Pathological features and clinical behavior of Lynch syndrome-associated ovarian cancer

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HIGHLIGHTS

• Lynch syndrome-associated ovarian cancer (LSAOC) is rare and difficult to study.
• This is the largest reported series of OC from proven Lynch syndrome carriers.
• Endometrioid OC was most common, followed by high grade serous, clear cell and mixed histology.
• Most LSAOC was detected at stage 1 and overall 5-year survival was excellent at 80%.
• Surveillance found 2 LSAOC; 3 more were diagnosed following surgery for screen-detected endometrial cancer.

ABSTRACT

Objective. Lynch syndrome (LS) is an inherited tumor predisposition condition caused by mutations in the mismatch repair (MMR) genes. Mutation carriers are at increased risk of various malignancies, including ovarian cancer (OC). Relatively little is known about the pathological features and clinical behavior of LS associated OC.

Methods. We analyzed the data of 1047 proven MMR mutated individuals from a prospectively maintained database at a large referral center for genomic medicine in the North West of England. Data were crosschecked with pathology reports, the National Cancer Registry and death certificates, where appropriate. Data from gynecological surveillance and risk reducing surgery were analyzed.

Results. We identified 53 cases of LSAOC in proven MMR mutated individuals. The cumulative risk of LSAOC was 20% at age 80 in those who retained their ovaries. LSAOC presented at an earlier age (average 51, range 24–70 years) than sporadic OC. The predominant histological subtype was endometrioid adenocarcinoma (53%). Most cases presented early (85% at stage I/II vs. 15% at stage III/IV, \(p < 0.001\)) and overall survival was excellent (80% 5-year survival), however, patients with advanced disease had a poor prognosis (40% 5-year survival). Most women were found to have LS after their OC diagnosis, however, two were detected at Stage Ic through gynecological surveillance and a further three were detected following surgery for screen-detected synchronous endometrial pathology.

Conclusion. The predominance of early stage disease in LSAOC is linked to its good prognosis. We support risk-reducing surgery for women whose families are complete especially if undertaking hysterectomy for endometrial risk, and ovarian surveillance as part of gynecological screening for those who have not.

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1. Introduction

Lynch syndrome (LS) is an autosomal dominant tumor predisposition condition caused by mutations in the mismatch repair (MMR) genes. The syndrome was first described in 1913 by Warthin and further delineated by Lynch in 1966 [1]. Lynch syndrome is thought to affect 1:2000 to 1:370 individuals [2,3]. As a result of a dysfunctional MMR system, cells become hyper-mutated with a high microsatellite (MSI-H) instability phenotype; mutations in the oncoprotective genes...
eventually lead to neoplastic changes and tumorigenesis. Mutation carriers are at high risk of colorectal cancer (CRC), endometrial cancer (EC) and a spectrum of other malignancies, including ovarian cancer (OC). Diagnosis is suspected from clinical presentation and family history, and confirmed with immunohistochemistry, MSI analysis and ultimately genomic sequencing of the known MMR genes.

OC is the leading cause of death from gynecological cancer in the developed world [4]. Symptoms are often vague at onset leading to a delayed diagnosis. The lifetime risk of Lynch syndrome-associated OC (LSAOC) is in the region of 6–14% [4,5], with around 2% of all ovarian cancers due to Lynch syndrome, although studies are lacking and sample sizes are small [6]. There is a clinical imperative to identify LSAOC since surveillance strategies can be used to identify and treat premalignant and early stage cancers of other anatomical sites, particularly those of the rectum and colon. In addition, potentially affected relatives can be offered diagnostic testing. Lynch syndrome-associated colorectal cancers have distinctive pathological features that arouse diagnostic suspicion [7–9], however, the clinicopathological features of LSAOC remain poorly defined. Here we present the largest case series of LSAOC in known Lynch syndrome mutation carriers. We explore the clinicopathological features of these tumors, associations between the genetics and the disease and disease-specific survival analysis.

2. Methods

The clinical records of the Manchester Centre for Genomic Medicine, a large tertiary referral genetics center in the North West of England in the United Kingdom, were searched for cases of LSAOC. This was facilitated by an electronic prospectively maintained clinical database, which is maintained by a dedicated data manager. All those included on the database have given formal consent to have their data analyzed anonymously and published. The genetic center serves a population of 5.6 million people. In total 1047 proven mutation carriers are included in the database. Of these, 577 are women. Only those with a confirmed diagnosis of Lynch syndrome based on germline sequencing were included in this study. Fig. 1 outlines the numbers of patients included and excluded at each stage of stratification. Patients at potential risk of LS are referred as either affected or unaffected individuals where there is young onset of colorectal, endometrial and/or ovarian cancer or a pattern of these cancers suggestive of LS. Testing is usually directed by immunohistochemistry (IHC) of relevant tumors with initial testing by next generation sequencing of MSH2, MLH1 and MSH6. PMS2 is only tested if there is loss of PMS2 protein on IHC. All mutations are assessed for pathogenicity utilizing the INSIGHT dataset. All Lynch diagnostic tests are performed within a nationally accredited genetics laboratory and with full consent from patients.

