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Characteristics of Lynch syndrome associated ovarian cancer

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HIGHLIGHTS

- Ovarian cancer in women with LS develops at an early age, with a wide age-range of onset and at an early stage.
- These LS associated ovarian cancers most often has an endometrioid or serous type histology with a good overall survival.
- The early stage of ovarian cancer, in women with LS, could not be attributed to annual gynecological surveillance.

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ABSTRACT

Objective. To describe clinical characteristics of Lynch syndrome associated ovarian cancer and the efficacy of surveillance in the early detection of these ovarian cancers.

Methods. All Lynch syndrome associated ovarian cancer cases identified in either the Dutch Lynch syndrome registry (DLSR) between 1987 and 2016, and/or the cohort at the University Medical Center Groningen (UMCG) between 1993 and 2016 were included. Clinical data on age at diagnosis, mutation type, histological type, FIGO stage, treatment, follow-up and gynecological surveillance were collected.

Results. A total of 46/798 (6%) women in the DLSR and 7/80 (9%) in the UMCG cohort were identified as LS associated ovarian cancer patients. The median age at ovarian cancer diagnosis was 46.0 years (range 20–75 years). The most frequently reported histological type was endometrioid adenocarcinoma (40%; $n = 21$) and serous carcinoma (36%; $n = 19$). Most tumors (87%; $n = 46$) were detected at an early stage (FIGO I/II). Forty-one of 53 (77%) patients were diagnosed with ovarian cancer before LS was diagnosed. In the other 12/53 (23%) women, ovarian cancer developed after starting annual gynecological surveillance for LS; three ovarian cancers were screen-detected in asymptomatic women. Overall survival was 83%.

Conclusion. Ovarian cancer in women with LS has a wide age-range of onset, is usually diagnosed at an early stage with predominantly endometrioid type histology and a good overall survival. The early stage at diagnosis could not be attributed to annual gynecological surveillance.

1. Introduction

Hereditary predisposition accounts for approximately 5% of endometrial cancers and up to 24% of epithelial ovarian cancers [1,2]. LS is an autosomal dominant tumor syndrome, caused by a germline mutation in one of the DNA mismatch repair (MMR) genes, which, after a

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loss of function mutation of the normal allele, leads to microsatellite instability (MSI) and increased cancer risk. It accounts for most inherited endometrial cancers and a minority of inherited ovarian cancers, whereas a germline mutation in a *BRCA1* or *BRCA2* gene accounts for most inherited ovarian cancers [3–6]. In women with LS, endometrial cancer is after colon cancer the most common tumor type, [7,8] with a cumulative lifetime risk of 15–60% and a mean age at diagnosis of 55–60 years, (range 30–80 years) depending on which gene is mutated [7,9–11]. The cumulative lifetime risk of ovarian cancer in LS varies between 6 and 12% with a reported mean age at diagnosis of around 45 years [7,11–15]. Endometrial surveillance by transvaginal ultrasound and endometrial sampling can be effective in diagnosing endometrial cancer at a pre-invasive or early stage [9,16,17]. The value of surveillance for ovarian cancer in LS has never been established and is under debate [9,14,18]. Ovarian cancer surveillance has not been proven effective in the general population and among women with a *BRCA1/2* gene mutation [19–24]. Most sporadic and *BRCA*-associated ovarian cancers are diagnosed at an advanced stage and interval ovarian cancers can present shortly after surveillance visits. In only a few surveillance studies a small number of women with LS are included, the information about clinical and histopathological characteristics of ovarian cancer in women with LS is therefore scattered and unclear [15,25–27].

The aim of this study was to analyze the clinical and histopathological characteristics of LS associated ovarian cancer and to investigate the role of surveillance in the early detection of these ovarian cancers.

2. Materials and methods

For this study, data of two prospective cohorts of ovarian cancer patients were used. The first cohort was derived from the Dutch Lynch Syndrome Registry (DLSR) between 1987 and 2016. The second cohort was from the Family Cancer Clinic at the University Medical Center Groningen (UMCG) between 1993 and 2016. The DLSR was started in 1987 and embedded in The Netherlands Foundation for the detection of Hereditary Tumors, which was established in 1985 [28]. Data managers of the Netherlands Foundation for the detection of Hereditary Tumors registry prospectively collect information on surveillance and cancer diagnosis in families with genetic cancer syndromes. All patients registered in the DLSR have given written informed consent before their medical information was collected in the DLSR.

The second cohort consists of all women with LS from the Family Cancer Clinic of the UMCG. All women gave written informed consent before their medical information was collected in the UMCG LS registry.

