous in the *MMR* group, resulting in a higher progression-free survival rate in the *BRCA/BRCA*-like group. Extra-colorectal cancers were more frequently observed in the *BRCA/BRCA*-like group. *BRCA2* and *BRCA1* variants were clustered in exons 11 and 4/7, respectively.

Conclusion: *BRCA* and *BRCA*-like variants in CRC patients with LS showed moderate penetrance. *BRCA/BRCA*-like variant carriers had a higher risk for extra-colorectal cancers. Surveillance of susceptible organs other than the intestine should be performed for probands and affected family members.

KEYWORDS
BRCA, BRCA-like, colorectal cancer, Lynch syndrome, mismatch repair

Yun Xu and Cong Li contributed equally to this work.

1 | INTRODUCTION

Lynch syndrome (LS) is the most common hereditary colorectal cancer (CRC) syndrome and is caused by germline variants in DNA mismatch repair (*MMR* [OMIM accession number: 276300]) genes. It is characterized by a marked increase in the lifetime risk of CRC and extra-colorectal cancers (Hampel et al., 2008). For clinical diagnosis of LS, diagnostic algorithms that take into account medical history, including Amsterdam I/II criteria (AC) (Vasen, Watson, Mecklin, & Lynch, 1999) and revised Bethesda guidelines (BG) (Umar et al., 2004), have been developed. The advances made in next-generation sequencing (NGS) technology over the last decade have made it possible to identify suspected LS patients and affected families on the basis of clinical history and the molecular tumor phenotype.

Multigene cancer panel testing of suspected LS patients along with diagnosis based on AC and BG criteria has allowed the identification of an increasing number of variants other than *MMR* variants. *BRCA* variants represent a large fraction of these new variants. *BRCA* is involved in homologous recombination (HR), which is an error-free repair mechanism for DNA double-strand breaks (Moynahan, Pierce, & Jasin, 2001). Defective *BRCA* can cause hereditary breast and ovarian cancers (Llort et al., 2015; Mavaddat et al., 2013). Breast cancer cells with variants in *BRCA1* (OMIM accession number: 113705), or *BRCA2* (OMIM accession number: 600185) develop extreme sensitivity to poly ADP-ribose polymerase (PARP) inhibitors and cytotoxic drugs (Abbotts et al., 2019). In addition to *BRCA* variants, variants of other genes involved in HR have been detected by multigene panel testing (Brandão et al., 2019; Feliubadaló et al., 2019). Abberation of other proteins in HR repair pathways, such as *RAD51* (OMIM accession number: 179617), *ATM* (OMIM accession number: 607585), and *ATR* (OMIM accession number: 601215), also results in impaired HR (Abbotts et al., 2019; Venkitaraman, 2003). Tumors bearing these abnormalities, described as "*BRCA*-like," are often sensitive to similar therapies (Byrum, Vindigni, & Mosammaparast, 2019; Lord & Ashworth, 2016).

A considerable number of *BRCA* variants have been identified based on NGS data of suspected LS patients, and some studies have revealed a higher incidence of CRC in subjects carrying *BRCA* variants (Kwong et al., 2016; Mersch et al., 2015; Phelan et al., 2014; Lin et al., 1999; Moran et al., 2012; Van Asperen et al., 2005; Brose et al., 2002; Chalasani, 1999; Suchy et al., 2010; Kirchhoff et al., 2004; Niell et al., 2004; Risch et al., 2001; Struewing et al., 1997; Yurgelun et al., 2015; Yurgelun et al., 2017). However, studies on phenotypic characteristics, variants, and the pedigrees of *BRCA* and *BRCA*-like variant carriers in suspected LS are scant. Therefore, this study compared phenotypic characteristics and pedigrees of *BRCA* and *BRCA*-like carriers among LS patients, and we conducted a literature review of the association between *BRCA* and CRC. To the best of our knowledge, this is the first study to describe *BRCA* variants in suspected LS patients. Further, we newly introduce the concept of an association between *BRCA/BRCA*-like variants and suspected LS. Our findings provide molecular evidence that may lead to the development of individualized treatments and screening strategies for this subset.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

All examinations and treatments were conducted at the Fudan University Shanghai Cancer Center and were in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of the Fudan University Shanghai Cancer Center. Written informed consent was obtained from all patients included in this study.

2.2 | Patients

Between June 2008 and September 2018, a total of 22,833 consecutive CRC patients received curative surgeries for tumors at different loci at the Fudan University Shanghai Cancer Centre. Multigene tests covering 139 genes were performed on 202 patients who met the AC or BG criteria. Some affected family members also received multigene tests. All patients provided informed consent for genetic analyses. When patients and family members carried the same variants, these variants were regarded germline variants, and genetic counseling was recommended in these cases. Of the 202 patients, 42 carrying a pathogenic variant (PV) in *MMR*, 9 carrying *BRCA* variants, and 11 carrying *BRCA*-like variants were enrolled in this study. The remaining 140 patients, identified as carrying *MMR* variants of unknown significance (VUS) or variants of other genes, were excluded. Patients carrying PVs in *MMR* were classified as the *MMR* group, whereas patients carrying *BRCA* and *BRCA*-like variants were classified as the *BRCA/BRCA*-like group.

2.3 | Clinical characteristics and follow-up

Clinical characteristics, including basic information, tumor characteristics, tumor histories, and pathologic findings, of the 62 enrolled patients were retrospectively collected. Follow-ups were conducted for all recruited patients every

2–3 months. During the follow-ups, occurrence of metachronous CRCs, distant metastases, and extra-colorectal cancers were recorded. Overall survival (OS) time was calculated from the date of surgery to the date of death or the last follow-up, whereas progression-free survival (PFS) was defined as the period between the date of surgery and the date of metachronous CRC, metastasis, extra-colorectal cancer, or last follow-up. The last follow-up date was December 30, 2019.

2.4 | Pedigree characteristics

Pedigree characteristics were obtained by interviewing the recruited patients and their family members, including all children, siblings, parents, grandparents, aunts, and uncles. Each patient and relative were asked to report whether the relative had ever been diagnosed with cancer. The sex of the patient, type of cancer, and age at diagnosis were recorded for each relative. Pathological records of cancers of relatives were systematically collected when available. Probands and their family members were grouped together in pedigree analyses.

2.5 | DNA extraction and genotyping

Peripheral blood samples (10 ml) collected from patients and affected family members were stored in ethylenediaminetetraacetic acid tubes and allowed to stand at 25°C for 2 hr. Genomic (g) DNA was extracted from blood lymphocytes using an AllPrep DNA/RNA Mini Kit (80204; Qiagen) according to the manufacturer's instructions. Fragment size, quality, and total concentration of the gDNA were determined using a 2200 Bioanalyzer (Agilent Technologies). gDNA libraries were generated using a KAPA Hyper Prep kit (Kapa Biosystems) according to the manufacturer's protocol. The libraries were quantified using a Qbit 3 (Thermo Fisher).

The 139 genes included in the multigene panel used in our research are listed in Table S1. The gDNA libraries were enriched for regions of this custom designed capture probes manufactured by Agilent. Next, 750 ng of prepared libraries were incubated with two different hybridization reagents and blocking agents in a Sure Select XT Target Enrichment System (Agilent Technologies). The enriched libraries were amplified using P5/P7 primers. After qualification using a 2200 Bioanalyzer and quantification using Qbit 3 and a qPCR NGS library quantification kit (Agilent Technologies), the libraries were sequenced on a HiSeq X10 platform (Illumina).

