

Mortality by age, gene and gender in carriers of pathogenic mismatch repair gene variants receiving surveillance for early cancer diagnosis and treatment: a report from the prospective Lynch syndrome database

Mev Dominguez-Valentin,^{a,*} Saskia Haupt,^{b,c} Toni T. Seppälä,^{d,e,f} Julian R. Sampson,^g Lone Sunde,^{h,i} Inge Bernstein,^{j,k} Mark A. Jenkins,^l Christoph Engel,^m Stefan Aretz,ⁿ Maartje Nielsen,^o Gabriel Capella,^p Francesc Balaguer,^q Dafydd Gareth Evans,^r John Burn,^s Elke Holinski-Feder,^{t,u} Lucio Bertano,^v Bernardo Bonanni,^w Annika Lindblom,^x Zohar Levi,^y Finlay Macrae,^{z,aa} Ingrid Winship,^{ab,ac} John-Paul Plazzer,^{ad} Rolf Sijmons,^{ae} Luigi Laghi,^{af} Adriana Della Valle,^{ag} Karl Heinemann,^{ah} Tadeusz Dębniak,^{ai} Robert Frusciak,^{aj} Francisco Lopez-Koestner,^{ak} Karin Alvarez-Valenzuela,^{al,ap} Lior H. Katz,^{am} Ido Lishchitz,^{an} Elez Vainer,^{ao} Carlos Vaccaro,^{ap} Dirce Maria Carrara,^{aq} Kevin Monahan,^{ar} Elizabeth Half,^{as} Aine Stakelum,^{at} Des Winter,^{au} Rory Kennedy,^{av} Nathan Gluck,^{aw} Harsh Sheth,^{ax} Naim Abu-Freha,^{ay} Marc Greenblatt,^{az} Benedito Mauro Rossi,^{ba} Mabel Bohorquez,^{bb} Giulia Martina Cavestro,^{bc} Leonardo S. Lino-Silva,^{bd} Karoline Horisberger,^{be,cf} Maria Grazia Tibiletti,^{cg} Ivana do Nascimento,^{ch} Huw Thomas,^{ci} Norma Teresa Rossi,^{ck} Leandro Apolinário da Silva,^{cl,cm} Attila Zaránd,^{cn} Juan Ruiz-Bañobre,^{co,cs} Vincent Hauveline,^{cc} Jukka-Pekka Medlin,^{bf,ca} Kirsi Pylvänäinen,^{ba} Laura Renkonen-Sinisalo,^{cf} Anna Lepistö,^{cf} Päivi Peltomäki,^{bh} Christina Therkildsen,^{bi} Mia Gebauer Madsen,^{bj} Stefan Kobbelaar Burgdorf,^{bk} John L. Hopper,^{bl} Aung Ko Win,^{bl} Robert W. Haile,^{bm} Noralan Lindor,^{bn} Steven Gallinger,^{bo} Loïc Le Marchand,^{bp} Polly A. Newcomb,^{bq} Jane Figueiredo,^{bq} Daniel D. Buchanan,^{br,bc} Stephen N. Thibodeau,^{bu} Magnus von Knebel Doeberitz,^{bu,cc} Markus Loeffler,^{bm} Nils Rahner,^{bw} Evelin Schröck,^{bx,ca,cc,cc} Verena Steinke-Lange,^{by,ca} Wolff Schmiegel,^{bc} Deepak Vangala,^{bc} Gaudia Perne,^{bn} Robert Hünburg,^{ca} Silke Redler,^{bw} Rainhard Büttner,^{cb} Jürgen Wätz,^{cc} Marta Pineda,^{cc} Nuria Duenas,^{cc} Joan Brunet Vidal,^{cc} Leticia Moreira,^{ca} Ariadna Sánchez,^{ca} Elinor Hovig,^{ca,cd} Sigve Nakken,^{ca,cd,ce} Kate Green,^{ca} Fiona Lalloo,^{ca} James Hill,^{ca} Emma Crosbie,^{ca,ca} Miriam Mints,^{ca} Yael Goldberg,^{ca} Douglas Tjandra,^{ca,ca} Sanne W. ten Broeke,^{ca} Revital Kariv,^{ca} Guy Rosner,^{ca} Suresh H. Advani,^{ca} Lidiya Thomas,^{ca} Pankaj Shah,^{ca} Mithun Shah,^{ca} Florença Neffa,^{ca} Patricia Esperon,^{ca} Walter Pavicic,^{ca} Giovana Tardin Torrezan,^{ca} Thiago Bassaneze,^{ca} Claudia Alejandra Martin,^{ca} Gabriela Moslén,^{ca} and Pål Møller^{ca}

