Height and Colorectal and Endometrial Cancer Risk for Persons with Lynch Syndrome

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Running head

Height and Cancer for Persons with Lynch Syndrome

Abstract

Persons with Lynch syndrome (LS – carrying a pathogenic mutation in a DNA mismatch repair gene) have an increased colorectal cancer (CRC) and endometrial cancer (EC) risk. A high reported variability in cancer risk suggests the existence of factors that modify cancer risk for LS. We aimed to investigate the association between height and CRC and EC for persons with LS using two large studies. Information of 1,213 men and 1,636 women with LS from the Colon Cancer Family Registry (1998-2007) and the GEOLynch cohort study (2006-2017) was harmonized. We used weighted Cox proportional hazard regression models with age on the time-axis to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for each 5 cm increment in self-reported height. CRC was diagnosed in 947 persons during 65,369 person-years of observation and 171 women were diagnosed with EC during 39,227 person-years of observation. Height was not associated with CRC for men (HR 1.00 per 5 cm, 95%CI: 0.91, 1.11) or women (HR 1.01 per 5 cm, 95%CI: 0.92, 1.11). Nor was height associated with EC (HR 1.08 per 5 cm, 95%CI: 0.94, 1.24). Hence, we observed no evidence for an association of height with either CRC or EC for persons with LS.

Key words Body height, colorectal cancer, endometrial cancer, hereditary cancer, Lynch syndrome, mismatch repair, weighted cohort

Abbreviations

CCFR	Colon Cancer Family Registry
CI	Confidence interval
CRC	Colorectal cancer
EC	Endometrial cancer
HR	Hazard ratio
LS	Lynch syndrome
MMR	Mismatch repair
PALGA	Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands
PH	Proportional hazard

Lynch syndrome (LS) is defined by a germline mutation in one of the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6* or *PMS2*(1), or the *EPCAM* gene(2). In persons with such MMR gene mutations, a disrupted DNA MMR system causes an increased risk of several cancer types. Even though not all persons with LS develop cancer, LS is the most common cause of hereditary colorectal cancer (CRC) and endometrial cancer (EC)(3). LS also increases the risk of colorectal adenomas (a precursor lesion of CRC(4)) as well as ovarian, stomach, small bowel, pancreas and several other cancers(2, 5-12).

Cancer risk estimates for persons with LS are highly variable between and within families, even for those with the same mutated gene(2, 8, 13). This suggests that factors other than the germline mutation may also influence cancer risk for persons with LS(14).

Height is a factor of interest since a person's tallness may be a surrogate for factors that may influence cancer development, i.e. the number of a person's body cells, a person's genetic make-up, exposure to environmental factors and exposure to several hormones and growth factors during maturation(15). For the general population, there is strong evidence that height is associated with the risk of sporadic colorectal, kidney, pancreatic, prostate, ovarian, endometrial, pre- and postmenopausal breast cancer and malignant melanomas(16). For instance, in this population a 5 cm increment in height has been associated with a 4% higher risk of CRC(17) and a 10 cm increment in height has been associated with a 15% increased risk of EC(18). LS-related tumors develop via a distinctive molecular pathway compared with non-LS related tumors(19-28), and therefore study findings from the general population might not be directly translatable to persons with LS.

Only two studies have been published on the association between height and colorectal neoplasia risk for persons with LS, with conflicting results. For persons suspected to have LS based on their family history, women taller than 1.55 meters were found to have a 47% to 127% increased CRC risk compared with those shorter than 1.55 meters in a Canadian study

while no evidence for an association was found for men(29). In contrast, for persons confirmed to have LS within a Dutch study (GEOLynch) , a 57% decreased risk of colorectal adenomas for each 5 cm increment in height in men was reported while no association was found for women (30). The conflicting results might be due to different study samples (suspected for LS vs. confirmed to have LS), exposure (categorical vs. continuous), outcome (CRC vs. colorectal adenoma) and study design (case-control vs. prospective cohort). In these analyses, we aimed to investigate the association between adult attained height and CRC and EC risk for men and women with LS separately using data from a large sample of persons confirmed to have LS.