Sequencing reads were mapped to a human reference genome (hg19) using the Burrows–Wheeler Aligner (Li & Durbin, 2010). Duplicate removal, local realignment, and base quality recalibration were performed using PICARD (http://broadinstitute.github.io/picard/) and Genome Analysis Toolkit (DePristo et al., 2011). Somatic single-nucleotide variations and small indels were called using Genome Analysis Toolkit. Consequences of variants were annotated using Oncotator (Ramos et al., 2015) and Variant Effect Predictor (McLaren et al., 2016), as well as an in-house database (GnentronDB). A variant was filtered out if (a) read depth was less than five, (b) variant allele frequency was less than 20%, or (c) it was recurrently detected in healthy individuals. Each candidate variant was visually reviewed in Integrative Genomics Viewer (Thorvaldsdóttir, Robinson, & Mesirov, 2013). PubMed was used to search and locate the exon harboring the mutation, ClinVar accessions were used to find the clinical significance of variants, and PolyPhen-2 was used for prediction of the pathogenicity of variants.

2.6 | Statistical analysis

Continuous variables are expressed as the mean ± standard deviation. Differences between groups of categorical variables or continuous variables were analyzed using the Chi-squared test and Fisher's exact test or Student's *t* test, respectively, in SPSS v. 21.0 software (SPSS). OS and PFS were evaluated using Kaplan–Meier curves and were compared using the log-rank test. A two-tailed $p < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics

Demographic and clinical characteristics of the two groups were compared; the results are summarized in Table 1. Significant differences were observed in the earliest-onset age of CRC and differentiation of CRC tumors between the two groups. The mean earliest CRC-onset age in the *BRCA/BRCA*-like group was 56.45 (±14.86) years, which was significantly higher than that in the *MMR* group (44.95 ± 10.86 years; $t = -3.450$, $p = .001$), and the proportion of early-onset (<50 years) CRC patients was 35% (7/20) in the *BRCA/BRCA*-like group, which was significantly lower than that in the *MMR* group (69.0% (29/42); $\chi^2 = 6.450$, $p = .011$). The proportion of poorly differentiated CRC tumors was 33% (14/42), which was significantly higher than the 5% (1/20) in the *BRCA/BRCA*-like group ($\chi^2 = 6.911$, $p = .032$).

A comparison of tumor histories revealed significant differences between the two groups in the total number of cancers, the earliest cancer-onset age, occurrence of metachronous CRCs, and the number of CRCs. The total number of cancers was 1.30 (±0.57) in the *BRCA/BRCA*-like group,

TABLE 1 Demographic and clinical characteristics of 62 patients with colorectal cancer in the two groups

Characteristic	*MMR* group (*N* = 42)	*BRCA/BRCA*-like group (*N* = 20)	χ^2/t value	*p* value
Gender			0.025	.874
Male	24 (57.1%)	11 (55.0%)		
Female	18 (42.9%)	9 (45.0%)		
Age (years)[a]	44.95 ± 10.86	56.45 ± 14.86	−3.450	.001
<50	29 (69.0%)	7 (35.0%)	6.450	.011
≥50	13 (31.0%)	7 (65.0%)		
CEA (ng/ml)			1.066	.302
<5.2	36 (85.7%)	15 (75.0%)		
≥5.2	6 (14.3%)	5 (25.0%)		
CA19-9 (μ/ml)			1.213	.217
<40	33 (78.6%)	18 (90.0%)		
≥40	9 (21.4%)	2 (10.0%)		
Primary location of colorectal cancer			4.232	.237
Right colon	16 (38.1%)	6 (30.0%)		
Left colon	16 (38.1%)	9 (45.0%)		
Rectal	5 (11.9%)	5 (25.0%)		
Multiple	5 (11.9%)	0 (0.0%)		
Multiple locations			3.243	.072
Occurrence	13 (31.0%)	2 (10.0%)		
Absence	29 (69.0%)	18 (90.0%)		
Multiple tumors			3.824	.070
Occurrence	10 (23.8%)	1 (5.0%)		
Absence	32 (76.2%)	19 (95.0%)		
Pathological classification			1.651	.438
Adenocarcinoma	31 (73.8%)	17 (85.0%)		
Adenocarcinoma with partial mucinous adenocarcinoma	4 (9.5%)	2 (10.0%)		
Mucinous adenocarcinoma	7 (16.7%)	1 (5.0%)		
Differentiation			6.911	.032
Well differentiated	2 (4.8%)	3 (15.0%)		
Moderately differentiated	26 (61.9%)	16 (80.0%)		
Poorly differentiated	14 (33.3%)	1 (5.0%)		
Vascular invasion			0.028	.868
Occurrence	7 (16.7%)	3 (15.0%)		
Absence	35 (83.3%)	17 (85.0%)		
Tumor size (cm)[a]	5.10 ± 2.68	4.50 ± 2.12	0.872	.387
T stage			0.712	.701
T1	7 (16.7%)	5 (25.0%)		
T2	6 (14.3%)	2 (10.0%)		
T3	29 (69.0%)	13 (65.0%)		
N stage			0.447	.800
N0	30 (71.4%)	13 (65.0%)		
N1	8 (19.0%)	4 (20.0%)		

(Continues)

TABLE 1 (Continued)

Characteristic	*MMR* group ($N = 42$)	*BRCA/BRCA*-like group ($N = 20$)	χ^2/t value	p value
N2	4 (9.6%)	3 (15.0%)		
Metastasis			0.616	.433
Occurrence	2 (4.8%)	2 (10.0%)		
Absence	40 (95.2%)	18 (90.0%)		
TNM stage			0.684	.877
I	12 (28.6%)	6 (30.0%)		
II	16 (38.1%)	7 (35.0%)		
III	12 (28.6%)	5 (25.0%)		
IV	2 (4.8)	2 (10.0%)		

[a]These data are presented as mean ± standard deviation; other values are presented as number of patients followed by percentage in parentheses.

which was lower than the 1.69 (±0.87) in the *MMR* group ($t = 2.108$; $p = .040$), and the earliest cancer-onset age was higher in the *BRCA/BRCA*-like group ($t = -3.470$, $p = .001$). Moreover, the observed metachronous CRCs ($\chi^2 = 3.853$, $p = .049$) as well as numbers of CRCs ($t = 2.645$, $p = .010$) were lower in the *BRCA/BRCA*-like group than those in the *MMR* group. The characteristics of tumor histories of the 62 patients in the two groups were compared and are summarized in Table 2.

For early-onset (<50 years) CRC patients, the total number of cancers was 1.13 (± 0.21) in the *BRCA/BRCA*-like group, which was lower than the 1.86 (± 0.92) in the *MMR* group ($t = 5.073$; $p < .001$), and metachronous CRCs were observed in 10 (34.5%, 10/29) patients of the *MMR* group, but in only 1 (14.3%, 1/7) patient in the *BRCA/BRCA*-like group ($\chi^2 = 5.178$, $p = .023$). For CRC patients older than 50 years, the total number of cancers was 1.46 (±0.66) in the *BRCA/BRCA*-like group and 1.31 (±0.63) in the *MMR* group ($t = -0.608$; $p = .549$). Metachronous CRCs were observed in four (30.8%, 4/13) patients of the *MMR* group and in one (7.7%, 1/13) patient of the *BRCA/BRCA*-like group ($\chi^2 = 2.229$, $p = .135$).