Protection of a patient's identity was guaranteed by assigning study specific unique patient numbers. The Medical Research Involving Human Subjects Act (Dutch: WMO) is not applicable to this study since it is a study using anonymized data from medical records. Therefore, the study was exempted from being approved by the Institutional Review Board.

2.1. Inclusion criteria

Women with LS associated ovarian cancer (i.e. proven carrier of a pathogenic mutation in either *MLH1*, *MSH2*, *MSH6* or *PMS2* or with a family history fulfilling the Amsterdam criteria) who developed ovarian cancer before or after the diagnosis of LS within the fore mentioned study period, were included in this study. There were no LS associated ovarian cancer patients who also carried a *BRCA 1/2* mutation.

2.2. Data collection

For all women with LS associated ovarian cancer in both cohorts, the following data was extracted: the age at diagnosis of ovarian cancer, type of gene mutation, histopathology report of the ovarian cancer (from the DLSR, from the UMCG or from the hospital in the Netherlands where the patient had been treated), primary treatment as well as adjuvant treatment (chemotherapy, radiotherapy, hormonal therapy), the occurrence of synchronous and metachronous cancer, the number and date of a recurrence and the disease specific survival. Pathology review has not been performed. Only patients who gave permission for registration in the DLSR cohort or the UMCG database were included.

Data about surveillance was extracted from the patient files; whether or not the woman was under annual surveillance for LS before ovarian cancer was diagnosed, whether the ovarian cancer was screen-detected or an interval cancer and the presence and type of symptoms at time of ovarian cancer diagnosis. All women with LS who underwent gynecological surveillance prior to diagnosis of ovarian cancer underwent annual transvaginal ultrasound, and measurement of CA125. According to the Dutch guideline on hereditary colon cancer, (2008, revised in 2015), it was also advised to perform standard endometrial sampling during gynecological surveillance in women with LS [29].

If data about the histopathology of ovarian cancer or surveillance were not available in the DLSR, this data was obtained from the hospitals in the Netherlands in which the surveillance and/or the treatment of the ovarian cancer were performed. If a woman with LS was registered in both databases ($n = 42$), she was counted in the DLSR only and not counted twice.

2.3. Data analysis

In this study, the median age at diagnosis of ovarian cancer was described and also the mean age, to be able to compare these data with other studies, which mostly report the mean age at diagnosis. Differences (in stage, histological type, treatment, and outcome) between screen-detected ovarian cancers and ovarian cancers found by symptoms were studied. Statistical analysis was performed by chi-square testing or Mann-Whitney U testing, depending on the type of variables. Overall survival was defined as the interval from the date of ovarian cancer diagnosis to the date of dead of disease. The Kaplan-Meier method was used to create overall survival curves. The data analysis was performed with SPSS statistics version 20.

3. Results

The DLSR contained 798 female LS carriers. The mean age of this cohort was 58 years with a median age of 58 years (range 23–98 years), at time of study entry. In this registry 241 (30%) women were carrier of a *MLH1* gene mutation, 276 (35%) of a *MSH2*, 237 (30%) of a *MSH6*, 41 (5%) had a *PMS2* gene mutation and for three women, (who were included in the early days from families fulfilling the Amsterdam criteria) the type of mutation was not recorded. (Table 1) The cohort of the UMCG consists of 80 female LS carriers with a mean age of 49 years (range 28–75 years) and a median age of 48 years at ovarian cancer diagnosis. In 27 (36%) women a *MLH1* gene mutation was present, 18 (24%) had a *MSH2*, 18 (24%) a *MSH6*, 13 (17%) a *PMS2* mutation and for four women the type of mutation is not known. (Table 1) In total 878 female LS women were included in this study of which only patients with LS associated ovarian cancer are analyzed.

Forty-six of 798 women (6%) of the DLSR had LS associated ovarian cancer and seven of 80 (9%) of the UMCG cohort. (Table 2) The mean age at ovarian cancer diagnosis in these 53 patients was 46 years, with a median age of 46 years (range 20–75 years). Twenty-five percent of the women with LS associated ovarian cancer were diagnosed before the age of 40. (Table 2 and Fig. 1) Of both cohorts 4,9% of all LS carriers had developed ovarian cancer by age 50 and 8.5% by age 70. (Table 1) In 48/53 women with LS associated ovarian cancer, the mutation status was known and consisted of 12 *MLH1*, 18 *MSH2*, 16 *MSH6* and 2 *PMS2* gene mutation carriers. (Table 2) In five cases LS was diagnosed based on family history fulfilling the Amsterdam criteria, however the type of mutation had not been noted.

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