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ABSTRACT

Introduction: Lynch syndrome (LS) is a hereditary cancer syndrome caused by pathogenic variants (PVs) in DNA mismatch repair genes, including *MSH6*. Although *MSH6*-associated LS (*MSH6*-LS) is known to increase the risk of several cancers, precise risk estimates—particularly for non-colorectal cancers—remain uncertain. This limits personalised clinical guidance for *MSH6*-LS. This study aims to refine cancer risk estimates for individuals with pathogenic or likely pathogenic *MSH6* variants.
Methods: A retrospective cohort study was conducted using data from 360 Dutch families, comprising 1117 *MSH6* PV carriers identified between 1995 and 2020. Pedigree data were collected from multiple clinical centres. Cancer diagnoses were confirmed through medical records where available. Age- and sex-specific hazard ratios (HRs) and cumulative risks (CRs) were calculated using segregation analysis, adjusted for ascertainment bias.
Results: By age 80, the cumulative CRC risk was 36 % for males (95 % CI: 25–48 %) and 21 % for females (95 % CI: 13–32 %). For endometrial cancer, the CR was 23 % in females (95 % CI: 15–43 %). At age 40, CRC risk remained low: 0.2 % in males and 0.9 % in females. Elevated lifetime risks were observed for ovarian cancer (6.4 %; HR 5.58), urinary tract cancers (10.1 % in males, 4.1 % in females; HR 2.52), and biliary tract cancers (4.9 % in males, 4.2 % in females; HR 2.76). No increased risk was found for prostate or breast cancer.
Conclusion: These refined, age- and sex-specific risk estimates for *MSH6* PV carriers inform tailored surveillance strategies, supporting delayed CRC screening and individualised counselling on risk-reducing surgery for women.

1. Introduction

Lynch syndrome (LS) is a hereditary condition characterised by a heterozygous (likely) pathogenic variant in one of the mismatch repair (MMR) genes: *MLH1, MSH2, MSH6, PMS2*, or *EPCAM* deletions [1]. For readability, we use the term 'pathogenic variant' (PV) throughout the manuscript to refer to both pathogenic and likely pathogenic variants. The estimated carrier frequency of LS is approximately 1 in 279 individuals [2]. LS is associated with an increased lifetime risk (LTR) of colorectal cancer (CRC) and endometrial cancer (EC), as well as higher

Abbreviations: CR, Cumulative Risk; EC, Endometrial Cancer; FDR, First-Degree Relative; HR, Hazard Ratio; LS, Lynch Syndrome; LP, likely pathogenic; LTR, Lifetime Risk; MMR, Mismatch Repair; NA, Not Applicable; OC, Ovarian Cancer; SD, Standard Deviation; SDR, Second-Degree Relative; UC, urinary tract cancer.

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risks for extracolonic cancers, including ovarian, stomach, small bowel, bile duct, and upper urinary tract cancers [3]. These risks vary by MMR gene [3,4] and, for CRC, also by geographic region, likely due to genetic and environmental factors [5]. Universal tumour screening for MMR deficiency and the growing use of multigene panel highlight the importance of these variations.

Individuals diagnosed with LS benefit from regular cancer screening and risk-reducing surgery. Frequent colonoscopies lower CRC risk [6–9], while prophylactic hysterectomy and salpingo-oophorectomy reduce the risk of EC and ovarian cancer (OC) [10]. However, accurate risk estimates, especially for *MSH6*-LS *patients*, remain uncertain, complicating patient surveillance and counselling with *MSH6*-LS.

Larger studies have reported varying LTRs for *MSH6*-LS. CRC risk ranges from 10.0 % to 20.3 %, and EC from 16 % to 41.1 % [3,11,12], with less clarity for OC and breast cancer risks Although these risks are consistently higher than those in the general population [13], the LTR for other cancers is less clear [3,14–16]. Therefore, more precise estimates are needed to guide surveillance.

Therefore, this study of 360 Dutch *MSH6*-LS families aims to refine cancer risk estimates for this specific subgroup of LS patients, using advanced statistical methods that minimise ascertainment bias. By doing so, we aim to improve the current guidelines and enhance surveillance and management strategies for individuals with *MSH6*-LS.