3.2 | Survival analysis

During follow-up, only four (9.5%) probands in the *MMR* group and two (10.0%) patients in the *BRCA/BRCA*-like group died due to tumor progression. The mean OS time was 123.2 (±86.8) months in the *MMR* group and 102.3 (±58.7) months in the *BRCA/BRCA*-like group ($\chi^2 = 3.16$, $p = .574$). The 1-, 3-, and 5-year OS rates were 100.0%, 97.0%, and 86.2%, respectively, in the *MMR* group, and 100.0%, 87.5%, and 72.9%, respectively, in the *BRCA/BRCA*-like group (Figure 1).

As for PFS, 23 probands experienced tumor progression, including 14 patients with metachronous CRC, 8 with metastasis, and 7 with extra-colorectal tumors in the *MMR* group. In the *BRCA/BRCA*-like group, five patients developed tumor progression, including two with metachronous CRC, three with metastasis, and two with extra-colorectal cancer. PFS was 84.6 (±43.5) months in the *BRCA/BRCA*-like group, which was significantly longer than the 54.4 (±50.9) months in the *MMR* group ($\chi^2 = 4.305$, $p = .038$). The 1-, 3-, and 5-year PFS rates were 81.0%, 63.3%, and 45.9%, respectively, in the *MMR* group, and 95.7%, 77.2%, and 77.2%, respectively, in the *BRCA/BRCA*-like group (Figure 2).

For early-onset CRC patients, 1-, 3-, and 5-year PFS rates were 75.9%, 54.1%, and 37.9%, respectively, in the in the *MMR* group, and 100.0%, 75.0%, and 75.0%, respectively, in the *BRCA/BRCA*-like group ($\chi^2 = 2.050$, $p = .152$). For CRC patients older than 50 years, 1-, 3-, and 5-year PFS rates were 92.3%, 84.6%, and 63.5%, respectively, in the *MMR* group, and 92.3%, 79.1%, and 79.1%, respectively, in the *BRCA/BRCA*-like group ($\chi^2 = 0.162$, $p = .688$).

3.3 | Pedigree characteristics

Pedigrees of the probands and their family members were analyzed. Comparison of cancer spectra showed that more left colon cancers were observed in *MMR* families ($t = 2.757$; $p = .008$), whereas more extra-colorectal cancers ($t = -2.464$, $p = .019$) were observed in *BRCA/BRCA*-like families. The earliest cancer-onset age, including CRCs ($t = -3.163$, $p = .004$) and extra-colorectal cancers ($t = -3.577$, $p = .001$), was significantly higher in *BRCA/BRCA*-like families than that in *MMR* families. Furthermore, synchronous (and) or metachronous CRCs developed in 50% (21/42) of *MMR* families, which was significantly higher than the 15% (3/20)

TABLE 2 Characteristic of tumor histories in patients ($N = 62$) with CRC of the two groups

Characteristic	*MMR* group ($N = 42$)	*BRCA/BRCA*-like group ($N = 20$)	χ^2/t value	*p* value
Total number of cancers[b]	1.69 ± 0.87	1.30 ± 0.57	2.108	.040
Total number of CRCs[b]	1.45 ± 0.74	1.10 ± 0.31	2.645	.010
Earliest onset age of cancer (years)[a]	44.24 ± 10.77	55.65 ± 14.57	−3.470	.001
Earliest onset age of extra-colorectal cancer (years)[a,b]	50.22 ± 13.28	57.75 ± 1.71	−1.102	.294
Metachronous CRC			3.853	.049
Occurrence	14 (33.3%)	2 (10.0%)		
Absence	28 (66.7%)	18 (90.0%)		
Distant metastasis			0.290	.590
Occurrence	8 (19.0%)	5 (25.0%)		
Absence	34 (81.0%)	15 (75.0%)		
Extra-colorectal cance			0.017	.897
Occurrence	9 (21.4%)	4 (20.0%)		
Absence	33 (78.6%)	16 (80.0%)		
Right colon cancer			2.740	.098
Occurrence	22 (52.4%)	6 (30.0%)		
Absence	20 (47.6%)	14 (70.0%)		
Left colon cancer			0.025	.874
Occurrence	24 (57.1%)	11 (55.0%)		
Absence	18 (42.9%)	9 (45.0%)		
Rectal cancer			0.603	.438
Occurrence	7 (16.7%)	5 (25.0%)		
Absence	35 (83.3%)	15 (75.0%)		
Endometrial carcinoma[b]			2.317	.128
Occurrence	12 (44.4%)	2 (18.2%)		
Absence	15 (55.6%)	9 (81.8%)		
Gastric cancer[b]			0.983	.321
Occurrence	10 (37.0%)	6 (54.5%)		
Absence	17 (63.0%)	5 (45.5%)		
Breast and Ovarian cancer[b]			0.410	.522
Occurrence	1 (11.1%)	1 (25.0%)		
Absence	8 (88.9%)	3 (75.0%)		
Synchronous or metachronous CRCs			6.995	.008
Occurrence	21 (50.0%)	3 (15.0%)		
Absence	21 (50.0%)	17 (85.0%)		
Synchronous or metachronous extra-colorectal cancer			0.017	.897
Occurrence	9 (21.4%)	4 (20.0%)		
Absence	33 (78.6%)	16 (80.0%)		

Abbreviation: CRC, colorectal cancer.

[a]These data are presented as mean ± standard deviation; other values are presented as number of patients followed by percentage in parentheses.

[b]These data are limited to families that developed extra-colorectal cancer.

seen in the *BRCA/BRCA*-like families ($\chi^2 = 5.067$, $p = .024$). No significant differences were observed in the incidence of breast cancers ($\chi^2 = 1.535$, $p = .215$) and ovarian cancers ($\chi^2 = 0.860$, $p = .354$) between the two groups. The characteristics of pedigrees in the two groups were compared and are summarized (Table 3).

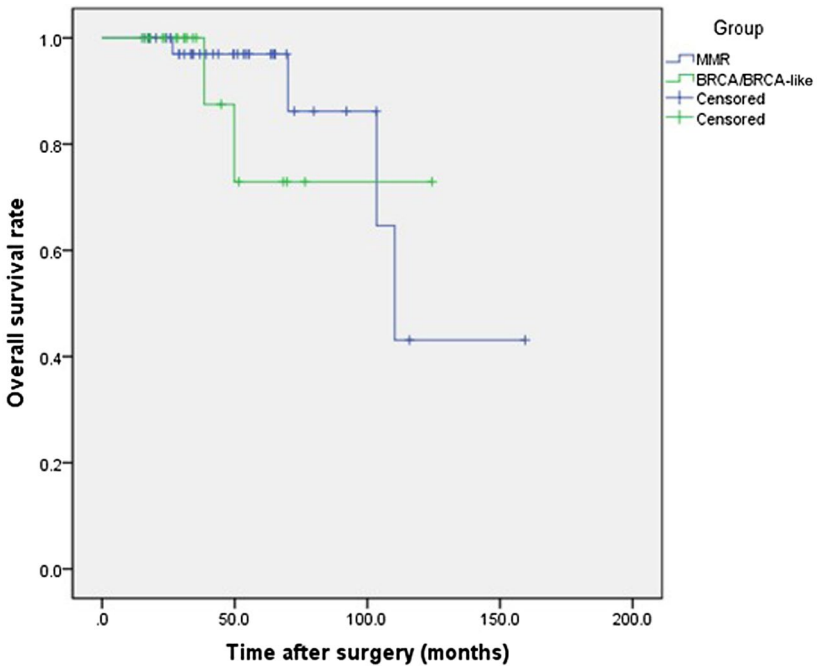

FIGURE 1 Overall survival curves in patients of *MMR* group and *BRCA/BRCA-like* group after surgery