Women with known Lynch syndrome and those considered at risk of LS or an LS-like syndrome are offered gynecological cancer surveillance even in the absence of a proven MMR mutation. This has been routine practice since 1997. Each year, women undergo an outpatient hysterectomy and vaginal ultrasound surveillance for endometrial pathology. Ovarian surveillance by ultrasound and serum cancer antigen 125 (CA125) testing is individualized according to family history. There are currently 87 women enrolled in this surveillance program, approximately two thirds of whom have not yet had their Lynch syndrome status tested or confirmed.

We collated clinical data from the database and the patients’ case notes for all women with proven LSAOC. Pedigree data were used to assess whether they met the Bethesda guideline criteria. Patients were tracked from the time of LSAOC diagnosis and censored at the time of death or last follow up. Individual date of death data were collected from the National Cancer Registry during the course of the patient’s clinical care. In addition, cause of death was established from official death certificates, where appropriate. Pathology reports were collected and cancers were staged, on the basis of these original reports, in line with the International Federation of Gynecology and Obstetrics (FIGO) 2009 criteria. This allowed for standardization of the disease picture. All data were anonymized the time of data extraction. Descriptive statistics were generated, including means, confidence intervals and proportions. Statistical analysis was performed using a combination of both Graphpad Prism version 7 (California USA) and StataSE version 13 (StataCorp Texas USA) software. Statistical hypothesis testing was completed with the use of analysis of variance or student t-test, as appropriate. Results were tabulated or presented graphically. Percentage survival was generated with the use of Kaplan-Meier algorithm.

3. Results

In our cohort, the lifetime cumulative risk of LSAOC was 2% at 40 years of age, 15% at 60 years and 20% at 80 years of age (Fig. 2). Twenty-four percent of women were censored at the time of bilateral salpingo-oophorectomy for LSAEC prevention or treatment. In total, 53 LSAOC tumors were identified. The mean age of diagnosis was 51 years (range 24–70 years). Diagnosis of OC dated from 1956 to 2015. Mean period of follow up, from the time of LSAOC diagnosis, was 64 months. Three of the four Lynch syndrome genes were represented in the population with the exception of PMS2. One individual carried a bi-allelic mutation in PMS2 giving her a diagnosis of constitutional mismatch repair deficiency (CMMRD) rather than Lynch syndrome.

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![Fig. 1. A flow diagram outlining the inclusion stratification for the study. Asterix (*) denotes patient with homozygous PMS2 mutation, excluded from further analysis.](Image)

![Fig. 2. Lifetime cumulative incidence of ovarian cancer in our cohort (n = 577). Those who had undergone bilateral oophorectomy (n = 140) were censored at the date of oophorectomy.](Image)
syndrome, and was excluded from analysis. In total, there were 17 MLH1, 28 MSH2 and 7 MSH6 proven mutation carriers. The mean age of LSAC in MLH1 was 48 years, in MSH2 it was 52 years and in MSH6 the average was 53 years. There was no significant difference between age at diagnosis of LSAC and mutated gene (p = 0.51 ANOVA), although numbers are small. Of the 36 women with complete datasets (Table 1), eight met the Bethesda criteria for diagnosis of Lynch syndrome; this constitutes just 22% of the cohort.

Table 1
Tabulated clinical information regarding LSAC and subsequent cancer diagnoses. Only cases with near complete data sets are shown. Abbreviations: NK: not known, CRC: colorectal cancer, AH: atypical hyperplasia, AC: adjuvant chemotherapy, EC: endometrial cancer, TCC: transitional cell carcinoma, RCC, renal cell carcinoma, DCIS: ductal carcinoma in situ. *signifies cause of death was attributed to OC. § is a patient with bi-allelic PMS2 mutation and therefore constitutional mismatch repair deficiency (CMMRD) rather than LS and is included here for information only.