2. Methods

2.1. Data collection

Family pedigrees from known *MSH6*-LS families with a PV identified between 1995 and January 2020 were collected from eight Dutch clinical genetic centres: Dutch Cancer Institute, Maastricht University Medical Centre, Amsterdam UMC, location Vrije Universiteit Amsterdam and location University of Amsterdam, University Medical Centre Groningen, University Medical Centre Utrecht, Erasmus Medical Centre, and Leiden University Medical Centre. Number of porbands, first and second degree relatives an confirmed carriers an non-carriers are depicted in table 1.A minority of carriers were identified through universal testing and analysed as population-based ascertainment. The rest were assumed to be tested based on family history and analysed as clinic-based. Centres provided coded pedigrees including: sex, carrier status (carrier, non-carrier, unknown), age at last contact or death, and where applicable: age at cancer diagnosis, age at first polypectomy or screening, hysterectomy, oophorectomy, or mastectomy. Data were checked and cleaned for quality and consistency.

Where possible, cancer diagnoses and surgical procedures were confirmed using pathology reports or medical records with consent. A subset of probands underwent tumour assessment using microsatellite instability (MSI) testing and immunohistochemistry (IHC). Details of discordant or atypical results are reported in a related study [17].

This study was approved by the Medical Ethical Committee of Leiden, The Hague, Delft (protocol P17.098).

2.2. Germline testing, variant analysis and clinical variant classification

Probands were tested based on immunohistochemistry and/or microsatellite instability results, while relatives of carrier probands were screened for their family's variant. Germline testing for *MSH6* variants was performed on DNA extracted from peripheral blood in all probands. Given the time span of the study (1995–2020), testing methodologies evolved over the years, ranging from Sanger sequencing and MLPA to next-generation sequencing (NGS) panels in later years. Variants were classified for pathogenicity according to the InSiGHT Variant Interpretation Committee Mismatch Repair Gene Variant Classification Criteria and published on the LOVD [18].

A full variant list is provided in Supplementary Table S1.

2.3. Statistical analysis

Cancer risks were estimated using segregation analysis, which accounts for familial relationships and ascertainment. Full methods are described elsewhere [19].

Family likelihoods were modelled using retrospective or ascertainment-corrected joint likelihood approaches [20–23]. More explicitly, clinic-based pedigree's data was conditioned on the proband's genotype and the ages and affected statuses of all family members, and each population-based pedigree's data was conditioned on the genotype, ages and affected statuses of the proband. This approach gives risk estimates that are unbiased by ascertainment, even when the exact ascertainment scheme for clinic-based families cannot be modelled, as long as their ascertainment only depends on the families' phenotypes [21].

Carrier cancer incidences were the product of an age- and sex-specific hazard ratio, which we estimated, multiplied by the corresponding non-carrier incidence. For non-carriers, cancer incidences were set equal to the sex- and age-specific population incidences from the IKNL database, averaged over the years from 2015 to 2019 [13]. This choice of non-carrier incidence is expected to have minimal impact on our cumulative risk estimates for carriers.

Hazard ratios were modeled as a piecewise linear function of age constant before age 40 and after age 60, and linear between these ages. We estimated hazard ratios for CRC and EC simultaneously; these estimates were then fixed, and the hazard ratios for the other cancer types were estimated one at a time. A potential effect for setting (clinic versus population) was included in the model by multiplying the CRC HR by a setting-specific HR that was constant in age.

We adopted a population allele frequency of 1/1516 [2]. We introduced a polygenic model to account for familial aggregation of colorectal cancer, incorporating factors beyond *MSH6* PVs, with a polygenic standard deviation of 1.682 based on European estimates from the International Mismatch Repair Consortium (IMRC) data [5].

We excluded seven families without any age information, and third- or higher-degree relatives of the proband from each family. Censoring occurred at the earliest of death, last follow-up, age 80, polypectomy (for CRC only), or hysterectomy (for EC only). Participants with missing sex (199 individuals) were censored at birth.

Cancer-affected individuals with missing ages at diagnosis (56 CRC, 16 EC, 188 other cancers) were given imputed ages equal to the median age at diagnosis for their sex and specific cancer type in the Netherlands 2015–2019. Unaffected individuals with missing ages (4945 individuals) were given imputed ages equal to (in order of decreasing preference) either the average age of their full siblings, their half-siblings, their spouses, their parents minus 25 years, or their offspring plus 25 years. These imputation rules were then iterated until no missing ages remained.

Analyses were performed in R version 4.2.0, utilising the *clipp* package to calculate pedigree likelihoods and maximising the likelihoods using the *mle* function [24]. Statistical significance was assessed with the likelihood ratio test.