METHODS

Study population

For this study, we harmonized data of 2,849 persons confirmed to have LS from two separate studies: the GEOLynch study(30) (ClinicalTrials.gov identifier NCT03303833) and the Colon Cancer Family Registry (CCFR)(31).

Briefly, within the GEOLynch study, persons with Lynch syndrome, i.e. a pathogenic variant in one of the MMR or the *EPCAM* genes, were recruited actively since 2006 through the Netherlands Foundation for the Detection of Hereditary Tumors and two university medical centers (Radboudumc and University Medical Center Groningen, all in the Netherlands). Since 2012 participants were also passively recruited through information published in a magazine of and on a website of the Lynch Polyposis society, a Dutch patient association. Adults with LS both with and without a cancer diagnosis before study enrolment were eligible for study inclusion(30).

The CCFR is an international consortium of six centers in North America and Australia. Its design and recruitment are described in detail by Newcomb *et al.*(31) and

Jenkins *et al.*(32). Briefly, in all six centers population-based probands were recently diagnosed CRC cases identified via cancer registries. Additionally, four centers also used identified clinic-based probands, i.e. cancer-affected and cancer-unaffected persons from families with multiple CRC cases presenting at familial cancer clinics. Population-based probands with MMR-deficient CRC and all clinic-based probands were tested for germline mutations in a DNA MMR gene. A pathogenic variant was identified as LS. Subsequently, where possible, first- and/or second-degree relatives of identified probands with LS were recruited for study participation and germline mutation testing of the variant found in their proband. In this study, we included population-based and clinic-based probands and their relatives with a confirmed germline MMR gene mutation.

Both studies were approved by local medical ethical review committees. Additionally, all individual participants provided informed consent.

Data collection

For both studies, self-reported height and other self-reported personal information (smoking habits, weight and for women: menstrual and reproductive history and menopausal status) and demographic characteristics (age, sex, ethnicity, education level) were collected at recruitment via study- and/or center- specific standardized questionnaires. Clinical information regarding bowel diseases, colorectal surgeries and hysterectomy were obtained from medical records, pathology reports and/or were self-reported (CCFR).

Cancer diagnoses

Cancer diagnoses were identified by several mechanisms. For GEOLynch, the majority of the participants (80.1%) provided consent for a linkage with the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (PALGA foundation).

PALGA has a full coverage of pathology tests since 1991. Reported cancer diagnoses within PALGA after 1991 were therefore used to identify any cancer diagnosis among GEOLynch participant with a linkage to PALGA. Cancer diagnoses obtained from medical records were used for those who did not give consent for a linkage with PALGA and for cancer diagnoses before 1991 which were not reported in PALGA.

In CCFR data, cancer diagnoses were obtained from cancer registries for population-based probands. Self- and/or second-hand reports by relatives of cancer diagnoses at study enrolment and/or 5-year follow up were confirmed, where possible, using pathology reports, medical records, and/or death certificates for all enrolled participants(31, 32).

Study sample

For this study, we included 757 persons with LS from the GEOLynch study and 2,092 persons with LS from the CCFR. Subsequently, we excluded participants with missing information on mutated gene (*n*=3), who also carried a germline *BRCA1* mutation (*n*=1), with missing clinical data (*n*=26), aged <18 years at questionnaire completion (*n*=1), with FAP (*n*=35), with missing data on height (*n*=44), missing age at cancer diagnosis (*n*=14) and participants with a cancer diagnosed before 18 years of age (*n*=5) . Additionally, for CRC analyses, persons were excluded if they had a total proctocolectomy but missing age at total proctocolectomy (*n*=3) or if no person time could be calculated (*n*=9). For EC analyses, men (*n*=1,159), women with a hysterectomy but missing age at hysterectomy (*n*=16) and women without person time (*n*=1) were excluded. This resulted in 2,708 persons included in the analyses for CRC risk and 1,544 women included in the analyses for EC risk. Characteristics of the participants included for the analyses were similar to those of the total cohort (data not shown).

