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The additional value of endometrial sampling in the early detection of endometrial cancer in women with Lynch syndrome

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HIGHLIGHTS

- Seventy five women with Lynch syndrome or first-degree relatives are offered annual gynecological screening between 2003 and 2012.
- All (pre)malignant endometrial lesions were found by transvaginal ultrasound.
- Adding standard endometrial sampling to annual transvaginal ultrasound has no additional value in detection of endometrial lesions.

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ABSTRACT

Objective. Based on previous studies, standard gynecological screening consisting of annual transvaginal ultrasonography (TVU) was added with endometrial sampling in women with Lynch syndrome (LS). The aim of this study was to evaluate the additional value of endometrial sampling in detecting (pre)malignancies of the endometrial tissue in women with LS or first-degree relatives.

Methods. All women above 30 years of age with LS or first-degree relatives at 50% risk of LS are offered annual gynecological screening in our family cancer clinic. Endometrial screening results from January 2003-December 2007 (period I: standard screening by transvaginal sonography and serum CA125) were compared with screening results from January 2008-June 2012 (period II: standard screening added with endometrial sampling).

Results. Seventy five women (300 patient years) were screened annually. There were 266 screening visits, 117 in period I and 149 in period II. In period I, four premalignant endometrial lesions were detected and one endometrial carcinoma (FIGO stage IB). In period II, two premalignancies were found. None of the lesions would have been missed without standard endometrial sampling. No interval endometrial cancers were detected in this study.

Conclusion. In this study, annual endometrial screening seems an effective screening tool in the detection of premalignancies and early endometrial cancer in women with LS. Adding standard endometrial sampling to annual TVU has no additional value in the early detection of (pre)malignant endometrial lesions in women with LS in this study.

Introduction

Women with Lynch syndrome (LS), previously called Hereditary Non Polyposis Colorectal Cancer (HNPCC), have an autosomal dominant inherited mutation in one of the DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6* or *PMS2*. LS is characterized by a high risk and early occurrence of colorectal cancer and extra colonic cancers [1]. The second most common cancer in female LS patients is endometrial cancer.

The estimated cumulative lifetime risk to develop endometrial cancer in women with LS varies in different reports between 21% and 71%. *MLH1* and *MSH2* mutation carriers have a lifetime risk up to 60% to develop endometrial cancer; carriers of an *MSH6* mutation have a risk up to 71%, [1–5] although lower risks (24%) have been reported as well [6]. For *PMS2* mutation carriers, a risk of 15% has been reported [7]. However, series of PMS2 mutation carriers are significantly smaller than those for the other mismatch repair genes and cancer risk therefore less well established. The overall annual incidence rate of developing endometrial cancer after the age of 40 years in LS is 2,5% [8].

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The high risk of endometrial cancer in LS and the earlier age of onset, together with a well-detectable and treatable premalignant or early malignant stage, is the reason to consider endometrial cancer screening in these women and their first degree relatives at 50% risk of LS [1,2,9,10]. A few studies have investigated the optimal gynecological screening protocol in women with LS [1,4,11–13]. Interval endometrial carcinomas occurred with annual screening of TVU alone in two studies [4,11]. In a study by Renkonen et al., mutation carriers were screened with TVU and standard endometrial sampling of the endometrial tissue at an interval of 2–3 years [1]. In their study, eight of fourteen carcinomas and premalignant lesions were diagnosed by endometrial sampling alone. However, despite endometrial sampling during most of the screening visits in this study, three interval carcinomas occurred. The tumour stage and the survival curve were more optimal in the group of patients who underwent screening than in 83 mutation positive endometrial cancers patients who had not attended screening [1]. In 2009 Gerritzen et al. also found significantly more (pre)malignancies in women with standard endometrial sampling together with annual TVU, than in women with screening by TVU alone [12]. It was concluded that TVU alone is insufficient to detect early endometrial cancer in all cases, especially among premenopausal women, and that adding endometrial sampling improves the effectiveness of gynecological screening in women with LS [1,12]. Recently Manchandra et al. found four (pre) malignant lesions with TVU and outpatient hysteroscopy with endometrial sampling in 41 women with LS. TVU alone detected two of four lesions [13]. In our hospital, the screening protocol was changed in women with LS or first-degree relatives at 50% risk of carrying the LS mutation and endometrial sampling was added to annual TVU from January 1st 2008. During endometrial sampling, some patients experience painful cramping but data about this symptom are lacking from other studies. Data about effectiveness of annual gynecological screening by TVU in women with LS or first degree relatives in our hospital between 1991 and 2002 have been published by Rijcken et al. [4]. In the current study screening data were analyzed of all women with LS or first degree relatives, who were annually screened between January 2003 and June 2012. The aim of the present study is to evaluate the additional value of endometrial sampling to annual TVU as a standard screening procedure in detecting (pre)malignant endometrial lesions in women with LS or first-degree relatives at 50% risk of carrying the LS mutation.