3. Results

3.1. Overview

A total of 360 families were accountable for 2582 first-degree and 5298 second-degree relatives, of whom 757 were confirmed carriers and 821 were confirmed non-carriers of a LP/P MSH6 variant (see also Table 1). Table 2 displays the cases and mean ages at diagnosis for each cancer site among first- and second-degree relatives. Supplementary Table 2 shows the number and mean age at diagnosis (with standard deviation) for various cancer sites among first- and second-degree relatives of *MSH6* PV carriers.

Table 1
Study data set description. Abbreviations: FDR = first-degree relative; SDR = second-degree relative, PV = pathogenic variant.

Individuals	No. of relatives		
	Total	Male	Female
Probands = (no. of families)	360	139	221
– FDR	2582	1292	1290
– SDR	5298	2633	2665
Confirmed *MSH6* PV carriers			
– FDR	476	230	246
– SDR	281	112	169
Confirmed *MSH6* PV non-carriers			
– FDR	493	209	284
– SDR	328	146	182

3.2. Cancer risks

An overview of cancer risks by site, sex, and age is presented in Tables 2 and 3, and Figs. 1 and 2.

3.2.1. Colorectal cancer

MSH6 PV carriers had elevated CRC risk, with hazard ratios (HRs) varying by age and sex. For males, the HR was 3.1 (95 % CI: 0.8–13.0 %) at age 40, corresponding to a cumulative risk (CR) of 0.2 % (95 % CI: 0.0–0.7 %). At age 70, the HR was 5.1 (3.4–7.3) and CR reached 22.2 % (14.8–32.0 %). For females, the HR at age 40 was 14.7 (5.1–39.9) with a CR of 0.9 % (0.3–2.5 %), and 3.4 (1.9–5.7) at age 70, corresponding to a CR of 13.5 % (8.3–21.8 %).

By age 80, the estimated CR was 35.7 % (25.4–47.7 %) for males and 21.0 % (13.4–32.0 %) for females. In contrast, the general Dutch population has CRC lifetime risks of 6.6 % for males and 4.7 % for females (Fig. 1).

3.2.2. Gynaecologic cancers

The CR at the age of 80 years for endometrial cancer was 23.4 % (95 %CI: 15.4–43 %), and 6.4 % (95 %CI: 3–14.8 %) for ovarian cancer (see also Fig. 1). Compared to the population risk, both cancer risks are increased.

3.2.3. Other cancers

The cumulative risk (CR) of urinary tract cancer at age 80 was 10.1 % (5.2 %–18.8 %) for males and 4.1 % (2.1 %–8.1 %) for females. For biliary tract cancer, the CR was 4.9 % (2.2 %–10.8 %) for men and 4.2 % (1.8 %–9.4 %) for women at age 80. See also Table 3 for further details. Additionally, Table 4 presents the hazard ratios (HR) for small bowel, biliary tract, ovarian, prostate, urinary tract, brain, and breast cancers. There was no evidence that HRs depended on sex (all $p > 0.7$) or age (all $p >= 0.2$), with the sole exception that ovarian cancer HRs depended on age ($p < 0.001$), with estimated HRs of 38.8 (13.9–108) at age 40 and 1.54 (0.43–5.53) at age 60.

3.2.4. Setting

There was no evidence that risks depend on the setting (clinic- versus population-based), with the cancer incidence in the clinic-based setting estimated to be higher than the incidence in the population-based setting by a factor of 1.49 (95 % CI 0.28–7.80, $p = 0.6$) for female CRC and 0.65 (95 % CI 0.16–2.6, $p = 0.6$) for male CRC. While we had limited power to detect any effect by setting, this null result is consistent with other Lynch syndrome studies [19].

4. Discussion

This study aimed to refine cancer risk estimates for *MSH6* PV carriers by analysing a large Dutch cohort using statistical methods that minimize ascertainment bias. Our findings confirm increased cancer risks for CRC and EC, with notable differenced by age and sex. These insights are crucial for refining surveillance and management strategies for LS patients with *MSH6* PVs.

Previous studies [3,11,12,25] have shown variability in risk estimates for *MSH6*-LS, partly due to differences in methodology and cohort composition. Our study aligns with earlier findings but provides a more nuanced understanding regarding age- and sex-specific risks for the Dutch population. These insights are crucial for refining clinical guidelines and improving patient counselling. A more tailored approach based on these age and sex variations could lead to better risk stratification, allowing clinicians to offer more precise advice regarding surveillance and preventive measures. This granularity in risk assessment is particularly useful for making informed decisions about when to initiate screening, and determining the appropriate intervals between screenings.