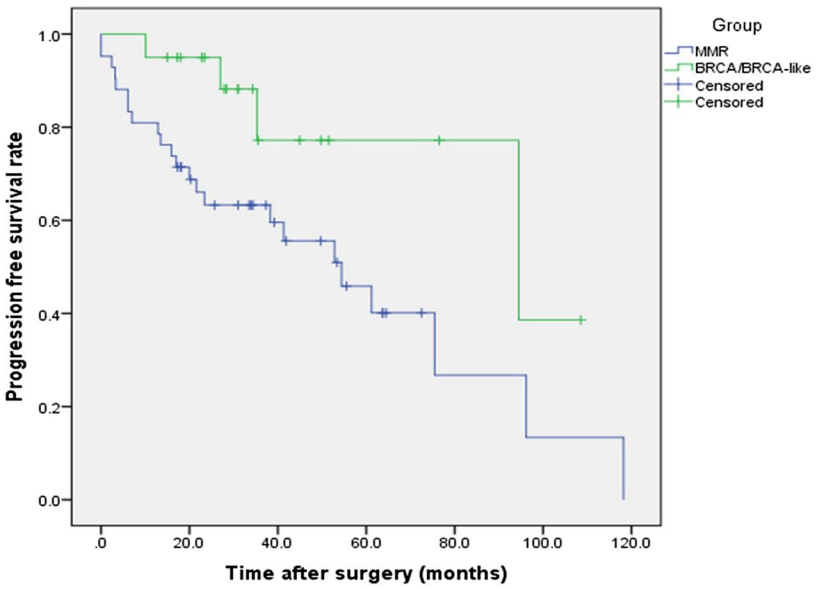

FIGURE 2 Progression free survival curves in patients of *MMR* group and *BRCA/BRCA-like* group after surgery

3.4 | Variant characteristics

In this cohort of 42 *MMR* probands, pathogenic *MLH1* (OMIM accession number: 120436) variants were identified in 16 patients, *MSH2* (OMIM accession number: 609309) variants in 17, and *MSH6* (OMIM accession number: 600678) variants in 9. In the *BRCA/BRCA*-like group, *BRCA1* variants were identified in five patients, *BRCA2* variants in three, *BRCA1/2* variants in one, *ATM* variants in three, *ATR* variants in two, *RAD51* variants in two, *RAD50* (OMIM accession number: 604040) variants in two, *BARD1* (OMIM accession number: 601539) variants in one, and *BRIP1* (OMIM accession number: 605882) variants in one.

PubMed was used to search and locate the exons harboring the mutation, whereas clinical significances of variants were determined based on ClinVar accessions. Of the five patients with *BRCA1* variants, three carried an identical single nucleotide variant c.154C>T (p.Leu52Phe) located in exon 4, whereas two carried an identical single nucleotide variant c.446A>C (p.Glu149Ala) located in exon 7. Of the three patients carrying *BRCA2* variants, two carried the single nucleotide variant c.5231G>T (p.Ser1744Ile) and one carried the single nucleotide variant c.2186T>C (p.Ile729Thr), both of which are located in exon 11. In the only case carrying *BRCA1/2* variants, c.1511G>A (p.Arg504His) of *BRCA1* was located in exon 10, whereas

TABLE 3 Comparison of pedigrees between *MMR* group and *BRCA/BRCA-like* group

Variable	*MMR* group ($N = 42$)	*BRCA/BRCA*-like group ($N = 20$)	χ^2 value	*p* value
Patients with cancer (cases)[a]	4.12 ± 2.24	4.35 ± 2.52	−0.347	.730
Male patients (cases)	2.33 ± 1.71	2.40 ± 1.50	−0.149	.882
Female patients (cases)	1.74 ± 1.50	1.95 ± 1.395	−0.532	.597
Patients with CRCs (cases)	3.31 ± 2.03	2.75 ± 1.74	1.059	.294
Colorectal cancers (cases)	4.12 ± 2.58	2.95 ± 1.67	2.143	.037
Right colon cancer[a]	1.62 ± 1.01	1.45 ± 1.36	0.550	.585
Occurrence	35 (83.3%)	14 (70.0%)	1.453	.228
Absence	7 (16.7%)	6 (30.0%)		
Left colon cancer[a]	1.69 ± 1.26	0.85 ± 0.75	2.757	.008
Occurrence	37 (88.1%)	13 (65.0%)	4.630	.031
Absence	5 (11.9%)	7 (35.0%)		
Rectal cancer[a]	0.43 ± 0.59)	0.20 ± 0.41	1.558	.124
Occurrence	16 (38.1%)	9 (45.0%)	0.268	.604
Absence	26 (61.9%)	11 (55.0%)		
Patients with extracolorectal cancer (cases)[a]	1.59 ± 1.28	3.27 ± 1.85	−3.218	.003
Extracolorectal cancers (cases)[a]	1.85 ± 1.51	3.27 ± 1.85	−2.464	.019
Types of extracolorectal cancer (cases)[a]	1.56 ± 0.81	2.18 ± 1.25	−1.538	.147
Extracolorectal cancer			0.492	.483
Occurrence	27 (64.3%)	11 (55.0%)		
Absence	15 (35.7%)	9 (45.0%)		
Breast cancer[a]			1.535	.215
Occurrence	3 (11.1%)	3 (17.3%)		
Absence	24 (88.9%)	8 (72.7%)		
Ovarian cancer[a]			0.860	.354
Occurrence	2 (7.4%)	0 (0.0%)		
Absence	25 (92.6%)	11 (100%)		
Synchronous or metachronous CRCs			5.067	.024
Occurrence	21 (50.0%)	4 (20%)		
Absence	21 (50.0%)	16 (80%)		
Synchronous or metachronous extracolorectal cancer			2.030	.154
Occurrence	16 (38.1%)	4 (20.0%)		
Absence	26 (61.9%)	16 (80.0%)		
Earliest onset age of cancer (years)	36.90 ± 7.14	47.30 ± 14.83	−2.975	.007
Earliest onset age of CRC (years)	36.29 ± 6.90	47.30 ± 14.83	−3.163	.004
Earliest onset age of extracolorectal cancer (years)[a]	46.70 ± 9.91	58.45 ± 6.96	−3.577	.001

Abbreviation: CRC, colorectal cancer.

[a]These data are limited to families that developed extracolorectal cancer.

c.7469T>C (p.Ile2490Thr) of *BRCA2* was located in exon 5.

All these variants are considered as missense variants and VUS. Among *BRCA1* variants, c.154C>T (p.Leu52Phe) is predicted to be probably damaging with a score of 1.000; c.446A>C (p.Glu149Ala) is predicted to be probably damaging with a score of 0.990; and c.1511G>A (p.Arg504His) is predicted to be benign with a score of 0.177. Among *BRCA2* variants, c.5231G>T (p.Ser1744Ile) is predicted to be probably damaging with a score of 0.919; c.2186T>C

(p.Ile729Thr) is predicted to be benign with a score of 0.119, and c.7469T>C (p.Ile2490Thr) is predicted to be benign with a score of 0.008.

