Endometrial cancer risk factors among Lynch syndrome women: a retrospective cohort study

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Background: Lynch syndrome (LS) is associated with a significant lifetime risk of endometrial cancer (EC). There are limited data on factors modifying the EC risk in LS patients.

Methods: The study cohort included 136 LS mutation-positive women. Exposure data were collected by postal questionnaires. Cox regression model was used to estimate the associations between lifestyle, hormonal, reproductive and medical factors and the risk of EC.

Results: Increased EC risk was associated with type II diabetes and hypercholesterolaemia in univariable (HR 3.21, (95% CI 1.34–7.78), \( P = 0.009 \) and HR 2.08, (95% CI 1.11–3.90), \( P = 0.02 \); respectively) and with diabetes and duration of hormone replacement therapy (HRT) in multivariable analysis (HR 4.18 (95% CI 1.52–11.52), \( P = 0.006 \) and HR 1.07 (95% CI 1.02–1.13), \( P = 0.010 \); respectively).

Conclusions: Prevention of diabetes and avoiding long-duration HRT are potential targets for reduction of EC risk in women with LS.

Lynch syndrome (LS) is a cancer predisposition syndrome with autosomal-dominant inheritance pattern caused by germ-line mutations in DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2 (Vasen et al, 1999). LS is associated with significantly increased lifetime risks of both colorectal and endometrial cancer (EC), ranging from 20% to 51% depending on the type of the mutation (Møller et al, 2015).

Factors increasing EC risk in general population all relate to conditions of oestrogen dominance over progesterone. EC risk has been shown to increase with nulliparity, early age at menarche, late age at menopause, obesity, metabolic syndrome, ovulation failure, non-use of hormonal contraceptives, and oestrogen or sequential hormone replacement therapy (HRT) (Ali, 2014; Barry et al, 2014; Trabert et al, 2015). Data on the influence of these risk factors on EC risk of genetically predisposed LS women are, however, limited. An intervention study of oral contraceptive and medroxyprogesterone acetate in LS women suggested a protective effect on endometrial proliferation similar to the general population (Lu et al, 2013). This was further supported by a recent large retrospective study, where EC risk in LS women decreased with parity, use of hormonal contraceptives and later age at menarche (Dashti et al, 2015).

The association of high body mass index (BMI) and other metabolic syndrome-related factors with EC risk of LS women is...
not clear. Studies addressing the association of BMI with MMR protein expression or microsatellite instability in unselected EC have been contradictory (McCourt et al, 2007; Cohn et al, 2008; Gonzalez et al, 2012; Joelhin-Price et al, 2014). Only few comprehensive studies have been conducted in well-characterised study populations with germ-line mutation testing. According to these studies, BMI may not be associated with EC risk among LS women (Win et al, 2011; Dashti et al, 2015).

To date, hysterectomy provides the only means for EC risk reduction or prevention in high-risk women. Therefore, research on the impact of environmental factors on EC risk in LS women is needed. Here we have estimated the associations between lifestyle, hormonal, reproductive and medical factors and the risk of EC in a cohort of MMR germ-line mutation carrier women.

MATERIALS AND METHODS

Study patients. This retrospective cohort study was carried out in Tampere University Hospital (TAUH), Finland. Study cohort included Finnish women with inherited pathogenic MMR gene mutation identified from the nationwide Finnish LS Registry (Jarvinen et al, 2009). The Finnish LS Registry consists data of original research cohort including 81 kindreds ascertained through family history strongly suggestive of LS and clinic-based cohort including patients referred to clinical genetic units of five University hospitals in Finland for suspected LS (Mecklin et al, 1987; Gylling et al, 2009). The index patients belonging to the research cohort have been directly tested for germ-line MMR mutations without prescreening for MMR protein loss in the tumours. Patients of clinic-based cohort have been screened for MMR deficiency in tumour tissue prior to germ-line testing from blood samples. Counselling and possible germ-line mutation testing have been systematically offered for family members of index patients up to second- or even to third-degree relatives. Mutation analyses have been performed by direct exon sequencing or by multiplex ligation-dependent probe amplification (Gylling et al, 2009). The pathogenicity of MMR gene sequence variants has been evaluated by InSiGHT criteria (Thompson et al, 2014). At present, the Finnish LS Registry includes 260 families and approximately 1400 verified germ-line MMR mutation carriers (http://www.hnpcc.fi/).