Statistical analyses

We used summary statistics to describe the study population across sex-specific medians of height.

Cox proportional hazard (PH) regression with age as the time scale was used to calculate hazard ratios (HRs) including 95% confidence intervals (CI) for height and CRC and EC. Height (cm) was modeled per 5 cm increase for CRC and EC since no evidence for any departure from a linear association was observed by using restricted cubic splines in Cox regression.

A weighted model was chosen in the HR calculations to adjust for ascertainment bias, which may occur due to oversampling of cancer cases in our population (Web Tables 1-3)(33). By using this method, ascertainment bias will be removed in case of accurate specification of the expected incidence rates of the external referent population and it will be reduced if specification is not completely accurate(33). Additionally, a robust sandwich-covariance estimate by clustering on family membership was applied to account for any dependence of observations within families(34, 35).

We used a retrospective approach to calculate CRC and EC risk estimates. For CRC, person time started at the age of 18 years since height plateaus around the age of 18 years for men and women(36). Person time ended at the age of the first occurrence of any of the following events: first diagnosed cancer excluding non-melanoma skin cancer, baseline interview (i.e. the first interview after study enrolment, CCFR), first colonoscopy of the first series of regular colonoscopies (GEOLynch; defined as at least two colonoscopies performed with an interval of maximal 2.5 years between the colonoscopies), last update of the medical records (GEOLynch), last linkage to PALGA (GEOLynch), or age at total proctocolectomy that diminishes the risk to develop CRC.

To calculate EC risk estimates, person time also started at the age of 18 years and ended at the age of the first occurrence of one of the following events: first diagnosed cancer excluding non-melanoma skin cancer, death, last contact (CCFR), clinical trial enrolment (GEOLynch), lost to follow-up (GEOLynch), last update of the medical records (GEOLynch), last linkage to PALGA (GEOLynch), or age at hysterectomy since a hysterectomy eliminates the risk to develop EC.

Risk estimate were adjusted for a priori identified confounding covariates(37): education level (low, middle, high), ethnicity (Caucasian vs. non-Caucasian), smoking status at the age of 18 years (ever vs. never), year of birth and country of residence (Australasia, Canada, The Netherlands, USA). Risk estimates for EC were additionally adjusted for age at menarche. No adjustments were made for factors during adulthood (e.g. smoking status during adulthood) that may influence the risk of CRC or EC because it is unlikely that factors during adulthood may have causally affected adult-obtained height that is reached at young adulthood. Furthermore, such factors may be in the causal pathway between height and CRC or EC and were, therefore, not identified as confounding covariates in our a priori created causal diagrams.

Schoenfeld residuals were used to judge if the PH assumption was met. Violation of the assumption was observed for height in the association between height and CRC for men. Therefore, CRC risk estimates for men were additionally partitioned at the age of 55 years. Moreover, year of birth was added as time-varying variable in regressions for CRC and EC risk estimates were calculated with a stratified Cox procedure over the strata of country of residence to correct for violation of the PH assumption seen for those variables.

Heterogeneity of the effect of height on the three CRC risk estimate, i.e. for men aged <55 years, men aged ≥55 years and women, was explored by adding an interaction term of height and those three groups into the model. Moreover, to explore a potential differential

effect by cohort (CCFR vs. GEOLynch), an interaction term of height and cohort was added to the models for CRC and EC to determine heterogeneity by cohort.

Two sensitivity analyses were performed. At first, to assess if self-reported cancer cases or reported cancer cases by relatives and/or spouses influenced the results, we excluded those cancer diagnosis (*n*=399). Secondly, since Møller et al.(38) showed that the incidence of a second primary cancer diagnosis in persons with LS was similar to the incidence of a first primary cancer diagnosis, a sensitivity analyses was performed in which person time ended at the first diagnosed CRC or EC only instead of the first diagnosed cancer.