Although a subset of our data (374 proven carriers) was previously submitted to the Prospective Lynch Syndrome Database (PLSD), this study includes a broader group—1117 confirmed carriers and over 5000 untested relatives. This wider scope enabled more precise risk stratification, especially by age. Unlike the PLSD's prospective design, our retrospective approach reflects cancer risks in the absence of surveillance, offering complementary insights.

4.1. Colorectal cancer risks and screening

Current NCCN Guidelines recommend colonoscopy from age 30–35 in MSH6-LS [26]. Our data support this timing. We observed low CRC risk before age 40, suggesting that earlier screening may not significantly improve outcomes but may increase unnecessary procedures and the associated medical and psychological burden without significantly reducing cancer risk. The NCCN also advises colonoscopy every 1–3

Table 2
Cancer risks are subdivided for men and women. HR = hazard ratio; CR = cumulative risk; NA = not applicable.

Organ	Age	Cancer risks			
		Males		Females	
		HR	CR %	HR	CR %
Colorectum	30	3.1 (0.8–13.5)	0 (0–0.1)	15.4 (5.1–45.1)	0.1 (0–0.3)
	40	3.1 (0.8–13)	0.2 (0–0.7)	14.7 (5.1–39.9)	0.9 (0.3–2.5)
	50	6.3 (3.8–11.6)	1.6 (0.9–3.7)	8.8 (4.4–18)	3.4 (1.4–8)
	60	7.2 (4.2–11.4)	8.9 (5.6–14.4)	3.9 (1.9–7.3)	7.7 (4.3–14.3)
	70	5.1 (3.4–7.3)	22.2 (14.8–32)	3.4 (1.9–5.7)	13.5 (8.3–21.8)
	80	4.0 (2.9–5.4)	35.7 (25.4–47.7)	3.0 (1.8–4.7)	21 (13.4–32)
Endometrium	30	NA	NA	10.8 (0.4–269.9)	0 (0–0.6)
	40			10.8 (0.4–269.9)	0.1 (0–1.4)
	50			12.7 (7.1–140.3)	0.9 (0.4–11.1)
	60			14.6 (7.2–30.3)	5 (3.3–24.2)
	70			14.6 (7.2–30.3)	13.3 (8.8–30)
	80			14.6 (7.2–30.3)	23.4 (15.4–43)

Table 3
extra colonic cancer risks, excluding endometrial cancer, subdivided for men and women. CR = cumulative risk; NA = not applicable.

Organ	Age	Male	Female
		CR % (95 % CI)	CR % (95 % CI)
Any LS cancer	30	0.2 (0.1–0.5)	0.4 (0.3–1)
	40	0.6 (0.3–1.5)	2.1 (1.5–4.3)
	50	2.7 (1.8–5.3)	7.8 (5.6–18.1)
	60	13.1 (9.5–19.5)	19.5 (16–36.6)
	70	33.6 (26.1–44.7)	36.5 (31–51.3)
	80	54.7 (45–67.3)	54.1 (46.9–68.6)
Ovarian	30	NA	0.4 (0.2–1.2)
	40		1.5 (0.5–4)
	50		3.5 (1.3–9.1)
	60		5.1 (2–12.8)
	70		5.6 (2.4–13.6)
	80		6.4 (3–14.8)
Biliary tract including:	30	0.0 (0.0–0.0)	0.0 (0.0–0.0)
stomach, bile duct,	40	0.0 (0–0.1)	0.0 (0–0.1)
gallbladder, and pancreas	50	0.2 (0.1–0.3)	0.1 (0.1–0.3)
	60	0.7 (0.3–1.6)	0.6 (0.3–1.4)
	70	2.2 (1–4.8)	1.9 (0.8–4.3)
	80	4.9 (2.2–10.8)	4.2 (1.8–9.4)
Urogenital tract including:	30	0 (0–0.1)	0 (0–0.1)
ureter, kidney	40	0.1 (0.1–0.3)	0.1 (0.1–0.2)
urinary bladder	50	0.5 (0.3–1)	0.3 (0.1–0.5)
	60	1.7 (0.9–3.4)	0.8 (0.4–1.7)
	70	4.7 (2.4–9.0)	2.0 (1.0–4.0)
	80	10.1 (5.2–18.8)	4.1 (2.1–8.1)
Small bowel	30	0 (0–0.1)	0 (0–0.1)
	40	0 (0–0.1)	0 (0–0.1)
	50	0 (0–0.1)	0 (0–0.1)
	60	0 (0–0.3)	0 (0–0.2)
	70	0.1 (0–1.2)	0 (0–0.7)
	80	0.2 (0–2.8)	0.1 (0.1–1.9)
Prostate	30	0 (0–0)	NA
	40	0 (0–0)	
	50	0.1 (0.1–0.3)	
	60	1.7 (0.8–3.4)	
	70	7.8 (3.8–15.1)	
	80	16.6 (8.4–30.6)	
Brain	30	0.1 (0–0.4)	0 (0–0.2)
	40	0.2 (0.1–0.8)	0.1 (0–0.4)
	50	0.4 (0.1–1.5)	0.2 (0.1–0.9)
	60	0.7 (0.2–2.8)	0.4 (0.1–1.7)
	70	1.2 (0.3–4.7)	0.7 (0.2–2.8)
	80	1.8 (0.5–7.2)	1.1 (0.3–4.4)
Breast	30	-	0.1 (0.1–0.2)
	40		0.7 (0.4–1.4)
	50		2.5 (1.4–4.6)
	60		5 (2.8–9)
	70		8 (4.5–14.3)
	80		10.8 (6.2–19)