3.5 | Literature review of the association between *BRCA* and CRC

Studies conducted during the past two decades have revealed a higher CRC risk in patients with *BRCA1/2* variants, especially in female patients with a history of breast or ovarian cancers. In the current study, only three cases developed breast cancer in families of the *BRCA/BRCA*-like group, whereas no ovarian cancers were found. A literature review of the association between *BRCA* variants and CRC is summarized (Table 4). *BRCA* variants are analyzed and discussed with reference to some findings in these published studies.

4 | DISCUSSION

In clinical practice, LS is mainly diagnosed on the basis of clinical phenotypes and pedigree analyses. Precision genomic profiling is considered the "gold standard" for diagnosis, as well as for guiding therapy, predicting responses, and defining prognoses. During the last decade, multigene cancer panel tests have been increasingly performed on CRC patients who met LS clinical criteria. As a result, variants in *BRCA* genes and numerous other genes involved in HR repair pathways other than the *MMR* variants have been identified. Although some studies revealed a potential association between *BRCA* and a higher risk for CRC, detailed clinical phenotypes of the carriers of *BRCA* and *BRCA*-like variants were left undescribed. Therefore, we compared phenotypic and pedigree characteristics of patients carrying *BRCA* and *BRCA*-like variants with those of LS patients. Based on the findings reported here, policies for the management of LS patients suspected of carrying *BRCA/BRCA*-like variants may be formulated.

Lynch syndrome is characterized by a marked increase in the risk for CRC at a young age. Compared with that of *MMR* variants, the carcinogenic risk for CRC of *BRCA* and *BRCA*-like gene variants is described as medium (Susswein et al., 2016; Yurgelun et al., 2017). A comparison of clinical characteristics indicated that the most obvious difference between the two groups in this study was the significantly lower onset age in the *MMR* group. Notably, earliest onset ages for sporadic CRCs in a previous study were 50–64 years (Siegel et al., 2017). The mean earliest CRC-onset age in the *BRCA/BRCA*-like group was 56.45 (±14.86) years, which was higher than that in the *MMR* group, but significantly lower than that of sporadic CRCs. Our results confirmed that cancer penetrance of the *BRCA* and *BRCA*-like variant is medium. While CRCs associated with LS are characterized by poorly differentiated tumors, mucinous differentiation, and an expanding growth pattern (Llor et al., 2005), the higher tumor differentiation may indicate a favorable biological feature of *BRCA/BRCA*-like variants.

Colorectal cancers along with extracolorectal cancers, such as those of the endometrium, stomach, small bowel, ovaries, and pancreas, are considered to be overrepresented in patients with LS (Lynch, Snyder, Shaw, Heinen, & Hitchins, 2015). We observed synchronous and metachronous CRCs in half of the patients in the *MMR* group, but in only a few patients in the *BRCA/BRCA*-like group. The occurrence of synchronous and metachronous CRCs remarkably shortened PFS, resulting in a higher PFS rate in the *BRCA/BRCA*-like group. In addition to the limited effect of *BRCA* variants on the tumor phenotype, the loss of this pathway may sensitize cells to DNA damaging agents, which may, at least in part, account for the higher PFS in the *BRCA/BRCA*-like group. Given the small sample size, we could not observe differences in PFS rates in subgroup analyses. A previous population-based analysis of outcomes associated with early-age CRCs revealed that the stage-adjusted PFS at 5 years for patients under 50 years was 0.96, 0.90, and 0.77 for stages I, II, and III, respectively, whereas the corresponding proportions were 0.88, 0.82, and 0.68, respectively, for patients aged 50–74 years (Saraste, Jaras, & Martling, 2020). The PFS rate of *BRCA/BRCA*-like patients in our study was comparable to that of sporadic CRCs. Given the medium penetrance of metachronous CRCs, postoperative colonoscopies may be needed as frequently for this subset as for sporadic CRCs.

Although NGS may provide more precise information pertinent to the diagnosis of the hereditary syndrome, pedigree analysis still plays a crucial role in clinical practice. Insights into pedigree characteristics can not only determine diagnoses but also improve the management of treatment and screening strategies. We observed only three cases of breast cancer and no ovarian cancers in *BRCA/BRCA*-like families, which was notably inconsistent with the epidemiology of hereditary breast and ovarian cancers. More extracolorectal cancers were observed in *BRCA/BRCA*-like families than in *MMR* families, indicating that *BRCA/BRCA*-like variants are associated with cancers exhibiting low organ preference. Thus, other systems should be regularly examined for this subset during follow-up. Another interesting finding was the higher incidence of left colon cancers in the *MMR* group, which was consistent with that of our earlier study, which revealed that among 124 CRCs associated with LS, 70 were left side, whereas 54 were right side (Liu et al., 2014). The fact that this phenomenon was observed in both studies may indicate that left side preference is a feature of LS in the Chinese population.

TABLE 4 The literature on association between *BRCA* mutation and colorectal cancer

Study	Year	Study population	Comparison population	CRC Exposed cases	Mutant sites	Result
Mersch et al.	2015	613 *BRCA1* mutation carriers; 459 *BRCA2* mutation carriers	United States Cancer statistics	6 *BRCA1* mutation carriers; 2 *BRCA2* mutation carriers	N/A	*BRCA1*: SIR = 1.58 (0.58–3.44) *BRCA2*: SIR = 0.53 (0.06–1.90)
Phelan et al.	2014	5,481 *BRCA1* mutation carriers; 1,474 *BRCA2* mutation carriers; 2,829 (40%) women had history of breast cancer	Cancer incidence in five continents	16 *BRCA1* mutation carriers; 5 *BRCA2* mutation carriers	N/A	*BRCA1*: SIR = 0.92 (0.54–1.40); *BRCA2*: SIR = 0.82 (0.30–1.80); Women: Ages <50 years: SIR = 3.81 (1.77–7.23); Ages ≥50 years: SIR = 0.60 (0.33–1.00)
Lin et al.	1999	42 CRC patients from 32 clinically determined HBC kindreds	755 unselected CRC patients	42 CRC patients with *BRCA* mutation	N/A	Mean age of onset for HBC patients with CRC: 60 ± 2 (years) versus 67 ± 0.4 (years) for the GP from the tumor registry
Moran et al.	2012	1,815 *BRCA1* mutation carriers; 1,526 *BRCA2* mutation carriers	Cancer incidence in England (1975–2005)	10 *BRCA1* mutation carriers; 103 *BRCA2* mutation carriers	N/A	*BRCA1*: SIR = 1.00 (0.50–1.70); *BRCA2*: SIR = 1.00 (0.50–1.80)
Van Asperen et al.	2005	1,811 *BRCA2* mutation carriers	Netherlands Cancer statistics (1990–2005)	20 *BRCA2* mutation carriers	N/A	All age: RR = 2.51 (2.02–3.07); <65 years: RR = 8.0 (3.4–15.7); ≥65 years: RR = 0.6 (0.3–1.1)
Brose et al.	2002	483 *BRCA1* mutation carriers	Cancer incidence in SEER (1973–1999)	19 *BRCA1* mutation carriers	N/A	RR = 2.00(/)
The BCLC	1999	3,728 *BRCA2* mutation carriers	Cancer incidence in SEER (1973–1999)	8 *BRCA2* mutation carriers	N/A	RR = 1.22 (0.43–3.43)
Suchy et al.	2010	2,398 CRC patients	4,570 cases without CRC	10 *BRCA1* mutation carriers	*BRCA1*: C61G, 4153del and 5382insC	Age ≤60 years: OR = 1.7 (0.7–4.0), >60 years: OR = 0.4 (0.1–1.3); First or second degree relative with CRC: OR = 1.9(0.6–6.5), with Breast or ovarian cancer: OR = 2.3(0.5–9.8)
Kirchhoff et al.	2004	586 CRC patients	5,012 cases without CRC	3 *BRCA1* mutation carriers; 3 *BRCA2* mutation carriers	*BRCA1*: 185delAG, 5382insC, *BRCA2*: 6174delT	OR = 0.50 (0.22–1.14)
Neill et al.	2004	1,422 CRC patients	1,585 cases without CRC	11 *BRCA1* mutation carriers; 13 *BRCA2* mutation carriers	*BRCA1*: 185delAG, 5382insC *BRCA2*: 6174delT	All ages: OR = 1.24 (0.68–0.26); <65 years: OR = 3.14 (0.64–15.43); ≥65 years, OR = 0.96 (0.48–1.91).

