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

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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 1 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
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 (Moyahan, Pierce, & Jasim, 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). Aberration of other proteins in HR repair pathways, such as RAD51 (OMIM accession number: 179617), ATM (OMIM accession number: 600185), 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; Struwing 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 OncoViz (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); χ² = 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 (χ² = 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) | χ²/t value | p value |
|-----------------------------------------------------|--------------------|--------------------------------|------------|---------|
| Gender                                              |                    |                                |            |         |
| Male                                                | 24 (57.1%)         | 11 (55.0%)                     | 0.025      | .874    |
| Female                                              | 18 (42.9%)         | 9 (45.0%)                      |            |         |
| Age (years)³                                        | 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)²                                     | 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)
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).

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 ($t = −3.470, p = .001$) 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.

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 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 ($\chi^2 = 0.162, p = .688$).

### Table 1 (Continued)

| Characteristic | MMR group (N = 42) | BRCA/BRCA-like group (N = 20) | $\chi^2$ / t value | p value |
|---------------|-------------------|------------------------------|-------------------|--------|
| N2            | 4 (9.6%)          | 3 (15.0%)                    | 0.616             | .433   |
| Metastasis    |                   |                              |                   |        |
| 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%)                    |                   |        |

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

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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).
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
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

### Table 3: Comparison of pedigrees between MMR group and BRCA/BRCA-like group

| Variable | MMR group (N = 42) | BRCA/BRCA-like group (N = 20) | $\chi^2$ 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 | .004 |
| 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.
(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.
| 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 |
| Monan 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(0.6–6.3), 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) |
| Struwing 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 *BRCA2* 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 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.

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**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.

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**SUPPORTING INFORMATION**

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

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