<table>
<thead>
<tr>
<th>ID</th>
<th>Mutation</th>
<th>Tumor</th>
<th>Age at diagnosis</th>
<th>Year of diagnosis</th>
<th>Screen detected</th>
<th>FIGO (2009)</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Other Neoplasms</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>MLH1</td>
<td>Endometrioid</td>
<td>42</td>
<td>2006</td>
<td>No</td>
<td>1b</td>
<td>Surgery</td>
<td>Alive</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>MLH1</td>
<td>Mixed</td>
<td>52</td>
<td>1997</td>
<td>No</td>
<td>2a</td>
<td>Surgery</td>
<td>Dead (1997)</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>MLH1</td>
<td>Clear cell</td>
<td>47</td>
<td>2004</td>
<td>No</td>
<td>1a</td>
<td>Surgery</td>
<td>Dead (2006)</td>
<td>Nil</td>
</tr>
<tr>
<td>4</td>
<td>MLH1</td>
<td>Endometrioid</td>
<td>38</td>
<td>2012</td>
<td>No*</td>
<td>2c</td>
<td>Surgery</td>
<td>Alive</td>
<td>Dukes A CRC and AH**</td>
</tr>
<tr>
<td>5</td>
<td>MLH1</td>
<td>Endometrioid</td>
<td>37</td>
<td>1997</td>
<td>No</td>
<td>1b</td>
<td>Surgery + AC</td>
<td>Alive</td>
<td>Nil</td>
</tr>
<tr>
<td>6</td>
<td>MLH1</td>
<td>Clear cell</td>
<td>60</td>
<td>2005</td>
<td>No</td>
<td>2b</td>
<td>Surgery + AC</td>
<td>Alive</td>
<td>Nil</td>
</tr>
<tr>
<td>7</td>
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<td>Endometrioid</td>
<td>45</td>
<td>1960</td>
<td>No</td>
<td>1a</td>
<td>Surgery</td>
<td>Dead (1996)</td>
<td>EC**</td>
</tr>
<tr>
<td>8</td>
<td>MLH1</td>
<td>Endometrioid</td>
<td>46</td>
<td>1988</td>
<td>No</td>
<td>3a</td>
<td>Surgery</td>
<td>Dead (1989)</td>
<td>EC**</td>
</tr>
</tbody>
</table>

The histopathological features of the LSAC tumors are presented in Table 2. There was a preponderance of high-grade endometrioid tumors (n = 19), with them constituting 53%. This was followed high-grade serous adenocarcinomas (n = 6), and mixed tumors (n = 4) constituting 17% and 11% respectively. Clear cell carcinoma (n = 4) constituted 11%. There were singular recorded cases of anaplastic neuroendocrine (n = 1), yolk sac (n = 1) and carcinosarcoma (n = 1) tumors, each constituting 3%. The stage of the disease was verified in 35 cases. Most patients
presented with stage 1 disease [stage 1a, 12 (34%); stage 1b, 4 (11%); stage 1c, 7 (20%)] Seven women (20%) presented with stage 2 disease, 4 (11%) with stage 3 and 1 (3%) with stage 4 disease, respectively.

Synchronous endometrial cancer or atypical hyperplasia was seen in 9 women (25%). Contemporaneous histological opinion favored synchronous primary ovarian pathology rather than metastasis. There were 11 deaths (29%) recorded within the cohort. Of these, six (17%) were stage 1, and the remaining three were documented as stage 2, 4.

Of the six stage 1 cases, one woman with stage 1a or 1b disease 

**Table 2** Distribution of histopathology by Lynch syndrome gene mutation.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Number</th>
<th>Mutation type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid</td>
<td>19</td>
<td>MLH1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>MSH6</td>
<td>2</td>
</tr>
<tr>
<td>Clear cell</td>
<td>4</td>
<td>MLH1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6</td>
<td>0</td>
</tr>
<tr>
<td>High grade serous</td>
<td>6</td>
<td>MLH1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6</td>
<td>0</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>1</td>
<td>MLH1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6</td>
<td>0</td>
</tr>
<tr>
<td>Mixed</td>
<td>4</td>
<td>MLH1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6</td>
<td>2</td>
</tr>
<tr>
<td>Other*</td>
<td>2</td>
<td>MLH1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6</td>
<td>1</td>
</tr>
</tbody>
</table>

* In the other category 1 × Yolk sac (MSH6) and 1 × Anaplastic neuroendocrine (MSH2).

**Discussion**

Here we present the largest single institution cohort study of ovarian cancer in proven Lynch syndrome carriers and the first from the United Kingdom. We add to the body of evidence that LSAOC presents at an earlier age than OC in non-Lynch syndrome carriers. The lifetime cumulative risk of OC in our cohort was 20%. It is likely that this is an overestimate as we have not corrected for testing bias, whereby affected family members are more likely to be tested for LS. In order to adjust for this, analyses need to take into account untested first-degree relatives who may still have up to a 50% chance of carrying the mutation. Our previous work accounting for this estimated cumulative lifetime risk of OC to be closer to 6–8% [10]. Here, we show that LSAOC generally presents at an early stage, in keeping with previous reports [10,11]. The most common histological subtype in our cohort was endometrioid adenocarcinoma but high-grade serous tumors were also seen.