Questionnaires addressing lifestyle factors, medical and reproductive history were mailed to 223 MMR germ-line mutation carrier women living across Finland and having previously consented for LS Registry inquiries. Content of postal questionnaires is summarised in Table 1. Questionnaires were re-sent to non-responding patients in 6 months after first mailing. EC diagnoses were confirmed from the pathology reports and medical records obtained from district hospitals. Informed consent was obtained from all study participants and the study protocol was approved by TAUH Ethical Committee.

Statistical analysis. SPSS statistics software (version 22, IBM, Armonk, NY, USA) was used for the statistical analyses. Cox regression model was used to estimate the associations between parity, age at menarche and menopause, duration of HRT or hormonal contraception, BMI, annual weight change, alcohol consumption and the risk of EC in LS women. Age was used as a timescale for EC risk estimation. The time at risk was considered to start from birth and end at the diagnosis of EC, prophylactic hysterectomy or the time of the survey, whichever occurred first. For the univariable analyses, age at menarche and menopause, BMI, annual weight change, duration of hormonal contraception and HRT were divided into two categories by the median values of the variables. These variables were also analysed as continuous variables in the regression model. In addition, BMI was also categorised using cutoff points 25 (= overweight) and 30 (= obese). The comparison of BMI as a continuous variable between diabetic and non-diabetic patients was performed using nonparametric testing.

As the LS women in the study were ascertained from multiple case families or because of EC diagnosis, the selection of women may not have been random with respect to disease status. Therefore, ascertainment was adjusted for in the multivariable analyses by taking into account the time of germ-line testing with respect to the end of time at EC risk (i.e., germ-line testing performed before EC diagnosis, prophylactic hysterectomy or survey in healthy non-hysterectomised women compared with germ-line mutation testing after EC diagnosis or prophylactic hysterectomy). Parity, age at menarche and duration of hormonal contraceptive use as continuous variables were also adjusted for in the multivariable analysis as they have been previously reported to associate with EC risk in LS women (Dashti et al, 2015).

Two-tailed P values of <0.05 were considered as statistically significant.

RESULTS

One hundred and thirty-six women returned the questionnaire resulting in a 61% response rate. Median age at survey was 58 years (range 29–85). Distribution of the different germ-line mutations was as follows: 82.4% of MLH1, 11% of MSH2, and 6.6% of MSH6 mutations. Fifty women (36.8%) had been diagnosed with EC at median age of 49.5 years. Prophylactic surgery had been performed in 52 out of 86 (60.5%) of EC unafflicted women at median age of 45 years. Characteristics of the study patients and exposure data are summarised in Table 2.

In univariable Cox regression analysis, non-insulin-dependent diabetes and hypercholesterolaemia were associated with an elevated risk of EC (HR 3.21 (95% CI 1.34–7.78), P = 0.009; HR 2.08 (95% CI 1.11–3.90), P = 0.02; respectively). Diabetic LS women were more overweight than non-diabetic LS women at survey (median BMI 29.7 vs 25.0, P = 0.012, Mann–Whitney U-test), but BMI at the age of 18 or 40 years or at survey did not associate with the risk of EC (HR 1.03 (95% CI 0.91–1.17), P = 0.6; HR 1.04, (95% CI 0.98–1.11), P = 0.19; HR 1.02 (95% CI 0.97–1.08), P = 0.42; respectively). Among ever users of HRT (n = 61), the duration of use (>9 years) showed a trend for association with EC risk (HR 2.03 (95% CI 0.89–4.62), P = 0.09). History of endometriosis showed also a trend for association with EC risk (HR 1.96 (95% CI 0.90–4.28), P = 0.09).

In multivariable Cox regression model, diabetes and duration of HRT use were associated with a statistically significant increase in the risk of EC (HR 4.18 (95% CI 1.52–11.52), P = 0.006; HR 1.07 (95% CI 1.02–1.13), P = 0.010; respectively).

Summary of univariable and multivariable Cox regression analyses is presented in Table 3.

