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 medroxyproges-terone 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; Joehlin-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 cancer 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 unaffected 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

Table 1. List of exposure data collected by postal questionnaires sent to MMR mutation carriers

	Description		
Height			cm
Weight		At age of 18 At age of 40 At present	Kg Kg Kg
Age at menarche	Age when you had your first periods		Years
Age at menopause if achieved	Age when you had your last periods		Years
Number of pregnancies			Number
Deliveries			Number
Spontaneous abortions			Number
Induced abortions			Number
Vaginal HRT use	Local/vaginal oestrogen therapy		Y/N
Systemic HRT use ever	Reply yes, if you have received any oestrogen therapy (pill, patch, gel) for postmenopausal symptoms (e.g., hot flushes, sweating)		Y/N
If yes:	Try to estimate the duration of use in years Describe here the type of oestrogen you use at present (pill, patch, gel).	Systemic HRT duration Systemic HRT at present	Years Y/N
Ovulation failure	Have you ever been diagnosed with irregular menstrual bleeding, which was caused by ovulation failure (i.e., the egg not being released from the ovary)?		Y/N
PCOS	Have you been diagnosed with polycystic ovary syndrome?		Y/N
Endometriosis	Have you been diagnosed with endometriosis, which can cause dysmenorrhea and/or pelvic pain? In endometriosis, tissue that normally lines the inside of your uterus (endometrium) can grow outside your uterus		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 Progesterone po Progesterone-IUD	Y/N Y/N Y/N
Cancer other than endometrial cancer	Have you been diagnosed with other cancers besides endometrial cancer?		Y/N
If yes:	Describe here which cancers and the time of diagnosis	GI[a] tract cancer Urinary tract cancer Breast cancer Ovarian cancer	Y/N Y/N Y/N Y/N
Operated for cancer	List here the type of cancer and the time of surgery		Y/N
Gynaecological follow-up duration	For how long have you participated in regular gynaecological follow-up (i.e., clinical examination, ultrasound and possibly endometrial sampling)? Describe here the time interval		Years
Regular smoking ever	Have you ever smoked regularly (at least one cigarette per day)?		Y/N
If yes:	Try to estimate for how long you have been smoking (years) and approximately how many cigarettes per day	Cigarettes per day Duration of smoking	Number Years
Alcohol consumption	Do you currently use or have you used alcohol?		Y/N
If yes:	Try to estimate how many servings per week you use or have used in average. 1 serving = 12 cl wine or 4 cl hard alcohol or 0.33 l bottle of beer/cider Try to estimate for how long you have used alcohol as you described above	Servings/week Duration of consumption	Number Years
Diabetes	Have you been diagnosed with diabetes, which means that you have too high level of blood glucose? Describe the year of diagnosis		
If yes:	Describe here the different treatments you have received for diabetes	Insulin treatment Tablet treatment	Y/N Y/N
Hypertension	Have you been diagnosed with hypertension, which means that your blood pressure is too high? Describe the year of diagnosis		Y/N
Hypothyreosis	Have you been diagnosed with impaired thyroid function (low levels of thyroxin hormone and high levels of thyroid-stimulating hormone)? Year of diagnosis?		Y/N
Hypercholesterolaemia	Have you been diagnosed with high blood levels of total cholesterol?		Y/N
Any other serious condition, which	Describe here	List	
Hormonal contraception	Have you used hormonal contraception?		Y/N
If yes	Describe here the duration of use in years.	Duration of use	Years
Medication	List here other regular medication you use or have previously used		List

Abbreviations: GI = gastrointestinal; HRT = hormone replacement therapy; IUD = intrauterine device; MMR = mismatch repair; N = no; PCOS = polycystic ovary syndrome; Y = Yes.
[a]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 (40.1)
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.)	24.0 (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)
Endometriosis[f], *n* (%)			
Yes	10 (11.6)	8 (16.0)	18 (13.2)
No	76 (88.4)	42 (84.0)	118 (86.8)
Diabetes[f,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)