(Continues)

TABLE 4 (Continued)

Study	Year	Study population	Comparison population	CRC Exposed cases	Mutant sites	Result
Risch et al.	2001	515 women diagnosed with epithelial ovarian tumors	455 mutation noncarriers	39 *BRCA1* mutation carriers and 21 *BRCA2* mutation carriers	Exon 11 in *BRCA2*: 2814del7, 3908delTG, 4075delGT, 4510insT, 4706del4, 4859delA, T5087G, 5102delAA, 5302insA, C5910G, 6174delT, 6181delTC, 6503delTT, 6602insA, 6633del5 and 6872del4	CRC occurred among first-degree relatives of carriers of *BRCA2* when mutations were within the cancer cluster region of exon 11, RR = 3.4(1.4–8.5)
Struewing et al.	1997	114 *BRCA* mutation carriers	4,759 mutation noncarriers	2 *BRCA1* mutation carriers and 6 *BRCA2* mutation carriers	*BRCA1*: 5382insC, 185delAG and the deletion of 11 bp at position 188 (188del11); *BRCA2*: 6174delT	N/A
Yurgelun et al.	2016	1,260 CRC patients, 1,112 met NCCN criteria for LS	N/A	15 *BRCA1/2* mutation carriers	*BRCA1*: 5382insC *BRCA2*: 6174delT	9/15 (60%) had a history of CRC, 4/15 (27%) had history of endometrial cancer, 1/15(7%) had history of ovarian cancer; 10/15 (66.6%) had family history of any LS cancer, 7/15 (47%) had family history of breast cancer
Yurgelun et al.	2017	7,015 women; 21 incident CRC cases	N/A	16 *BRCA1* mutation carriers and 5 *BRCA2* mutation carriers	N/A	Risk of CRC was 4 folds greater than young women, at age: 30–49 years; HR = 3.81(1.77–7.23)

Note: All estimated data were expressed as ratio (95% confidence interval).

Abbreviations: BCLC, Breast Cancer Linkage Consortium; CRC, colorectal cancer; HR, hazard ratio; LS, Lynch syndrome; N/A, not applicable; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio.

The clinical significance and exon locations of the *BRCA* variants were determined according to ClinVar accessions. While previous studies have described PVs of *BRCA* in breast and ovarian cancers, none of these variants were identified in our study. To date, only a few studies have described *BRCA* variants in CRCs. A previous study analyzing the prevalence and penetrance of germline *BRCA1* and *BRCA2* variants in women with ovarian cancer demonstrated that CRC occurred among first-degree relatives of *BRCA2* carriers when variants were confined to the cancer cluster region of exon 11 (Risch et al., 2001). Comprehensive profiling of *BRCA1* and *BRCA2* variants in breast and ovarian cancers in Chinese patients demonstrated that 57.1% and 59.6% of PVs were distributed in exon 10 of *BRCA1* and exon 10/11 of *BRCA2*, respectively (Gao et al., 2019). Two more studies supported the high prevalence of variants in exon 11 of *BRCA 2*, although the distribution of *BRCA1* variants did not reveal significant clustering (Bhaskaran et al., 2019; Mahdavi et al., 2019). All *BRCA2* variants detected in our study were located in exon 11, which was consistent with results in previous studies. Among *BRCA1* cases, three patients carried an identical variant (c.154C>T [p.Leu52Phe]), located in exon 4, whereas two patients carried an identical variant (c.446A>C [p.Glu149Ala]), located in exon 7, and both variants were predicted as probably damaging. Variant distribution in our study revealed high clustering in *BRCA1*. Although these *BRCA* variants were VUS, their typical phenotypes still necessitate specified screening strategies for the subset in clinical practice. For patients carrying variants in exons 4 and seven of *BRCA1*, supervision and examinations of the gastrointestinal tract, such as colonoscopy, should be performed regularly. For patients carrying variants in exon 11 of *BRCA2*, both the intestine and breasts should be closely monitored.

Multiple, redundant mechanisms of DNA repair coexist within cells, such as MMR, base excision repair, and HR repair pathways. *BRCA* and *BRCA*-like genes, including *ATM, ATR, RAD51, RAD50, BARD1,* and *BRIP1*, are all involved in HR repair pathways. *BRCA*-like variants are associated with a higher risk for breast and ovarian cancers (Lu et al., 2019), however, such tumors are sensitive to treatment with PARP inhibitors and cytotoxic drugs. A case report described a male patient with locally advanced rectal cancer who was identified as carrying the *BRCA1* variant c.4302C>T, Gln1395X. Following two cycles of mFolfox6, pathologic findings from surgical specimens showed a complete pathologic response (Soyano, Baldeo, & Kasi, 2018). Although the phenotypes of *BRCA* variant carriers were not different from those of LS, the effect of the variants was limited, whereas loss of the HR repair pathway along with loss of the *MMR* pathway may sensitize cells to DNA damaging agents. Therefore, we assumed that chemotherapies using cytotoxic drugs may elicit a considerable response in patients carrying *BRCA/BRCA*-like variants. The application of PARP inhibitors in CRCs has not been reported. Nevertheless, it may provide a new prospective for patients carrying *BRCA/BRCA*-like variants who are neither sensitive nor resistant to chemotherapy. Unfortunately, the variants in our study were VUS. Therefore, their significance remains uncertain and needs further verification via functional experiments to provide precise evidence of their phenotypic effects as well as their effects on the response to therapies targeting *BRCA*.

The current study was beset with several limitations. First, as this was a retrospective study, the potential bias in patient selection could not be eliminated. Second, this was a preliminary study on the relation between mutations in the BRCA and HR pathways and CRC, and the sample size was small. We hope that patients carrying variants in HR pathways will attract the attention of clinicians. Furthermore, we are making efforts to enroll more patients with hereditary CRC in future studies. Lastly, as we used NGS, all variants detected in our study were missense and VUS; some VUS are currently being investigated in functional experiments, the results of which will be reported in future.

In conclusion, suspected LS patients carrying *BRCA* and *BRCA*-like variants exhibited moderate cancer penetrance and less aggressive biological characteristics, with an older cancer-onset age, less synchronous and metachronous CRCs, and well-differentiated tumors. Despite being associated with a higher PFS, *BRCA/BRCA*-like variants carry a higher risk for extracolorectal cancer. A stringent surveillance protocol involving regular examination of other susceptible organs is recommended for probands and affected family members of this subset. Due to their high sensitivity to cytotoxic drugs, such as platinum drugs and paclitaxel, chemotherapy using such drugs may elicit a considerable response in patients carrying *BRCA/BRCA*-like variants. The application of PARP inhibitors may provide new prospects for treating this subset of patients who are insensitive or resistant to chemotherapy.