DISCUSSION

We report here the associations between EC risk and lifestyle, medical and hormonal factors in a retrospective cohort of verified MMR mutation carriers. These findings suggest that type II diabetes and postmenopausal hormone therapy may associate with an elevated risk of EC in LS. Even though diabetic LS women were more overweight than non-diabetic women at survey, BMI at any time point or annual weight change did not associate with the risk of EC. Our results are in contrast to the previous observations of BMI as an EC risk factor in general population (Jenabi and Poorolajal, 2015) but are in line with studies reporting no
| Description                                                                 |   |
|------------------------------------------------------------------------------|---|
| Height cm                                                                     |   |
| Weight Kg at age of 18 Kg at age of 40 Kg at present                          |   |
| Age when you had your first periods                                           | Years |
| Age when you had your last periods                                            | Years |
| Number of pregnancies                                                         | Number |
| Deliveries                                                                   | Number |
| Spontaneous abortions                                                         | Number |
| Induced abortions                                                             | Number |
| Vaginal HRT use Y/N                                                           |   |
| Systemic HRT use ever Y/N                                                     |   |
| If yes: Try to estimate the duration of use in years                          | Years |
| Describe here the type of oestrogen you use at present (pill, patch, gel).   |   |
| PCOS Y/N                                                                     |   |
| Endometriosis Y/N                                                             |   |
| If yes, any treatment                                                        |   |
| Describe here the modalities of treatments that you have received for        |   |
| endometriosis? Estimate here the duration of use for each treatment modality |   |
| Contraceptive tablets Y/N                                                     |   |
| Progesterone po Y/N                                                           |   |
| Progesterone-IUD Y/N                                                          |   |
| Cancer other than endometrial cancer Y/N                                       |   |
| Operated for cancer                                                           |   |
| Gynaecological follow-up duration Years                                        |   |
| Regular smoking ever Y/N                                                      |   |
| If yes: Try to estimate how long you have been smoking (years) and approximately how many cigarettes per day |   |
| Alcohol consumption Y/N                                                       |   |
| If yes: Try to estimate how long you have been smoking (years) and approximately how many cigarettes per day |   |
| Diabetes Y/N                                                                  |   |
| If yes: Describe here the different treatments you have received for diabetes |   |
| Hypertension Y/N                                                              |   |
| Hypothyreosis Y/N                                                             |   |
| Hypercholesterolaemia Y/N                                                     |   |
| Any other serious condition, which                                             |   |
| Hormonal contraception Y/N                                                    |   |
| If yes: Describe here the duration of use in years.                           |   |
| Medication                                                                   |   |

Abbreviations: GI = gastrointestinal; HRT = hormone replacement therapy; IUD = intrauterine device; MMR = mismatch repair; N = no; PCOS = polycystic ovary syndrome; Y = Yes.

*Data are available only from 100 study participants, and no patient reported to have been diagnosed with the condition."
Table 2. Characteristics of study women with Lynch syndrome

