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The results of gynecologic surveillance in families with hereditary nonpolyposis colorectal cancer☆

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HIGHLIGHTS

- EC surveillance should only be targeted at MMR mutation carriers starting from the age of 35–40.
- Research into attitudes toward screening is needed to clarify the low attendance at gynecological surveillance in MMR-mutation carriers.

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ABSTRACT

Objective. We aimed to estimate the incidence rate of endometrial cancer (EC) and to evaluate the results of EC-surveillance in hereditary nonpolyposis colorectal cancer (HNPCC) families.

Methods. All at-risk women recommended for EC-surveillance by the HNPCC-register—2959 women (19,334 women years)—were included. Data on EC-surveillance were available for 871 women (6894 women years), who had performed 1945 surveillance visits. The average surveillance period was 7.9 (range 0.1−21.7) years and 46% of the women had had less than 3 years between their visits.

Results. During 19,334 women years, 60 women with gynecological malignancies or premalignancies were diagnosed. Thirty-nine women had EC. Of these, 31 were from families with identified MMR gene mutations with the median age at diagnosis of 54 (39–83) years (Incidence Rate, IR = 0.63 per 100 women years) and four women from each Amsterdam (AMS)-positive and AMS-like families (median age 64 (55–73) years, IR = 0.06 and 0.05 per 100 women years, respectively, $p < .0001$).
Among the 871 surveilled women, 13 EC were found: 7/13 cases were diagnosed by surveillance examination—two as prevalent cancers, diagnosed at the first visit—and 6/13 based on symptoms. In addition, five complex atypical hyperplasias and four ovarian cancers (OCs) were diagnosed. All these women were MMR mutation carriers.

Conclusion. Based on 19,334 women years of EC-surveillance, our analysis provides a thorough estimation of the EC risk in women with an MMR mutation, or suspected of having Lynch syndrome. We conclude that EC surveillance should only be targeted at MMR-mutation carriers.

Introduction

Endometrial carcinoma (EC) and epithelial ovarian carcinoma (OC) are the most common extracolonic cancers in women from families with hereditary nonpolyposis colorectal cancer syndrome (HNPCC) or Lynch syndrome (LS). HNPCC is a dominantly inherited cancer predisposition syndrome caused by germline mutations in certain DNA mismatch repair (MMR) genes, namely *MLH1*, *MSH2*, *MSH6*, and *PMS2* [1–3]. Female carriers of MMR-germline mutations have a lifetime risk of 20–40% for CRC, 30–60% for EC, and 4–12% for OC [4–7]. The lifetime risk of EC and OC differs depending on the mutated MMR gene [8–10]. Because of the high risk of EC in female MMR mutation carriers, current HNPCC guidelines recommend gynecological surveillance. In Denmark, the EC surveillance has been recommended to women with MMR gene mutation and to women from families that fulfill the clinical criteria for HNPCC, Amsterdam I or II criteria (AMS-positive families). Furthermore, women at risk from AMS-like families have been offered

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surveillance according to the Danish guidelines (Table 1). The surveillance includes biennial gynecological examination and transvaginal ultrasound (TVUS) starting from the age of 25 years.

The benefit of EC surveillance in HNPCC families is unclear, and there is no consensus on the optimal surveillance program. Recently, Auranen and Joutsiniemi performed a systematic review in order to find studies that addressed the effect of gynecological cancer surveillance in HNPCC families [11]. Five studies were identified [12–16]. Two studies with TVUS as the surveillance modality [12,13], two with combined TVUS and endometrial biopsy [14,15], and one study with hysteroscopy and endometrial biopsy as the surveillance method [16]. Auranen and Joutsiniemi concluded that the available studies do not form the basis of evidence-based clinical decisions. More recently, another retrospective study of the impact of gynecological screening in 54 women with *MSH2* germline mutation was published. The conclusion of this study was that gynecological surveillance did not result in the detection of gynecological cancer at an earlier stage [17].

However, due to the favorable overall prognosis of the EC and the lack of evidence of improvement of the survival in women at risk who attended EC surveillance, the question is, whether the gynecological surveillance is at all necessary in all HNPCC families, or should it be targeted at MMR mutation carriers.

We estimated the incidence of EC among women from LS, AMS-positive, and AMS-like families in the period 1991–2011 and evaluated the results of the EC surveillance during this period among these women who had been advised to attend EC surveillance.