years, depending on personal and family history. In light of our findings, we propose a modified cadence: colonoscopies at ages 30 and 35, followed by biennial screening from age 40 onward. This may optimise adherence an reduce patient burden without compromising detection.

Comparison with other studies shows variability in cancer risks. Dominguez-Valentin et al. [27] reported lower CRC risks *MSH6*-LS at age 70 (males: 13.5 %, 95 % CI: 7.1–24.8; females: 17.3 %, 95 % CI:11.2–26.3), though differences in surveillance protocols and study design likely account for these discrepancies. Direct comparison with the PLSD is challenging, as it does not report cumulative risks up to age 80. Moreover, PLSD estimates are derived from carriers under regular surveillance and often undergoing polypectomies.

Interestingly, a comparative study by the PLSD and the IMRC reported similar CRC risks at age 70 for *MSH6*-LS (males: 13 %, 95 %CI: 7–25 %; females: 17 %, 95 %CI: 11–26 %) despite different surveillance context [28]. This suggest that factors beyond surveillance, such as genetic background or selection bias, may influence risk estimates.

Recent UK Biobank data (2024) also reported lower cumulative CRC risks by age 80 (males: 18.7 %, 95 %CI: 11.7–28.9; females: 12.9 %, 95 %CI: 7.7–21.2 %) [29]. However, it remains unclear whether participants were diagnosed with LS or undergoing surveillance, which may have influenced risk estimates [30]. Notably, the reported CRC risk before age 40 was low (males: 0.7 %, 95 %CI: 0.1–5.1; females: 0 %) consistent with this study.

In contrast, a recent Israeli study reported that 5.5 % (11/197 individuals) of *MSH6*-LS PV carriers developed advanced neoplasia before age 35 [31]. The authors suggested that initiating surveillance at age 30–35 *MSH6*-LS may be too late. However, possibly selection bias limits the generalisability of these finding [32].

Our study also observed sex-specific differences in early-onset CRC risk, with lower risks in females than males before age 40. This could suggest the potential for a later surveillance start in males. However, this conflicts with findings from the PLSD and UK Biobank, which reported higher early CRC risks in females. Additional longitudinal studies are needed to explore these sex differences before recommending differential surveillance strategies.

4.2. *Endometrial cancer risks and risk reducing surgery*

For women with *MSH6* PV, the decision to pursue risk-reducing hysterectomy and oophorectomy depends on cancer risk, fertility considerations, and personal preferences. We found a lifetime EC risk of 23.4 % (95 %CI: 15.4–43 %), and OC risks of 6.4 % (95 %CI: 3–14.8 %). Differences may reflect geographic or population sampling variation. Although lower than the PLSD's EC estimate of 49.6 % an UK Biobank's 32.4 % (95 %CI: 23.5–43.5 %) [29], our results still support a proactive clinical approach.

