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Review

Ovarian cancer in Lynch syndrome; a systematic review

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Abstract ***Objective:*** The aim was to systematically review the characteristics of ovarian cancer in women with Lynch syndrome (LS) and evaluate the role of surveillance in detection of ovarian cancer in LS.
Methods: All studies between 1979 and 2015 of women with ovarian cancer and LS or at 50% risk of LS were evaluated. Two reviewers independently evaluated eligible studies and extracted data on age at diagnosis, histological type, FIGO stage, and way of detection according to pre-specified criteria. The studies were assessed for quality using the Newcastle-Ottawa quality assessment scales.
Results: The quality score of the 49 identified studies was at least 6 out of 8 and provide clinical information on 747 LS women with ovarian cancer. The mean age at diagnosis was 45.3 (range 19–82) years. Most frequent mutations were MSH2 (47%) and MLH1 (38%). Histopathological data were available for 445 women. The most frequently reported histological type was mixed type (mucinous/endometrioid/clear cell carcinomas) (n = 136; 31%). Most tumours (281, 65%) were diagnosed at an early stage (FIGO I/II). Six studies evaluating the effect of surveillance of ovarian cancer, reported that seven of 22 (32%) ovarian cancers were found during surveillance, 6/7 (86%) were detected at an early stage.
Conclusion: This systematic review describes that ovarian cancer in women with LS has a wide age-range of onset, is often diagnosed at an early stage with frequently endometrioid/

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clear cell histology. Data about the role of surveillance in detection of ovarian cancer in women with LS are scarce however detection at an early stage seems possible.

1. Introduction

Lynch syndrome (LS) is an autosomal dominant predisposition to develop cancer characterised by germline mutations in one of four DNA mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6* and *PMS2* [1,2]. *MLH1* and *MSH2* predominate in LS with mutations in one or the other found in between 80–90% of affected LS families, with *MSH6* and *PMS2* mutation causing the remaining 10–20% [3–5]. In female carriers with LS, endometrial cancer is after colon cancer the most common tumour type [6,7], with a cumulative lifetime risk of 21–71%, depending on which gene is mutated. Women with *MSH6* mutation have a risk of 40–70% to develop endometrial cancer [7–11]. For women with LS, there is a 24–63% cumulative lifetime risk of developing colorectal cancer [7,12–16]. The cumulative lifetime risk of ovarian cancer varies between 6–12% [7–9,13,16–18].

Due to these high cancer risks, women with LS are regularly surveyed with the aim of early detection of these cancers. Endometrial cancer surveillance could be effective [19–21], however the value of surveillance for ovarian cancer is under debate [19,22]. In general, ovarian cancer surveillance has not been proven effective in the general population and among women with *BRCA 1/2* mutations. Most ovarian cancers are found in an advanced stage and interval ovarian cancers develop between two surveillance visits [23–28]. As in most studies only a small number of LS women are included, the information about clinical and histopathological characteristics of the screen detected versus the clinically detected ovarian cancer in women with LS or their first degree relatives is scattered. The aim of this systematic review was to analyse all published studies on ovarian cancer in women with LS, regarding the age of onset of ovarian cancer, the histopathological type and FIGO stage and evaluate the role of surveillance in the detection of (early stage) ovarian cancer in LS.

2. Methods

This systematic review was performed following the PRISMA statement guidelines (http://www.prisma-statement.org/stagement.htm). We conducted a systematic search in the MEDLINE database from January 1979 until April 2015. The following search terms were used; 'ovarian cancer', 'ovarian carcinoma', 'HNPCC', 'Lynch Syndrome', 'screening' and 'surveillance'. An overview of the search strategy and the results is shown in Fig. 1. After reading the titles and abstracts of all potentially relevant articles, the full texts were assessed for eligibility by two independent reviewers (JHW and EB). In addition, the references of the included publications were screened to evaluate if relevant articles might have been missed. If there was disagreement about inclusion or exclusion of an article a consensus meeting was organised between the reviewers (JHW and EB) and if indicated with the other authors of this review.

2.1. Inclusion criteria

Studies were included if they contained information on ovarian cancer patients that carry an LS mutation or patients who are a first degree relative of a family member with LS or patients that fulfilled the Amsterdam II criteria (see Fig. 2) and if they presented data on the women's age of onset of ovarian cancer, and/or the histopathology, and/or FIGO stage. Excluded were studies describing ovarian cancer in women without LS mutation or first degree relatives. Also excluded were studies with ovarian cancer in women with LS or first degree relatives without information on any of the following items: age of onset, histopathology or FIGO stage.

A total of 50 studies were included in this systematic review (see Table 1). As data on the same patients were reported in two studies [29,30], the study of Crijnen et al. [29] was excluded and finally 49 studies were included.

2.2. Data extraction

For all 49 studies the following data were extracted: design of study (cohort, case control, case report); the number of patients and the number of ovarian cancers (Table 1). In addition, the following information was retrieved for women with LS or their first degree relatives and their ovarian cancer: type of mutation, the age of onset (mean or median and standard deviation or range), the FIGO stage of the ovarian cancer (Table 1) and the histopathology report. (Table 2). For the studies that evaluated the role of surveillance in the detection of ovarian cancer the following was retrieved: the number of women in surveillance; the number of ovarian cancers found during surveillance, the number of interval ovarian cancers, the surveillance interval (in years); the FIGO stage of the ovarian cancer found during surveillance and in interval and the related survival time (in