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The gynecological surveillance of women with Lynch syndrome in Sweden

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HIGHLIGHTS

- Gynecological surveillance of women with Lynch syndrome leads to earlier detection of precancerous lesions of endometrial cancer.
- Prohphylactic surgery reduces the cancer incidence.

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ABSTRACT

Objective. Women with Lynch syndrome (LS) have up to a 60% lifetime risk of endometrial cancer (EC) and up to a 24% risk of ovarian cancer (OC). Gynecological surveillance is recommended, but the benefit and how it should be performed remain unclear. The purpose of this study was to assess diagnostic modalities for gynecological screening of LS patients in Sweden and clinical outcome.

Methods. A retrospective nationwide study of 170 women with molecularly confirmed LS. Data including gynecological LS screening history, biopsy results (if any), genetic records, number of screening visits, results from screening including transvaginal ultrasound (TVUS), endometrial biopsy (EB), blood test for tumor marker cancer antigen (CA) 125, prophylactic surgery including age at procedure, and setting from which screening data were obtained from medical records.

Results. A total of 117 women were eligible for gynecological screening and of these, 86 patients attended screening visits. Of these, 41 underwent prophylactic hysterectomy and/or bilateral salpingo-oophorectomy. Two patients (4.9%) were diagnosed with EC and two (4.9%) with precancerous lesions in conjunction with prophylactic surgery. Total incidence of gynecological cancer in the surveillance group (45 women) was 20% EC, 4% OC. Five patients had endometrial cancer or complex hyperplasia with atypia (n = 2) detected by endometrial biopsy. Four additional cases were detected due to interval bleeding. Both cases of ovarian cancer were detected by transvaginal ultrasound in patients with ovarian cysts under surveillance. The youngest woman with endometrial cancer was diagnosed at 35 years of age, before she was aware of her diagnosis of Lynch syndrome.

Conclusions. Gynecological surveillance of women with Lynch syndrome may lead to earlier detection of precancerous lesions, which might have some impact on the morbidity from endometrial cancer although further studies are needed to prove this. Prophylactic hysterectomy with or without bilateral salpingo-oophorectomy reduces the cancer incidence. A practical approach to surveillance in Lynch syndrome women would be to offer annual surveillance beginning at age 30 years including probably both TVUS and EB in order to increase diagnostic yield with prospective data registry for follow-up studies. Prophylactic surgery could be performed at a suitable age after childbearing to obtain a balance between reducing the risk of cancer and minimizing long-term complications from premature menopause.

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1. Introduction

Lynch syndrome (LS) is also known as hereditary nonpolyposis colorectal cancer. Female LS patients are also at high risk of developing endometrial cancer (EC). LS, with an incidence between 1:660–1:2000 [1], is an autosomal dominant disorder caused by defective DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6* or *PMS2*) [2,3]. About 2% of uterine cancer is attributable to LS and 9% of women <50 years diagnosed with uterine cancer have LS [4]. Women with LS have a 16–60% lifetime risk of developing endometrial cancer [5]; about half of these women are first diagnosed with endometrial cancer [6–8].

The median age of onset for endometrial cancer in women with LS is 46–62 years. They also have an increased lifetime risk of ovarian cancer (3–24%) [6,9–11] as well as of cancer of the stomach, small bowel, urinary tract, hepatobiliary tract, skin (sebaceous gland), and the brain [4,12,13]. Currently, the Amsterdam II criteria [13] or Bethesda criteria [14] are used to identify suspected cases of LS.

The benefit of gynecological surveillance for Lynch syndrome patients remains to be proven and controversy exists regarding optimal screening modalities, with great variation internationally [8,12,15–17]. The Swedish recommendations for Lynch syndrome from 2012 contain no definite gynecological surveillance program, but suggest that surveillance may be offered from 30 to 35 years of age and may contain gynecological examination, transvaginal ultrasound and if indicated also endometrial biopsy. The screening visits should be conducted by a gynecologist who is familiar with hereditary cancer syndromes. The screening interval is suggested to be 1–2 years [16]. However, no follow-up of the Swedish Lynch syndrome population has been conducted and it is not known whether these guidelines are followed. The purpose of this study was to examine which diagnostic modalities were used for gynecological surveillance of LS patients in Sweden and their clinical outcome.