Materials and methods

Study population

The Danish HNPCC-register was established in 1991 and is a national database with clinical and genetic data from all known families with confirmed MMR gene mutation (LS-families), families that fulfill the clinical AMS I or II criteria (AMS-positive families), and AMS-like families (Table 1). The HNPCC-register and the departments of clinical genetics in Denmark identify the families and collect genetic and clinical data from each family member. All at-risk members are informed about HNPCC-related cancer risks and the recommended surveillance program. The HNPCC-surveillance guidelines in Denmark include colonoscopy and EC surveillance with gynecological examination and TVUS biennially from the age of 25 years.

Table 1
Classification of HNPCC families in the Danish HNPCC-register.

Lynch syndrome
Families with a pathogenic MMR germline mutation
Amsterdam criteria I
At least three relatives with CRC, and:
One affected is 1° relative of the other two
At least two successive generations affected
At least one CRC diagnosed before the age of 50 years
Tumors are verified by histology reports, medical records[a] or death certificates[a]
Familial adenomatous polyposis is excluded
Amsterdam criteria II
At least three relatives with CRC, EC, small bowel, ureter, or renal pelvis cancer; all the rest of Amsterdam criteria I are met
Amsterdam-like
Families fulfill Amsterdam criteria I/II except that:
One of the cancers is not verified by medical/histology reports or death certificates
One CRC is replaced by an adenoma with severe dysplasia or an HNPCC-related cancer not included in the Amsterdam II criteria (e.g. ovaries, stomach, hepatobiliary system, pancreas, or brain)

CRC, colorectal cancer.
[a] In the original definition, only histopathological report is accepted as verification.

The study population was identified through the HNPCC-register's database and included all at-risk women from LS, AMS-positive and AMS-like families (Table 1) who had been advised to participate in gynecologic surveillance since January 1, 1991 through September 15, 2011. Women who had undergone hysterectomy before they attended the HNPCC surveillance program were excluded.

A total of 2959 women including all mutation carriers, women with HNPCC-related cancer, or a first-degree relative of such a person were included. The cohort was traced for gynecological malignant and premalignant diagnoses in the Danish Cancer Registry, the National Patients Register and the Danish Pathology Databank, which are all national databases of medical data and diagnoses of all Danish persons and patients.

Surveillance data

Our surveillance data consisted of results from the HNPCC-related gynecological surveillance collected in the HNPCC-register by from January 1, 1991 to September 15, 2011. Surveillance consisted of a biennial gynecological examination and TVUS. Endometrial sampling was only taken if indicated in case of post menopausal/irregular bleeding and/or abnormal findings at TVUS according to the standard endometrial thickness cut offs used for pre and postmenopausal women (irregular endometrium in both pre- and post-menopausal women, and endometrial thickness of 4 mm or more in postmenopausal women). The tumor marker CA125 was taken if indicated in case of abnormal findings of ovaries. Surveillance-data of 1946 surveillance visits performed by 871 out of 2959 (29%) women were collected (Fig. 1). For each of the women the surveillance period (the amount of surveilled years) was from the time of being advised gynecological surveillance until hysterectomy, death, or the end of the study period (September 15, 2011).

All diagnoses were based on the original pathology reports. Survival data were checked at the Danish Central Personal Register.

Statistical methods

The statistical calculations were performed with the SAS software (SAS Inc.).

The Fischer's exact test and Chi-square test were used to test the difference between the incidence rate of EC in LS, AMS-positive and AMS-like families, as well as the difference between women's use of gynecological surveillance in the respective subgroups.

Results

Incidence rate of gynecologic cancers

In total, 2959 women (19,334 women years) were advised to attend gynecological surveillance; 676 women (4904 women years) from families with confirmed MMR mutation (LS families); 892 women (6784 women years) from AMS-positive families; and 1391 women (7647 women years) from AMS-like families. The mean time of surveillance was 6.5 years (range: 0.1–21.7 years).

Altogether, 60 women were diagnosed with gynecological malignancies or premalignancies. Of these, 39 cases had EC (adenocarcinoma in all): 31 of these women were from families with confirmed MMR gene mutation (Incidence Rate, IR = 0.63 per 100 women years), diagnosed at a median age of 54 (39–83) years and four from each AMS-positive and AMS-like families (IR = 0.06 and IR = 0.05 per 100 women years, respectively, $p < .0001$). Two of the 39 women had additional synchronous carcinomas: one OC and one carcinoma of the Fallopian tubes. Eight of the 60 cases were diagnosed with complex atypical hyperplasia (CAH). Twelve women were diagnosed with OC and one woman with a mucinous borderline ovarian tumor (Table 2).