All *P*-values were two-sided. Data analyses were performed in SAS software version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, North Carolina).

RESULTS

Participants' characteristics

A total of 1,155 men and 1,553 women contributed to 28,279 and 37,090 person-years respectively. Median height (range) for men was 180.0 (150.0-213.0) cm and 165.0 (134.0-190.0) cm for women. Taller participants were heavier at young adulthood, more often highly educated and were more often enrolled in the GEOLynch study compared with shorter participants. Ever smoking at the age of 18 years was less often reported by taller men compared with shorter men. Person time ended less often at CRC diagnosis for taller compared with shorter participants. For taller women, person time ended less often at the age of EC diagnosis compared with shorter women (Table 1). Person time ended more often at CRC (40.9% vs. 18.7%), but not EC (10.9% vs. 11.6%), diagnosis for CCFR participants compared with GEOLynch participants (data not shown).

Colorectal cancer

A 5 cm increment in height was not associated with the risk of CRC in men (HR 1.00, 95%CI: 0.91, 1.11) (Table 2). When we partitioned CRC risk estimates for men because the PH assumption was violated for height, we observed a HR of 1.03 (95%CI: 0.93, 1.14) per 5 cm increment in height for CRC for men aged <55 years, and a HR of 0.72 (95%CI: 0.51, 1.02) per 5 cm increment in height for men aged ≥55 years (Table 2). No evidence for an association between height and CRC was observed for women (HR 1.01, 95%CI: 0.92, 1.11).

Heterogeneity of the effect of height on CRC between men aged <55 years, men aged ≥55 years and women was not observed (*P*-value=0.09). No evidence for heterogeneity by cohort was found either (*P*-value=0.58).

Endometrial cancer

A 5 cm increment in height was not associated with EC (HR 1.08, 95%CI: 0.94, 1.24) (Table 3). No evidence for a differential effect of height on EC by cohort was observed (*P*-value=0.40).

Sensitivity analyses

Excluding self-reported cancer diagnoses and cancer diagnoses reported by relatives or spouses, or ending person time at the first diagnosed CRC or EC only instead of the first diagnosed any cancer did not result in different CRC or EC risk estimate for both men and women (data not shown).

DISCUSSION

In this study with a large number of persons with LS, we did not observe evidence for an association between height and CRC for men and women. Height was not associated with EC for women with LS either.

To the best of our knowledge, this is the first study that investigated the association between height and both CRC and EC in persons confirmed to have LS. While we did not observe evidence for an association between height and CRC, a 4% (95%CI: 1.02, 1.05) increased CRC risk per 5 cm increment in height was suggested for men and women in the general population (17). Moreover, being taller increased CRC risk for women but not for men in a Canadian study with persons suspected for LS based on their family cancer history(29). Our current analyses in persons with a germline MMR gene mutation leading to LS only may show different results compared to analyses performed among persons suspected to have LS since persons expected to have LS will consist of persons with LS but also of persons with sporadic cancers or other familial cancer syndromes. Additionally, our observation of no association between height and CRC for men is in contrast to the results of previous analyses in the GEOLynch study in which a 5 cm increment in height was associated with a 57% decreased risk of colorectal adenomas for men with LS. However, for women, results of the current study are consistent with the previous analyses in the GEOLynch study since no evidence for an association between height and colorectal adenoma risk was found for women with LS in the previous analysis(30).

For EC, we did not find evidence for an association between height and EC risk for persons with LS (HR per 5 cm increment in height 1.08, 95%CI: 0.94, 1.24). In the general population, evidence has been presented in a meta-analysis for a 15% (95%CI: 1.09, 1.22) increased EC risk for each 10 cm increment in height(18) which is similar to the risk estimate

observed in our current analyses if an increment in height of 10 instead of 5 cm is used (HR per 10 cm increment in height 1.16, 95%CI: 0.88, 1.53).