ACKNOWLEDGMENTS

We would like to thank all clinicians from department of colorectal surgery, Fudan University Shanghai Cancer Center, who provided clinical data of this paper. Funding for this study was provided by the National Natural Science Foundation of China (No. 81472620), Shanghai National Natural Science Foundation (No. 16ZR1406700), and th e Development Foundation for Shanghai Talents (No. 2017120).

CONFLICT OF INTEREST

Authors declares no conflict of interest in relation to this manuscript.

AUTHOR CONTRIBUTIONS

Yun Xu and Ye Xu conceived and designed the study. Yun Xu, Cong Li, Fangqi liu, and Zhimin Wang collected and analyzed the data. Yun Xu wrote the paper. Cong Li, Ye Xu, and Fangqi Liu reviewed the paper.

DATA AVAILABILITY STATEMENT

The authors declare that the data supporting the findings of this study are available within the article.

REFERENCES

Abbotts, R., Topper, M. J., Biondi, C., Fontaine, D., Goswami, R., Stojanovic, L., … Rassool, F. V. (2019). DNA methyltransferase inhibitors induce a BRCAness phenotype that sensitizes NSCLC to PARP inhibitor and ionizing radiation. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(45), 22609–22618. https://doi.org/10.1073/pnas.1903765116

Bhaskaran, S. P., Chandratre, K., Gupta, H., Zhang, L., Wang, X., Cui, J., … Wang, S. M. (2019). Germline variation in BRCA1/2 is highly ethnic-specific: Evidence from over 30,000 Chinese hereditary breast and ovarian cancer patients. *International Journal of Cancer*, *145*(4), 962–973. https://doi.org/10.1002/ijc.32176

Brandão, R. D., Mensaert, K., López-Perolio, I., Tserpelis, D., Xenakis, M., Lattimore, V., … Blok, M. J. (2019). Targeted RNA-seq successfully identifies normal and pathogenic splicing events in breast/ovarian cancer susceptibility and Lynch syndrome genes. *International Journal of Cancer*, *145*(2), 401–414. https://doi.org/10.1002/ijc.32114

Brose, M. S., Rebbeck, T. R., Calzone, K. A., Stopfer, J. E., Nathanson, K. L., & Weber, B. L. (2002). Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. *Journal of National Cancer Institute*, *94*(18), 1365–1372. https://doi.org/10.1093/jnci/94.18.1365

Byrum, A. K., Vindigni, A., & Mosammaparast, N. (2019). Defining and modulating 'BRCAness'. *Trends in Cell Biology*, *29*(9), 740–751. https://doi.org/10.1016/j.tcb.2019.06.005

Chalasani, P.; The Breast Cancer Linkage Consortium. (1999). Cancer risks in BRCA2 mutation carriers. *Journal of the National Cancer Institute*, *91*(15), 1310–1316. https://doi.org/10.1093/jnci/91.15.1310.

DePristo, M. A., Banks, E., Poplin, R., Garimella, K. V., Maguire, J. R., Hartl, C., … Daly, M. J. (2011). A framework for variation discovery and genotyping using next-generation DNA sequencing data. *Nature Genetics*, *43*(5), 491–498. https://doi.org/10.1038/ng.806

Feliubadaló, L., López-Fernández, A., Pineda, M., Díez, O., Del Valle, J., Gutiérrez-Enríquez, S., …Balmaña, J. (2019). Opportunistic testing of BRCA1, BRCA2 and mismatch repair genes improves the yield of phenotype driven hereditary cancer gene panels. *International Journal of Cancer*, *145*(10), 2682–2691. https://doi.org/10.1002/ijc.32304

Gao, X., Nan, X., Liu, Y., Liu, R., Zang, W., Shan, G., … Song, L. (2019). Comprehensive profiling of BRCA1 and BRCA2 variants in breast and ovarian cancer in Chinese patients. *Human Mutation*, *41*(3), 696–708. https://doi.org/10.1002/humu.23965

Hampel, H., Frankel, W. L., Martin, E., Arnold, M., Khanduja, K., Kuebler, P., …de la Chapelle, A. (2008). Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *Journal of Clinical Oncology*, *26*(35), 5783–5788. https://doi.org/10.1200/JCO.2008.17.5950

Kirchhoff, T., Satagopan, J. M., Kauff, N. D., Huang, H., Kolachana, P., Palmer, C., … Offit, K. (2004). Frequency of BRCA1 and BRCA2 mutations in unselected Ashkenazi Jewish patients with colorectal cancer. *Journal of National Cancer Institute*, *96*(1), 68–70. https://doi.org/10.1093/jnci/djh006

Kwong, A., Shin, V. Y., Ho, J. C., Kang, E., Nakamura, S., Teo, S. H., … Kim, S. W. (2016). Comprehensive spectrum of BRCA1 and BRCA2 deleterious mutations in breast cancer in Asian countries. *Journal of Medical Genetics*, *53*(1), 15–23. https://doi.org/10.1136/jmedgenet-2015-103132

Li, H., & Durbin, R. (2010). Fast and accurate long-read alignment with Burrows-Wheeler transform. *Bioinformatics*, *26*(5), 589–595. https://doi.org/10.1093/bioinformatics/btp698

Lin, K. M., Ternent, C. A., Adams, D. R., Thorson, A. G., Blatchford, G. J., Christensen, M. A., … Lynch, H. T. (1999). Colorectal cancer in hereditary breast cancer kindreds. *Diseases of the Colon & Rectum*, *42*(8), 1041–1045. https://doi.org/10.1007/bf02236700

Liu, F., Yang, L., Zhou, X., Sheng, W., Cai, S., Liu, L., … Xu, Y. (2014). Clinicopathological and genetic features of Chinese hereditary non-polyposis colorectal cancer (HNPCC). *Medical Oncology*, *31*(10), 223. https://doi.org/10.1007/s12032-014-0223-1

Llor, X., Pons, E., Xicola, R. M., Castells, A., Alenda, C., Piñol, V., … Gassull, M. A. (2005). Differential features of colorectal cancers fulfilling Amsterdam criteria without involvement of the mutator pathway. *Clinical Cancer Research*, *11*(20), 7304–7310. https://doi.org/10.1158/1078-0432. CCR-05-0965.