|                               | No endometrial cancer, \( N = 86 \) (63%) | Endometrial cancer, \( N = 50 \) (37%) | Total \( N = 136 \) |
|--------------------------------|-------------------------------------------|----------------------------------------|---------------------|
| **Age (years)**a               |                                           |                                        |                     |
| Mean (s.d.)                    | 46.6 (8.7)                                | 48.4 (6.9)                             | 47.2 (8.1)          |
| Median (range)                 | 45 (29–72)                                | 49.5 (28–62)                           | 47 (28–72)          |
| **Mismatch repair gene mutated, n (%)** |                                     |                                        |                     |
| MLH1                           | 72 (83.8)                                 | 40 (80.0)                              | 112 (82.4)          |
| MSH2                           | 7 (8.1)                                   | 8 (16.0)                               | 15 (11.0)           |
| MSH6                           | 7 (8.1)                                   | 2 (4.0)                                | 9 (6.6)             |
| **GI-tract cancer**            |                                           |                                        |                     |
| Yes                            | 26 (30.2)                                 | 24 (48.0)                              | 50 (36.8)           |
| No                             | 60 (69.8)                                 | 26 (52.0)                              | 86 (63.2)           |
| **Urinary tract cancer**       |                                           |                                        |                     |
| Yes                            | 3 (3.5)                                   | 6 (12.0)                               | 9 (6.6)             |
| No                             | 83 (96.5)                                 | 44 (88.0)                              | 127 (93.4)          |
| **Age at menarche**            |                                           |                                        |                     |
| Mean (s.d.)                    | 13.2 (1.5)                                | 13.4 (1.5)                             | 13.3 (1.5)          |
| Median (range)                 | 13.0 (10–17)                              | 13.0 (11–16)                           | 13.0 (10–17)        |
| **Age at menopause**           |                                           |                                        |                     |
| Mean (s.d.)                    | 50.4 (3.0)                                | 50.7 (3.3)                             | 50.5 (3.1)          |
| Median (range)                 | 50.0 (46–55)                              | 50.0 (43–58)                           | 50.0 (43–58)        |
| **Number of live births, n (%)** |                                         |                                        |                     |
| No                             | 9 (10.5)                                  | 9 (18.0)                               | 18 (13.2)           |
| 1–2                            | 51 (59.3)                                 | 26 (52.0)                              | 77 (56.6)           |
| >3                             | 26 (30.2)                                 | 15 (30.0)                              | 41 (30.2)           |
| **Ever use of hormonal contraception,n (%)b** |                                 |                                        |                     |
| Yes                            | 66 (76.7)                                 | 28 (56.0)                              | 94 (69.1)           |
| No                             | 20 (23.3)                                 | 21 (42.0)                              | 41 (30.2)           |
| Missing                        | 0 (0)                                     | 1 (2.0)                                | 1 (0.8)             |
| **Duration of hormonal contraception use (years)**c |                  |                                        |                     |
| Mean (s.d.)                    | 9.2 (6.9)                                 | 6.6 (5.7)                              | 8.4 (6.7)           |
| Median (range)                 | 7.00 (1–30)                               | 4.5 (1–24)                             | 6.0 (1–30)          |
| **Ever use of hormone replacement therapy, n (%)** |                                      |                                        |                     |
| Yes                            | 36 (41.9)                                 | 25 (50.0)                              | 61 (44.9)           |
| No                             | 50 (58.1)                                 | 25 (50.0)                              | 75 (55.1)           |
| **Duration of hormone replacement therapy (years)**c |                                      |                                        |                     |
| Mean (s.d.)                    | 9.1 (6.8)                                 | 11.3 (8.0)                             | 10.0 (7.4)          |
| Median (range)                 | 7.5 (1–35)                                | 10.0 (2–36)                            | 9.0 (1–36)          |
| **Ever use of vaginally administered hormone replacement therapy, n (%)** |                              |                                        |                     |
| Yes                            | 23 (26.7)                                 | 24 (48.0)                              | 47 (34.6)           |
| No                             | 63 (73.3)                                 | 26 (52.0)                              | 89 (65.4)           |
| **Ovulation failure, n (%)**   |                                           |                                        |                     |
| Yes                            | 11 (12.8)                                 | 4 (8.0)                                | 15 (11.0)           |
| No                             | 75 (87.2)                                 | 46 (92.0)                              | 121 (89.0)          |
| **Body mass index at age 18 years** |                                          |                                        |                     |
| Mean (s.d.)                    | 20.9 (2.6)                                | 21.5 (2.1)                             | 21.1 (2.4)          |
| Median (range)                 | 20.3 (16.0–28.3)                          | 21.6 (16.9–26.9)                       | 20.8 (16.0–28.3)    |
| **Body mass index at age 40 years**d |                              |                                        |                     |
| Mean (s.d.)                    | 23.0 (4.9)                                | 24.3 (4.5)                             | 24.2 (4.7)          |
| Median (range)                 | 23.2 (17.4–45.0)                          | 23.4 (18.0–41.2)                       | 23.2 (17.4–45.0)    |
| **Body mass index at survey**  |                                           |                                        |                     |
| Mean (s.d.)                    | 25.9 (4.8)                                | 27.2 (5.3)                             | 26.4 (5.0)          |
| Median (range)                 | 24.6 (17.8–43.1)                          | 26.3 (15.2–43.7)                       | 25.4 (15.2–43.7)    |
| **Change in weight per year (kg)**e |                                      |                                        |                     |
| Mean (s.d.)                    | 0.4 (0.4)                                 | 0.3 (0.3)                              | 0.4 (0.4)           |
| Median (range)                 | 0.3 (–0.2–1.96)                           | 0.3 (–0.4–1.4)                        | 0.3 (–0.4–1.96)     |
| **Endometriosisf, n (%)**      |                                           |                                        |                     |
| Yes                            | 10 (11.6)                                 | 8 (16.0)                               | 18 (13.2)           |
| No                             | 76 (88.4)                                 | 42 (84.0)                              | 118 (86.8)          |
| **Diabetesf, g, n (%)**        |                                           |                                        |                     |
| Yes                            | 1 (1.2)                                   | 6 (12.0)                               | 7 (5.1)             |
| No                             | 85 (98.8)                                 | 44 (88.0)                              | 129 (94.9)          |
Table 2. (Continued)