Strengths of this study include the large number of persons confirmed to have LS from three continents. Additionally, we were able to adjust for confounding covariates, we used a weighted cohort approach to reduce potential ascertainment bias and a robust co-variance estimate was used to adjust for any dependence of observations within families.

It should be noted that the retrospective approach of our data analyses may have introduced survival bias since the mean age at study enrolment was 48.4 years while person time started at the age of 18 years. This may have influenced our results if many CRC- or EC-related deaths occurred between the age of 18 years and the moment of participant recruitment. Survival after a CRC or EC diagnosis in persons with LS, however, is high with an estimated 5- and 10-year survival of 96% and 88% for colon cancer and 93% and 93% for EC respectively(39). Hence, we do not expect a large impact of this potential bias on our risk estimates. Additionally, height was self-reported instead of measured which may have led to an inflated reported height(40, 41). Though, the correlation between self-reported height and measured height is reported to be high (r>0.9)(41). Nevertheless, even though an inflated report of height may have occurred, this is expected to be non-differential with respect to CRC/EC diagnosis and therefore any estimates of associations would be expected to be biased towards the null. Moreover, participants were asked to report their current height instead of their height at the age of 18 years which may not reflect their tallest adult-attained height since aging comes with a decrease in height(42). As a consequence, height reported at study enrolment of older participants versus younger participants is more likely to be an underestimation of the tallest adult-attained height. However, self-reported current height is not expected to be differentially reported for those with a taller vs. shorter adult-attained height. Using self-reported current height instead of height at the age of 18 years may hence

have introduced a bias towards the null for our risk estimates. Finally, the majority of our participants were of Caucasian origin. Therefore, generalizability of our results to non-Caucasian LS populations may be hampered.

In conclusion, no evidence was observed for an association between height and both CRC and EC for men and women with LS.

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Table 1. Characteristics of Study Participants by Sex-specific Median of Height, Colon Cancer Family Registry (1998-2007; Australasia, Canada, USA) and GEOLynch Cohort Study (2006-2017; the Netherlands).[a]

Characteristic	Men						Women					
	<180.0 cm (N=577)			≥180.0 cm (N=578)			<165.0 cm (N=698)			≥165.0 cm (N=855)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Age (yr) at study enrolment			50.2 (13.4)			46.3 (13.7)			50.8 (14.1)			46.5 (14.0)
Smoking at age 18 years												
Ever	238	41.3		201	34.8		200	28.7		246	28.8	
Weight (kg) at young adulthood[b,c]	70.0 (64.0-77.0)			79.0 (72.0-85.0)			54.0 (50.0-59.0)			60.0 (55.0- 67.0)		
Age (yr) at menarche	-			-			12.8 (1.5)			13.2 (1.6)		
Education level[d]												
Low	144	25.0		100	17.3		223	32.0		164	19.2	
Medium	273	47.3		258	44.6		338	48.4		390	45.6	

High	157	27.2		216	37.4		133	19.1		296	34.6	
Mutated MMR gene												
MLH1	201	34.8		211	36.3		263	37.7		299	35.0	
MSH2	271	47.0		243	42.0		306	43.8		362	42.3	
MSH6	69	12.0		84	14.5		90	12.9		122	14.3	
PMS2	31	5.4		33	5.7		29	4.2		61	7.1	
EPCAM	5	0.9		7	1.2		10	1.4		11	1.3	
Ethnicity												
Caucasian	535	92.7		562	97.2		656	94.0		823	96.3	
Country of residence												
Australasia	257	44.5		202	35.0		345	49.4		274	32.1	
Canada	66	11.4		45	7.8		86	12.3		90	10.5	
The Netherlands	93	16.1		202	35.0		115	16.5		316	37.0	
USA	161	27.9		129	22.3		152	21.8		175	20.5	
Cohort												
CCFR	484	83.9		376	65.1		583	83.5		539	63.0	
GEOLynch	93	16.1		202	35.0		115	16.5		316	37.0	
End of person	278	48.2		233	40.3		210	30.1		226	26.4	

time due to CRC diagnosis											
End of person time due to EC diagnosis[e,f]							90	13.0		81	9.5	
Age (yr) at the end of person time for CRC[g]			44.4 (11.9)			40.6 (11.9)			43.8 (12.1)			40.3 (11.8)
Age (yr) at the end of person time for EC[e,f,h]	-			-					44.5 (11.0)			42.5 (10.2)

Abbreviations: BMI: body mass index, CCFR: Colon Cancer Family Registry, CRC: colorectal cancer, EC: endometrial cancer, Q: quartile, SD: standard deviation, USA: United States of America.