Our results support the NCCN guidelines, which recommend considering risk-reducing surgery after childbearing, generally around age 35–40 [33], as well as with the Manchester International Consensus

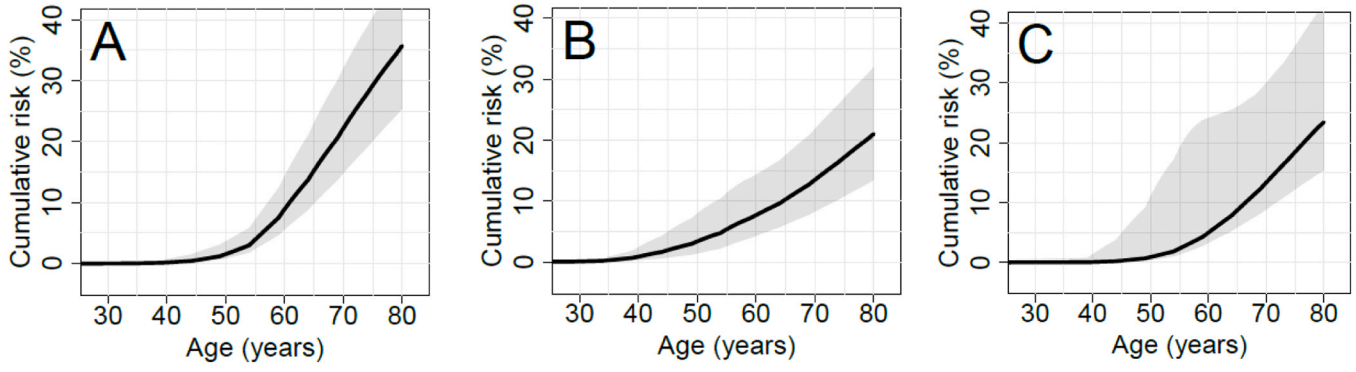

Fig. 1. Cumulative cancer risks A= colorectal cancer risk for males, B= colorectal cancer risk for females, C= endometrial cancer.