| Hypertension\(^f\), \(n\) (%) | No endometrial cancer, \(N = 86\) (63%) | Endometrial cancer, \(N = 50\) (37%) | Total \(N = 136\) |
|--------------------------------|----------------------------------------|----------------------------------|-----------------|
| Yes                           | 17 (19.8)                              | 18 (36.0)                        | 35 (25.7)       |
| No                            | 69 (80.2)                              | 32 (64.0)                        | 101 (74.3)      |

| Hypercholesterolaemia\(^f\), \(n\) (%) | No endometrial cancer, \(N = 86\) (63%) | Endometrial cancer, \(N = 50\) (37%) | Total \(N = 136\) |
|----------------------------------------|----------------------------------------|----------------------------------|-----------------|
| Yes                                    | 8 (9.3)                                | 14 (28.0)                        | 22 (16.2)       |
| No                                     | 78 (90.7)                              | 36 (72.0)                        | 114 (83.8)      |

| Hypothyreosis\(^f\), \(n\) (%) | No endometrial cancer, \(N = 86\) (63%) | Endometrial cancer, \(N = 50\) (37%) | Total \(N = 136\) |
|---------------------------------|----------------------------------------|----------------------------------|-----------------|
| Yes                             | 10 (11.6)                              | 6 (12.0)                         | 16 (11.8)       |
| No                              | 76 (88.4)                              | 44 (88.0)                        | 120 (88.2)      |

| Smoking\(^h\), \(n\) (%) | No endometrial cancer, \(N = 86\) (63%) | Endometrial cancer, \(N = 50\) (37%) | Total \(N = 136\) |
|--------------------------|----------------------------------------|----------------------------------|-----------------|
| Yes                      | 40 (46.5)                              | 15 (30.0)                        | 55 (40.4)       |
| No                       | 46 (53.5)                              | 35 (70.0)                        | 81 (59.6)       |

| Smoking as pack years\(^i\) | No endometrial cancer, \(N = 86\) (63%) | Endometrial cancer, \(N = 50\) (37%) | Total \(N = 136\) |
|----------------------------|----------------------------------------|----------------------------------|-----------------|
| Mean (s.d.)                | 8.5 (7.8)                              | 5.5 (4.5)                        | 7.7 (7.2)       |
| Median (range)             | 5.0 (1.0–30.0)                         | 3.0 (1.0–16.0)                   | 5.0 (1.0–30.0)  |

| Number of alcoholic servings consumed per week | No endometrial cancer, \(N = 86\) (63%) | Endometrial cancer, \(N = 50\) (37%) | Total \(N = 136\) |
|-----------------------------------------------|----------------------------------------|----------------------------------|-----------------|
| Mean (s.d.)                                   | 2.0 (2.5)                              | 1.2 (1.7)                        | 1.7 (2.3)       |
| Median (range)                                | 1.0 (0–12)                             | 0.5 (0–7)                       | 0.5 (0–12)      |

Abbreviation: GI = gastrointestinal.
\(^a\)Age of diagnosis of endometrial cancer for affected women; age of prophylactic hysterectomy or survey for endometrial cancer-unaffected women (whichever occurred first).
\(^b\)Ever use was defined as regular use lasting for at least 1 year.
\(^c\)Data presented only from women reported to have regularly used hormonal contraception (\(n = 94\)) or postmenopausal hormone therapy (\(n = 61\)).
\(^d\)BMI at 40 years is available from 127 women aged \(>40\) years at survey.
\(^e\)Change in weight per year was calculated as kilograms starting from age 18 years until the date of survey.
\(^f\)Medical conditions (endometriosis, hypertension, diabetes, hypercholesterolaemia and hypothyreosis) were reported only if diagnosed by a medical doctor and/or having required regular medication.
\(^g\)All reported cases of diabetes were non-insulin dependent.
\(^h\)Smoking was defined as current or ever smoking (regularly minimum of 1 cigarette per day for at least 1 year) as compared with never smoking.
\(^i\)Pack year is defined as smoking 20 cigarettes a day for 1 year. Pack years were calculated only for current and ever smokers (\(n = 55\)).