2. Material and methods

This nationwide study includes all Swedish female patients with molecularly confirmed LS identified between 1994 and 2013 recruited from the regional clinical genetics departments in Stockholm, Uppsala, Linkoping, Gothenburg, and Lund. These regional clinics cover the entire country except the north. All 260 women with Lynch syndrome from these registries were asked to participate.

Medical records including gynecological screening history of LS patients, biopsy results (if any), and genetic records were obtained for all women included in the study. Information concerning screening visits including transvaginal ultrasound (TVUS), endometrial biopsy (EB), blood test for tumor marker cancer antigen (CA) 125, number of visits, prophylactic surgery (if any) and age at time of procedure, patient's current age, age at LS diagnosis, and name of screening facility were obtained from the medical records of each patient. All diagnoses were based on the original pathology reports. TVUS includes assessment of uterus size, endometrial thickness and examination of the ovaries including position, size and presence of any abnormalities.

2.1. Statistics

Statistical analyses were performed with the Statistica® software (Statsoft.se) package. $p < 0.05$ was considered significant. Pearson's chi-squared test and Fisher's exact test and Kaplan–Meier estimator were used to calculate proportional differences. The Kruskal–Wallis

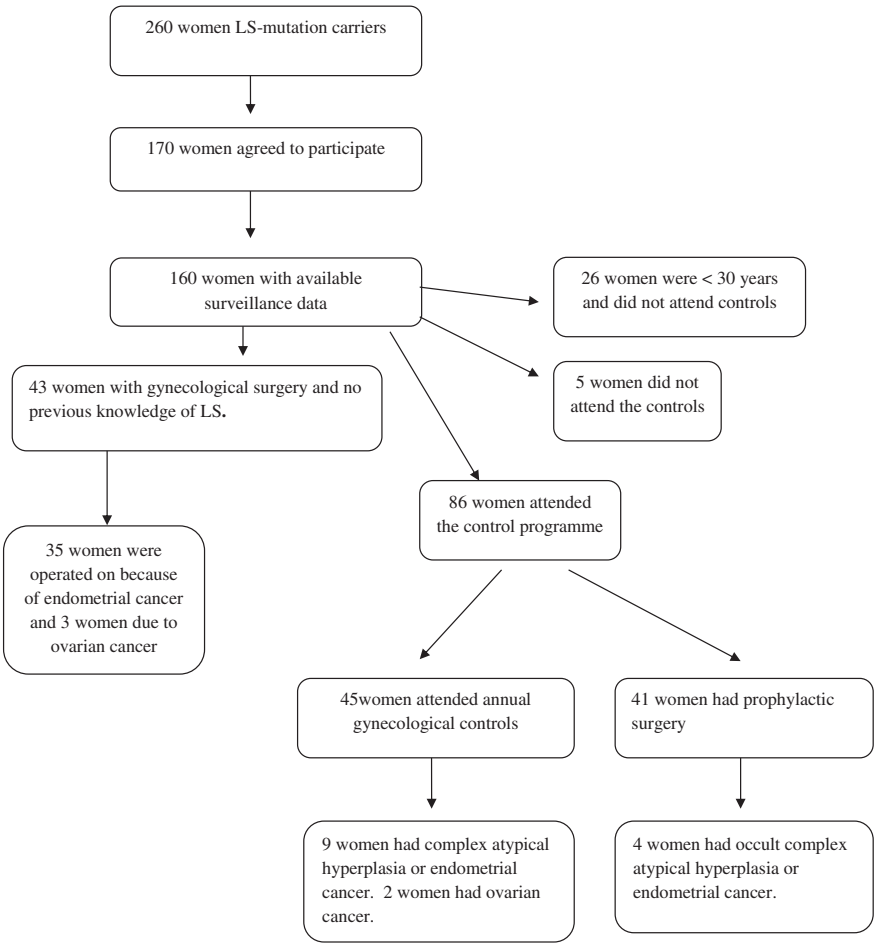

Fig. 1. Flow diagram of the study group.