Llort, G., Chirivella, I., Morales, R., Serrano, R., Sanchez, A. B., Teulé, A., … Graña, B. (2015). SEOM clinical guidelines in Hereditary Breast and ovarian cancer. *Clinical & Translational Oncology*, *17*(12), 956–961. https://doi.org/10.1007/s12094-015-1435-3

Lord, C. J., & Ashworth, A. (2016). BRCAness revisited. *Nature Reviews Cancer*, *16*(2), 110–120. https://doi.org/10.1038/nrc.2015.21

Lu, H. M., Li, S., Black, M. H., Lee, S., Hoiness, R., Wu, S., … Elliott, A. (2019). Association of breast and ovarian cancers with predisposition genes identified by large-scale sequencing. *JAMA Oncology*, *5*(1), 51–57. https://doi.org/10.1001/jamaoncol.2018.2956

Lynch, H. T., Snyder, C. L., Shaw, T. G., Heinen, C. D., & Hitchins, M. P. (2015). Milestones of Lynch syndrome: 1895–2015. *Nature Reviews Cancer*, *15*(3), 181–194. https://doi.org/10.1038/nrc3878

Mahdavi, M., Nassiri, M., Kooshyar, M. M., Vakili-Azghandi, M., Avan, A., Sandry, R., … Gopalan, V. (2019). Hereditary breast cancer; Genetic penetrance and current status with BRCA. *Journal of Cellular Physiology*, *234*(5), 5741–5750. https://doi.org/10.1002/jcp.27464

Mavaddat, N., Peock, S., Frost, D., Ellis, S., Platte, R., Fineberg, E., … Easton, D. F. (2013). Cancer risks for BRCA1 and BRCA2 mutation carriers: Results from prospective analysis of EMBRACE. *Journal of National Cancer Institute*, *105*(11), 812–822. https://doi.org/10.1093/jnci/djt095

McLaren, W., Gil, L., Hunt, S. E., Riat, H. S., Ritchie, G. R., Thormann, A., … Cunningham, F. (2016). The ensembl variant effect predictor. *Genome Biology*, *17*(1), 122. https://doi.org/10.1186/s13059-016-0974-4

Mersch, J., Jackson, M. A., Park, M., Nebgen, D., Peterson, S. K., Singletary, C., … Litton, J. K. (2015). Cancers associated with BRCA 1 and BRCA 2 mutations other than breast and ovarian. *Cancer*, *121*(2), 269–275. https://doi.org/10.1002/cncr.29041

Moran, A., O'Hara, C., Khan, S., Shack, L., Woodward, E., Maher, E. R., … Evans, D. G. (2012). Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. *Familial Cancer*, *11*(2), 235–242. https://doi.org/10.1007/s10689-011-9506-2

Moynahan, M. E., Pierce, A. J., & Jasin, M. (2001). BRCA2 is required for homology-directed repair of chromosomal breaks. *Molecular Cell*, *7*(2), 263–272. https://doi.org/10.1016/s1097-2765(01)00174-5

Niell, B. L., Rennert, G., Bonner, J. D., Almog, R., Tomsho, L. P., & Gruber, S. B. (2004). BRCA1 and BRCA2 founder mutations and the risk of colorectal cancer. *Journal of National Cancer Institute*, *96*(1), 15–21. https://doi.org/10.1093/jnci/djh008

Phelan, C. M., Iqbal, J., Lynch, H. T., Lubinski, J., Gronwald, J., Moller, P., … Narod, S. A. (2014). Incidence of colorectal cancer in BRCA1 and BRCA2 mutation carriers: Results from a follow-up study. *British Journal of Cancer*, *110*(2), 530–534. https://doi.org/10.1038/bjc.2013.741

Ramos, A. H., Lichtenstein, L., Gupta, M., Lawrence, M. S., Pugh, T. J., Saksena, G., … Getz, G. (2015). Oncotator: Cancer variant annotation tool. *Human Mutation*, *36*(4), E2423–E2429. https://doi.org/10.1002/humu.22771

Risch, H. A., McLaughlin, J. R., Cole, D. E., Rosen, B., Bradley, L., Kwan, E., … Narod, S. A. (2001). Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *American Journal of Human Genetics*, *68*(3), 700–710. https://doi.org/10.1086/318787

Saraste, D., Jaras, J., & Martling, A. (2020). Population-based analysis of outcomes with early-age colorectal cancer. *British Journal of Surgery*, *107*(3), 301–309. https://doi.org/10.1002/bjs.11333

Siegel, R. L., Miller, K. D., Fedewa, S. A., Ahnen, D. J., Meester, R. G. S., Barzi, A., & Jemal, A. (2017). Colorectal cancer statistics. *CA-A Cancer Journal for Clinicians*, *67*(3), 177–193. https://doi.org/10.3322/caac.21395

Soyano, A. E., Baldeo, C., & Kasi, P. M. (2018). BRCA mutation and its association with colorectal cancer. *Clinical Colorectal Cancer*, *17*(4), e647–e650. https://doi.org/10.1016/j.clcc.2018.06.006

Struewing, J. P., Hartge, P., Wacholder, S., Baker, S. M., Berlin, M., McAdams, M., … Tucker, M. A. (1997). The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *New England Journal of Medicine*, *336*(20), 1401–1408. https://doi.org/10.1056/NEJM199705153362001

Suchy, J., Cybulski, C., Górski, B., Huzarski, T., Byrski, T., Dębniak, T., … Narod, S. A. (2010). BRCA1 mutations and colorectal cancer in Poland. *Familial Cancer*, *9*(4), 541–544. https://doi.org/10.1007/s10689-010-9378-x

Susswein, L. R., Marshall, M. L., Nusbaum, R., Vogel Postula, K. J., Weissman, S. M., Yackowski, L., … Chung, W. K. (2016). Pathogenic and likely pathogenic variant prevalence among the first 10,000 patients referred for next-generation cancer panel testing. *Genetics in Medicine*, *18*(8), 823–832. https://doi.org/10.1038/gim.2015.166

Thorvaldsdóttir, H., Robinson, J. T., & Mesirov, J. P. (2013). Integrative Genomics Viewer (IGV): High-performance genomics data visualization and exploration. *Brief Bioinformatics*, *14*(2), 178–192. https://doi.org/10.1093/bib/bbs017

Umar, A., Boland, C. R., Terdiman, J. P., Syngal, S., de la Chapelle, A., Rüschoff, J., … Srivastava, S. (2004). Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *Journal of National Cancer Institute*, *96*(4), 261–268. https://doi.org/10.1093/jnci/djh034

Van Asperen, C. J., Brohet, R. M., Meijers-Heijboer, E. J., Hoogerbrugge, N., Verhoef, S., & Vasen, H. F. (2005). Cancer risks in BRCA2 families: Estimates for sites other than breast and ovary. *Journal of Medical Genetics*, *42*(9), 711–719. https://doi.org/10.1136/jmg.2004.028829

Vasen, H. F., Watson, P., Mecklin, J. P., & Lynch, H. T. (1999). New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology*, *116*(6), 1453–1456. https://doi.org/10.1016/s0016-5085(99)70510-x

Venkitaraman, A. R. (2003). A growing network of cancer-susceptibility genes. *New England Journal of Medicine*, *348*(19), 1917–1919. https://doi.org/10.1056/NEJMcibr023150

Yurgelun, M. B., Allen, B., Kaldate, R. R., Bowles, K. R., Judkins, T., Kaushik, P., … Syngal, S. (2015). Identification of a variety of mutations in cancer predisposition genes in patients with suspected Lynch syndrome. *Gastroenterology*, *149*(3), 604–613. https://doi.org/10.1053/j.gastro.2015.05.006

Yurgelun, M. B., Kulke, M. H., Fuchs, C. S., Allen, B. A., Uno, H., Hornick, J. L., … Syngal, S. (2017). Cancer susceptibility gene mutations in individuals with colorectal cancer. *Journal of Clinical Oncology*, *35*(10), 1086–1095. https://doi.org/10.1200/JCO.2016.71.0012

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Xu Y, Li C, Wang Z, Liu F, Xu Y. Comparison of suspected Lynch syndrome patients carrying *BRCA* and *BRCA*-like variants with Lynch syndrome probands: Phenotypic characteristics and pedigree analyses. *Mol Genet Genomic Med*. 2020;8:e1359. https://doi.org/10.1002/mgg3.1359