Table 3. Univariable and multivariable Cox regression analyses for associations between the risk of endometrial cancer and reproductive, medical and lifestyle-related factors for women with Lynch syndrome

| Univariable analysis | Number of women with endometrial cancer (%) | Total number of women | HR (95% CI) | \(P\) value |
|----------------------|---------------------------------------------|-----------------------|-------------|-------------|
| Age at menarche, years | | | | |
| < 13 years           | 16 (35.5)                                   | 45                    | 1.00        | 0.81        |
| > 13 years           | 34 (37.4)                                   | 91                    | 1.08 (0.59–1.96) | 0.81        |
| Live births          | | | | |
| Nulliparous          | 9 (50.0)                                    | 18                    | 1.00        | 0.42        |
| Parous               | 41 (34.7)                                   | 118                   | 0.74 (0.36–1.52) | 0.42        |
| Ever use of hormonal contraceptive | | | | |
| No                   | 21 (51.2)                                   | 41                    | 1.00        | 0.85        |
| Yes                  | 28 (29.8)                                   | 94                    | 1.06 (0.59–1.9) | 0.85        |
| Use of hormonal contraceptive\(^a\) | | | | |
| < 6 years            | 38 (44.7)                                   | 85                    | 1.00        | 0.23        |
| > 6 years            | 11 (22.0)                                   | 50                    | 0.66 (0.34–1.30) | 0.23        |
| Ever use of systemic hormone replacement therapy | | | | |
| No                   | 25 (33.3)                                   | 75                    | 1.00        | 0.80        |
| Yes                  | 25 (41.0)                                   | 61                    | 0.93 (0.53–1.63) | 0.80        |
| Use of hormone replacement therapy\(^b\) | | | | |
| < 9 years            | 9 (30.0)                                    | 30                    | 1.00        | 0.09        |
| > 9 years            | 16 (51.6)                                   | 31                    | 2.03 (0.89–4.62) | 0.09        |
| Ever use of vaginally administered hormone therapy | | | | |
| No                   | 26 (52.0)                                   | 63                    | 1.00        | 0.18        |
| Yes                  | 24 (48.0)                                   | 23                    | 1.48 (0.84–2.58) | 0.18        |
| Endometriosis        | | | | |
| No                   | 42 (35.6)                                   | 118                   | 1.00        | 0.09        |
| Yes                  | 8 (44.4)                                    | 18                    | 1.96 (0.90–4.28) | 0.09        |
| Ovulation failure    | | | | |
| No                   | 46 (92.0)                                   | 121                   | 1.00        | 0.21        |
| Yes                  | 4 (8.0)                                     | 15                    | 0.52 (0.19–1.44) | 0.21        |
association among MMR mutation carriers (Win et al., 2011; Dashti et al., 2015). Our data regarding BMI therefore partially supports the view that pathogenesis of EC in LS could be independent of oestrogenic pathway (Win et al., 2011). However, hormonal risk factors have been shown to act similarly on EC risk in both general and LS population (Lu et al., 2013; Ali, 2014; Dashti et al., 2015). Recently, a large retrospective cohort study showed a reduction of EC risk in LS women with longer use of hormonal contraceptives, later age at menarche and parity (Dashti et al., 2015). These findings were not repeated in our cohort possibly owing to different ethnic background or smaller sample size and therefore lack of statistical power. An association between postmenopausal HRT and EC risk was detected in multivariable analysis, which can be interpreted as in-line with previous findings concerning the influence of hormonal factors. However, it should be noted that neither the type of hormonal contraceptives nor the type of HRT (i.e., unopposed oestrogen or oestrogen opposed by sequential or continuous progestin) was specified in our study.

The reported positive associations between diabetes and HRT use and increased EC risk are novel in verified MMR germ-line mutation carriers and are in line with studies regarding EC risk in general population (Trabert et al., 2013; Liao et al., 2014). In the present study, five out of six women had been diagnosed with diabetes prior to EC diagnosis. All reported cases of diabetes in the present study were non-insulin dependent, which generally are strongly linked to obesity (Nathan, 2015). Even if BMI itself may not affect the EC risk in MMR mutation carriers,