Previous work suggests that the lifetime risk of OC in Lynch syndrome is around 6–14% [12] depending on the particular gene that is mutated. A 20% lifetime risk of OC for MLH1, 24% MSH2 and a 1% risk for MSH6 mutation was reported in one large series of carriers from 537 families [4]. In our cohort, similar proportions of women with MLH1, MSH2 and MSH6 mutations developed OC (Fig. 1), however only one woman with a PMS2 mutation developed OC. She had a biallelic PMS2 mutation and thus a diagnosis of constitutional mismatch repair deficiency (CMMRD) rather than Lynch syndrome. There were no cases of OC amongst our 21 heterozygous PMS2 mutation carriers.

This study adds to the substantial evidence reporting an earlier age of onset of LSAOC compared to sporadic OC [10,13–15]. The median age was 48 years and 79% of women in our cohort were under the age of 50 when they were diagnosed with OC. This compares to a median age of 63 years in the general population [16]. Our data highlight the importance of a low threshold for Lynch syndrome diagnostic testing alongside BRCA testing in women who present with OC under the age of 50 years. Established clinical criteria for Lynch testing, specifically the Bethesda guidelines, are not sensitive in the diagnosis of LSAOC, with only 9 women meeting the criteria.

Historically, ovarian cancer has been categorized based on morphology into Type I and Type II disease [16], although modern genetic approaches call into question the utility of such an approach, favoring genetic categorization based on mutation status as it better predicts prognosis and treatment response [16–18]. Indeed there is evidence that LSAOC is genetically distinct from sporadic OC [19]. Nonetheless, Type I disease is typically low grade with an improved overall survival rate compared with high grade, type II disease [16,18]. We found a predominance of Type I tumors in our cohort, with over 50% of endometrioid morphology. This may help to explain the good survival rates in our population. In non-Lynch syndrome and BRCA-associated OC, high-grade serous cancers predominate [17]. We found a smaller proportion of high-grade serous OC in our cohort, similar to the results of Heldcr-voordink et al. [9]. Their systematic review draws its historical projections from studies where subjects were not proven Lynch syndrome carriers, in contrast to the current study [15]. The 10-year overall survival of LSAOC was 75% in our cohort. This compares with a 10-year survival of 35% for non-Lynch syndrome associated OC [19].

Fig. 3. Overall survival for women diagnosed with Lynch syndrome associated ovarian cancer in our cohort.
their MMR genes. A dedicated data manager prospectively maintains our database to ensure its accuracy and completeness. It forms the basis by which clinical follow-up is organized and is regularly audited for quality assurance. Cause of death is confirmed through vertical sources including the National Cancer Registry and through death certification. This ensures the robustness of our survival analyses. Our study is limited by small numbers because LSAOC is rare. The accuracy of the cause of death data is uncertain since it is based on expert opinion in death certification rather than post-mortem findings. We also have limited events for our survival analysis; this is especially true of deaths in advanced staged disease, mainly because most women presented early. Our work needs validation through international collaboration. Our survival data are comparable with the largest cohort described in the literature [10]. However, only prospective studies can fully investigate the impact of stage, early detection and treatment modality on survival from LSAOC.

OC prevention and early detection may improve disease specific outcomes in the general population and BRCA mutation carriers [17–19]. The evidence for such an impact in LSAOC is poorly established. There is general consensus that women with Lynch syndrome should be offered risk-reducing prophylactic hysterectomy and bilateral salpingo-oophorectomy at around 45 years of age [20–22]. The utility of OC surveillance in Lynch syndrome is not yet evidence based [23]. Nonetheless, we are encouraged by the results in our cohort with two of five OCs detected at stage 1 through our local surveillance program, and another three with occult disease diagnosed at hysterectomy for screen-detected endometrial abnormalities. Surveillance can be tailored to individual women since MSH6 carriers have a high risk of endometrial cancer but a lower risk of OC [14,24]. Women with PMS2 mutations appear to be at lowest risk of OC. Large collaborative retrospective studies, or adequately powered prospective studies, are needed to provide new insights into LSAOC.

Contribution to authorship

All authors contributed to study design, data collection and interpretation. NR and EC prepared the first draft of the manuscript. All authors reviewed and agreed the final version of the manuscript.

Conflicts of interest

The authors report no conflicts of interest.

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