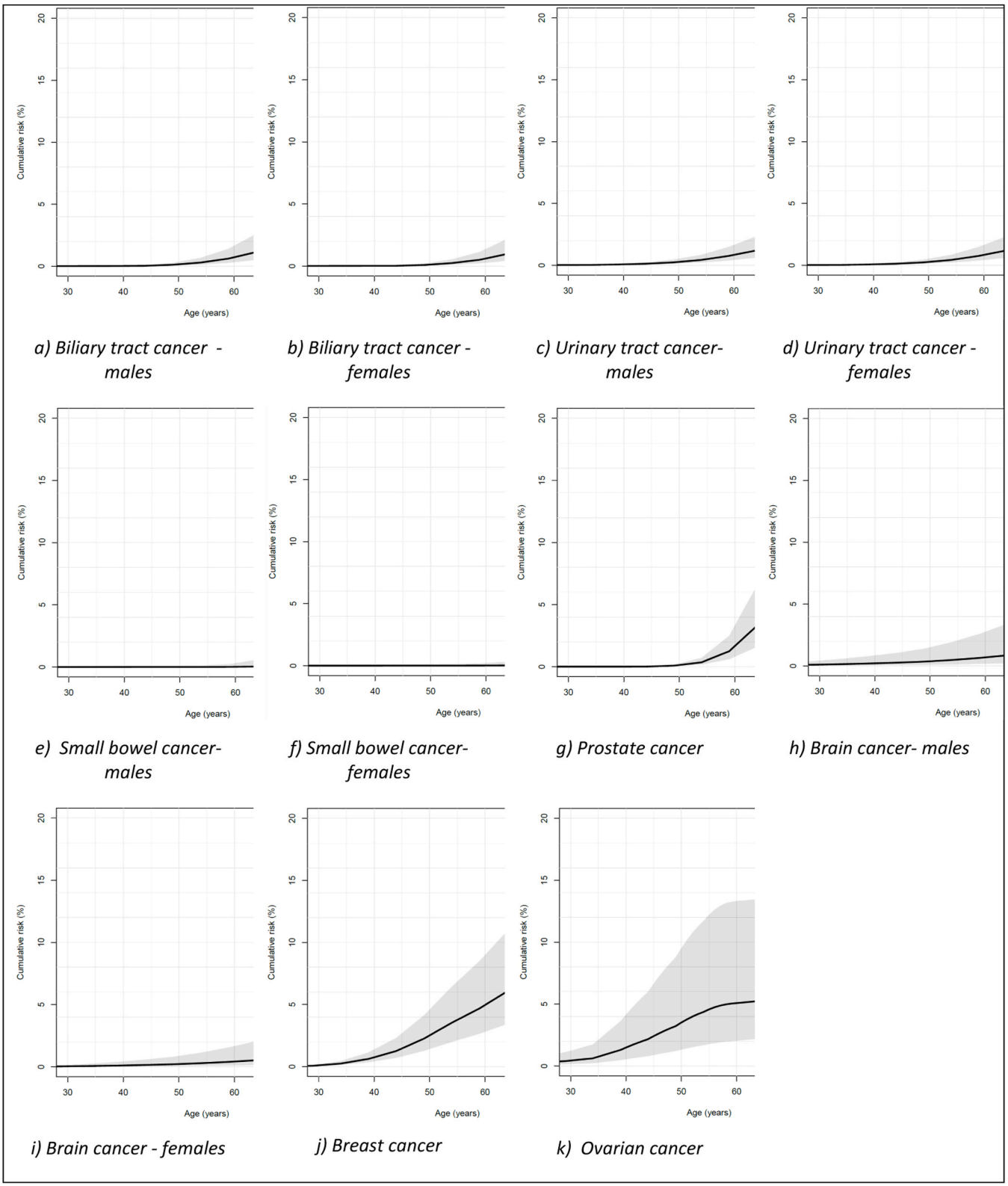

Fig. 2. Cumulative cancer risks in %.

Group *MSH6*-LS [34]. Favourable survival rates for LS-associated cancers further support individualised decision-making [27].

4.3. Other cancer risks

We observed increased risks for urinary and biliary tract cancers in *MSH6* PV carriers, in line with recent PLSD finding [27]. However, no effective surveillance strategies exists for these cancer [35].

Regarding breast cancer, our results indicate a risk of 8 % (95 % CI, 4.5–14.3 %) by age 70 and 10.8 % (95 % CI, 6.2–19 %) by age 80, which is lower than general population estimates in the Netherlands (14 %) [13]. This suggests that *MSH6* PV carriers do not face significantly

Table 4
HR extracolonic cancers.

Site	HR	p
Small bowel	1.61 (0.1–25.01)	0.74
Biliary tract	2.76 (1.22–6.27)	0.031
Ovary	5.58 (2.25–13.8)	0.00037
Prostate	1.37 (0.67–2.81)	0.41
Urinary tract	2.52 (1.28–4.94)	0.012
Brain	2.41 (0.6–9.63)	0.28
Breast	0.88 (0.48–1.61)	0.67

higher breast cancer risk, consistent with recent studies recent studies [29,36–38]. These findings reinforce the importance of avoiding exaggerated risk estimates and ensuring accurate, evidence-based counselling.

4.4. Limitations

Our study has limitations. Cancer histories were often based on self-report from probands or relatives; although medical records were used when possible, confirmation was not always feasible for untested or distant relatives. This introduces potential misclassification, particularly for cancers like EC. [39].

We were unable to quantify the effect of age imputation on the uncertainty of our risk estimates, due to the long run-times of our analyses making multiple imputation or similar approaches infeasible.

Furthermore, we did not take into account genetic and environmental risk modifiers. Our cohort primarily represents individuals of Dutch ancestry. As such, the results may not fully generalise to other ethnicities or populations with differing environmental exposures or genetic backgrounds. Prior research has shown that cancer risks can vary by region and by specific variant [5], which indicate modest inter-regional differences, potentially reflecting lifestyle or population-level modifier effects.

Future international collaborations and multi-ethnic analyses – integrating data from the PLSD and IMRC - will be essential to refine gene- and ancestry-specific cancer risk estimates for *MSH6* pathogenic variant carriers. While our homogeneously Dutch cohort minimises internal variability, such factors should be explored in future studies to enhance the generalisability of these findings.

5. Conclusions

In conclusion, our study provides valuable insights for refining clinical guidelines for *MSH6*_LS. The data support delaying CRC surveillance to age 35 or 40, without significantly increasing risk. For females, heightened vigilance for EC remains crucial, and risk reducing surgeries should be discussed proactively. Also, there is a need for effective surveillance tools for urinary and biliary tract cancers in *MSH6* PV carriers. Finally, our findings highlight the need for personalised risk estimates and surveillance strategies based on causative gene, age and sex, which can improve patient outcomes while minimising unnecessary interventions.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.116098.

Data availability

Data cannot be shared for ethical/privacy reasons.

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