	No endometrial cancer, N = 86 (63%)	Endometrial cancer, N = 50 (37%)	Total N = 136
Hypertension[f], n (%)			
Yes	17 (19.8)	18 (36.0)	35 (25.7)
No	69 (80.2)	32 (64.0)	101 (74.3)
Hypercholesterolaemia[f], n (%)			
Yes	8 (9.3)	14 (28.0)	22 (16.2)
No	78 (90.7)	36 (72.0)	114 (83.8)
Hypothyreosis[f], n (%)			
Yes	10 (11.6)	6 (12.0)	16 (11.8)
No	76 (88.4)	44 (88.0)	120 (88.2)
Smoking[h], n (%)			
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]			
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			
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	
⩾13 years	34 (37.4)	91	1.08 (0.59–1.96)	0.81
Live births				
Nulliparous	9 (50.0)	18	1.00	
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	
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	
⩾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	
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	
⩾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	
Yes	24 (48.0)	23	1.48 (0.84–2.58)	0.18
Endometriosis				
No	42 (35.6)	118	1.00	
Yes	8 (44.4)	18	1.96 (0.90–4.28)	0.09
Ovulation failure				
No	46 (92.0)	121	1.00	
Yes	4 (8.0)	15	0.52 (0.19–1.44)	0.21

Table 3. (Continued)

Univariable analysis	Number of women with endometrial cancer (%)	Total number of women	HR (95% CI)	P value
Diabetes				
No	44 (34.1)	129	1.00	
Yes	6 (85.7)	7	3.21 (1.34–7.68)	0.009
Hypertension				
No	32 (31.6)	101	1.00	
Yes	18 (51.4)	35	1.63 (0.91–2.92)	0.10
Hypercholesterolaemia				
No	36 (72.0)	114	1.00	
Yes	14 (28.0)	22	2.08 (1.11–3.90)	0.02
Hypothyreosis				
No	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[c]				
<20.8	17 (25.8)	66	1.00	
⩾20.8	33 (47.1)	70	1.55 (0.86–2.79)	0.14
Body mass index at age 40 years[c]				
<23.2	24 (38.1)	63	1.00	
⩾23.2	26 (40.6)	64	1.18 (0.64–1.95)	0.69
Body mass index at survey[c]				
<25.4	20 (29.9)	67	1.00	
⩾25.4	30 (43.5)	69	1.20 (0.68–2.11)	0.53
Gain in weight per year (kg)[d]				
<0.3	26 (40.6)	64	1.00	
⩾0.3	24 (33.3)	72	0.81 (0.47–1.42)	0.47
Smoking				
No	35 (43.2)	81	1.00	
Yes	25 (45.5)	55	0.74 (0.40–1.35)	0.33
Alcohol consumption[e]				
No	19 (57.6)	33	1.00	
Yes	31 (30.1)	103	0.83 (0.47–1.48)	0.53
	Total number of women n = 136		**HR (95% CI)**	**P value**
Multivariable analysis[f]				
History of diabetes			4.18 (1.52–11.52)	0.006
History of hypercholesterolaemia			1.47 (0.70–3.09)	0.308
Duration of hormone replacement therapy (years)[g]			1.07 (1.02–1.13)	0.010
History of endometriosis			0.97 (0.39–2.42)	0.943

Abbreviations: CI = confidence interval; HR, hazard ratio.

[a]The duration of hormonal contraceptive use was categorised using the median duration (6 years) as the cutoff point.

[b]The 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).

[c]Body mass index variables at ages 18 and 40 years and at survey were categorised using median value as the cutoff point.

[d]Gain in weight per year (kg) variable was categorised using median value as the cutoff point.

[e]Alcohol intake was categorised either as full abstinence or any consumption.

[f]Adjusted 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).

[g]Continuous variable.

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 (the mean time interval between diabetes and EC diagnoses was 5 years). 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,

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.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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