### Table 3. (Continued)

| Univariable analysis | Number of women with endometrial cancer (%) | Total number of women | HR (95% CI) | P value |
|----------------------|---------------------------------------------|-----------------------|-------------|---------|
| Diabesyes | 44 (34.1) | 129 | 1.00 |
| Yes | 6 (85.7) | 7 | 3.21 (1.34–7.68) | 0.009 |
| Hypertensionyes | 32 (31.6) | 101 | 1.00 |
| Yes | 18 (51.4) | 35 | 1.63 (0.91–2.92) | 0.10 |
| Hypercholesterolaemayes | 36 (72.0) | 114 | 1.00 |
| Yes | 14 (28.0) | 22 | 2.08 (1.11–3.90) | 0.02 |
| Hypothyreoses | 44 (88.0) | 120 | 1.00 |
| Yes | 6 (12.0) | 16 | 0.81 (0.34–1.91) | 0.63 |
| Body mass index at age 18 years | 17 (25.8) | 66 | 1.00 |
| Yes | 33 (47.1) | 70 | 1.55 (0.86–2.79) | 0.14 |
| Body mass index at age 40 years | 24 (38.1) | 63 | 1.00 |
| Yes | 26 (40.6) | 64 | 1.18 (0.64–1.95) | 0.69 |
| Body mass index at survey | 20 (29.9) | 67 | 1.00 |
| Yes | 30 (43.5) | 69 | 1.20 (0.68–2.11) | 0.53 |
| Gain in weight per year (kg) | 26 (40.6) | 64 | 1.00 |
| Yes | 24 (33.3) | 72 | 0.81 (0.47–1.42) | 0.47 |
| Smokingyes | 35 (43.2) | 81 | 1.00 |
| Yes | 25 (45.5) | 55 | 0.74 (0.40–1.35) | 0.33 |
| Alcohol consumptionyes | 19 (57.6) | 33 | 1.00 |
| Yes | 31 (30.1) | 103 | 0.83 (0.47–1.48) | 0.53 |
| Multivariable analysis | 4.18 (1.52–11.52) | 0.006 |
| History of diabetes | 1.47 (0.70–3.09) | 0.308 |
| History of hypercholesterolaemia | 1.07 (1.02–1.13) | 0.010 |
| Duration of hormone replacement therapy (years) | 0.97 (0.39–2.42) | 0.943 |
| History of endometriosis | Abbreviations: CI = confidence interval; HR, hazard ratio. |

*aLower duration of hormonal contraceptive use was categorised using the median duration (6 years) as the cutoff point.*

*bLower duration of hormonal replacement therapy use was categorised using the median duration (9 years) as the cutoff point. Data are presented only from ever users of hormone replacement therapy (n = 61).*

*cBody mass index variables at ages 18 and 40 years and at survey were categorised using median value as the cutoff point.*

*dGain in weight per year (kg) variable was categorised using median value as the cutoff point.*

*eAlcohol intake was categorised either as full abstinence or any consumption.*

*fAdjusted for age at survey (as continuous variable), parity (nulliparous vs parous), duration of hormonal contraceptive use (as continuous variable), age at menarche (as continuous variable) and ascertainment (as categorised variable).*

| Total number of women | HR (95% CI) | P value |
|-----------------------|-------------|---------|
| n = 136 | 4.18 (1.52–11.52) | 0.006 |
| 1.47 (0.70–3.09) | 0.308 |
| 1.07 (1.02–1.13) | 0.010 |
| 0.97 (0.39–2.42) | 0.943 |
the positive association between diabetes and EC risk suggests weight control to be beneficial for LS women in prevention of diabetes and therefore also EC.

There are several limitations to the study. The sample size of the cohort was relatively small but, on the other hand, included only verified MMR mutation carriers. Exposure data were collected by self-reported questionnaires possibly causing bias. For instance, patients older at the time of survey had to recall their weight and duration of hormonal contraception back a long time. Nevertheless, it has been shown that recalled weight measures actually correlate well (Perry et al, 1995). Finally, the cohort was subjected to potential immortal bias and may have been overrepresented with EC cases of a more favourable outcome, as they represent survivors who may have been fit enough to complete the questionnaires.

In conclusion, our data suggest that diabetes and use of postmenopausal HRT may increase the risk of EC in LS women. If these results are replicated, lifestyle modifications aiming at prevention of diabetes may be beneficial for MMR mutation carrier women in terms of reduction of EC risk. As regards to postmenopausal HRT, the present results imply that long-term HRT should not be encouraged.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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