[a]Characteristics based on number of participants included in CRC (N=2708) analyses unless specified differently.

[b]Weight at young adulthood reflects weight at the age of 18 years for GEOLynch participants and weight at the age of 20 years for CCFR participants.

[c]Values are expressed as median (interquartile range).

[d]Values do not add up to 100% due to 7 and 9 missing values for education level in men and women respectively.

[e]Women with missing age of hysterectomy were excluded for the EC analyses, i.e. 7 of the 701 women <165.0 cm and 9 of the 860 women >=165.0 cm. One woman >=165.0 cm without person time was also excluded.

[f]Based on number of women for EC analyses (N=1544).

[g]Age of the first occurrence of one of the following events: first diagnosed cancer excluding non-melanoma skin cancers, baseline interview (CCFR), first colonoscopy of the first series of regular colonoscopies (GEOLynch), last update of the medical records (GEOLynch), last linkage to PALGA (GEOLynch) or age at total proctocolectomy.

[h]Age of the first occurrence of one of the following events: first diagnosed cancer excluding non-melanoma skin cancers, death, last contact (CCFR), last update of the medical records (GEOLynch), last linkage to PALGA (GEOLynch), trial inclusion (GEOLynch), age at study exclusion (GEOLynch) or age at hysterectomy.

Table 2. Hazard Ratio and 95% Confidence Intervals of Colorectal Cancer for each 5 cm Increment in Height t, Colon Cancer Family Registry (1998-2007; Australasia, Canada, USA) and GEOLynch Cohort Study (2006-2017; the Netherlands).

Sex	Total number	Number of CRC cases	Total person years	Crude analysis			Multivariable analysis[a]		
				HR	95% CI	*P*-value	HR	95% CI	*P*-value
Men[b]									
All men	1,155	511	28,279	0.95	0.87, 1.04	0.25	1.00	0.91, 1.11	1.00
<55 yr	1,155	449	27,016	0.98	0.89, 1.07	0.58	1.03	0.93, 1.14	0.60
≥ 55 yr	171	62	1,263	0.68	0.50, 0.92	0.01	0.72	0.51, 1.02	0.06
Women	1,553	436	37,090	0.97	0.89, 1.05	0.41	1.01	0.92, 1.11	0.84

Abbreviations: CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; yr, year.

[a]Adjusted for education level, ethnicity, smoking at the age of 18 years, year of birth and country of residence. Year of birth was added as time-varying covariate since year of birth violated the proportional hazard assumption.

[b]Violation of the proportional hazard assumption was observed for height in men. Therefore, CRC risk estimates for men were also partitioned at the age of 55 years.

Table 3. Hazard Ratio and 95% Confidence Intervals of Endometrial Cancer for each 5 cm Increment in Height t, Colon Cancer Family Registry (1998-2007; Australasia, Canada, USA) and GEOLynch Cohort Study (2006-2017; the Netherlands).

Sex	Total number	Number of EC cases	Total person years	Crude analysis			Multivariable analysis[a]		
				HR	95% CI	*P*-value	HR	95% CI	*P*-value
Women	1,544	171	39,227	1.01	0.90, 1.14	0.81	1.08	0.94, 1.24	0.29

Abbreviations: CI, confidence interval; EC, endometrial cancer; HR, hazard ratio.

[a]Adjusted for education level, ethnicity, smoking at the age of 18 years, year of birth and age at menarche and stratified for country of residence due to a violation of the proportional hazard assumption.

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