Patients and methods

Setting

Since 1991, a gynecological screening program for females with LS and first-degree relatives at 50% risk of carrying the LS mutation was introduced at the Family Cancer Clinic (FCC) of the University Medical Center Groningen at a recommended age to start of 30 years [14]. In all women with LS, a pathogenic mutation in either *MLH1*, *MSH2*, *MSH6* or *PMS2* had been detected using methods published previously [15–17]. All clinical data from LS carriers and first-degree relatives at 50% risk of carrying the LS mutation are prospectively registered in a database. The first-degree relatives at 50% risk of carrying the LS mutation were women who did not wanted to be screened because of implications for life insurance. In some other patients the genetic results were not available yet. All first degree relatives at 50% of carrying the LS mutation were regarded as a carrier until the genetic test showed no genetic mutation.

During Period I (2003–2007) annual gynecological screening was performed by TVU and serum CA125 measurement. Endometrial sampling or hysteroscopy and endometrial biopsy was performed only in symptomatic women (irregular, postcoïtal or postmenopausal bleeding), or in women with increased endometrial thickness on TVU (double layer above 12 mm in premenopausal women, or above 4 mm in postmenopausal women). [18,19].

From 2008, when the new Dutch guideline for LS was introduced which recommended annual endometrial sampling (Pipelle®) after TVU as the standard gynecological screening procedure in women with LS, annual endometrial sampling was added to the screening protocol [14]. During Period II (2008–2012), gynecological screening was performed according to this new guideline. If endometrial sampling was too painful or not possible, in case of symptoms or an increased endometrial thickness, a hysteroscopy and curettage under general anesthetics was offered [14]. Histopathological examinations were performed by one dedicated gyneco-pathologist (HH).

Patients included in the here presented analysis

From January 2003 until June 2012, 98 women with LS or first-degree relatives at 50% risk of carrying the LS mutation were included (Fig. 1). Twenty-three women were excluded from the study: 18 patients underwent a hysterectomy before January 2003 and in 5 patients no sufficient clinical information was available. A total number of 75 women fulfilled all inclusion criteria and were enrolled in this analysis.

All relevant data were entered into a separate password protected database. Protection of a patient's identity was guaranteed by assigning study specific unique patient numbers. Only two dedicated data managers, who also have daily responsibility for the large database, know the patient numbers. Therefore, according to the Dutch law no further Institutional Review Board approval was needed for this study.

Data collection

For each woman, patient characteristics and clinical data including the age at the first surveillance, menopausal status, time since first screening, clinical symptoms, number of screening visits, extra visits because of symptoms, findings and number of TVU´s, findings and number of endometrial sampling, pathology reports, Ca 125 levels and clinical data on histo pathological results were collected.

Data analysis

Data analysis was performed with SPSS statistics version 18. In period I and II, results of all screening visits were collected and analyzed if the endometrial lesion was detected by TVU (enlarged endometrial thickness) and/or by endometrial sampling. The findings of the screening in period I (January 2003-December 2007: annual TVU and only endometrial sampling in case of enlarged endometrial thickness or symptoms) with screening visits in period II (January 2008-June 2012: standard annual TVU and endometrial sampling) were compared. We also analysed if the lesions in period II would have been picked up if we had not introduced the standard endometrial sampling in period II. The occurance of interval carcinomas during both study periods was analysed.

Results

From 2003 to 2012, 61 women were premenopausal and 14 were postmenopausal. The median age at the first gynecological screening was 38 years (range 26–61) and 41 years (range 23–67 years) in periods I and II, respectively. However three women (23–26–26 years of age) received information about the screening program starting from age 30, and asked to be screened during the first visit. At that visit standard gynaecological screening was performed. Two 26 year old women returned for screening according to the protocol at age 30. The women of 23 years returned after one year and asked to be screened because her sister developed cancer at a very young age. Fifteen women were carrier of a MLH1 gene mutation, 14 MSH2 (of which 3 EPCAM), 12 MSH6, 6 PMS2, and 28 women were first-degree relatives at 50% risk of carrying the LS mutation (Table 1).

The participants had a total of 266 screening visits in 300 patient years, and 13 extra visits because of symptoms of abnormal bleeding.