Summary

Background The Prospective Lynch Syndrome Database (PLSD) collates information on carriers of pathogenic or likely pathogenic MMR variants (*path_MMR*) who are receiving medical follow-up, including colonoscopy surveillance, which aims to achieve early diagnosis and treatment of cancers. Here we use the most recent PLSD cohort that is larger and has wider geographical representation than previous versions, allowing us to present mortality as an outcome, and median ages at cancer diagnoses for the first time.

Methods The PLSD is a prospective observational study without a control group that was designed in 2012 and updated up to October 2022. Data for 8500 carriers of *path_MMR* variants from 25 countries were included, providing 71,713 years of follow up. Cumulative cancer incidences at 65 years of age were combined with 10-year crude survival following cancer, to derive estimates of mortality up to 75 years of age by organ, gene, and gender.

Findings Gynaecological cancers were more frequent than colorectal cancers in *path_MSH2*, *path_MSH6* and *path_PMS2* carriers [cumulative incidence: 53.3%, 49.6% and 23.3% at 75 years, respectively]. Endometrial, colon and ovarian cancer had low mortality [8%, 13% and 15%, respectively] and prostate cancers were frequent in male *path_MSH2* carriers [cumulative incidence: 39.7% at 75 years]. Pancreatic, brain, biliary tract and ureter and kidney and urinary bladder cancers were associated with high mortality [83%, 66%, 58%, 27%, and 29%, respectively]. Among *path_MMR* carriers undergoing colonoscopy surveillance, particularly *path_MSH2* carriers, more deaths followed non-colorectal Lynch syndrome cancers than colorectal cancers.

Interpretation In *path_MMR* carriers undergoing colonoscopy surveillance, non-colorectal Lynch syndrome cancers were associated with more deaths than were colorectal cancers. Reducing deaths from non-colorectal cancers presents a key challenge in contemporary medical care in Lynch syndrome.

Site	Median age of onset for path_MLH1 carriers		Median age of onset for path_MSH2 carriers		Median age of onset for path_MSH6 carriers		Median age of onset for path_PMS2 carriers	
	Males	Females	Males	Females	Males	Females	Males	Females
Any organ	48.4 [45.8–50.9]	51.3 [49.1–53.3]	53.6 [51.0–56.0]	50.6 [48.1–52.9]	55.8 [NA–64.7]	57.5 [53.0–61.7]	59.6 [NA–73.7]	63.8 [NA]
Colon ^a	47.8 [44.8–50.6]	55.5 [51.84–59.2]	53.6 [50.4–58.0]	55.7 [49.3–61.1]	57.1 [NA–73.0]	60.8 [41.0–67.4]	70.5 [NA]	66.1 [NA]
Sigmoid/Rectum ^a	62.5 [50.2–70.8]	59.3 [46.9–69.2]	57.6 [49.9–64.8]	63.6 [55.0–67.4]	61.3 [NA]	61.2 [NA]	NA	62.5 [NA]
Colorectal ^a	47.4 [44.3–50.4]	54.6 [51.0–58.5]	53.9 [50.0–57.5]	56.2 [50.3–61.3]	55.1 [NA–73.3]	60.1 [42.2–67.1]	71.3 [NA]	66.1 [NA]
Endometrium		51.7 [49.7–53.6]		51.7 [49.4–53.9]		60.0 [55.5–64.1]		61.2 [NA]
Ovary		49.0 [42.1–55.9]		47.4 [42.8–60.8]		65.5 [NA]		57.5 [NA]
Endometrium/ovary		51.2 [49.1–53.0]		50.4 [48.4–52.6]		59.9 [55.5–64.2]		59.5 [NA]
CRC/Endometrium/ovary cancer		51.4 [49.5–53.2]		51.0 [48.7–53.5]		57.7 [50.6–62.6]		64.4 [NA]
Urine bladder	63.0 [56.2–73.5]	68.8 [58.8–74.4]	67.4 [58.7–72.6]	65.1 [54.1–71.9]	71.2 [NA–74.7]	61.1 [NA]	NA	NA
Ureter/kidney	63.9 [50.6–73.7]	63.6 [NA]	61.1 [56.7–64.6]	65.1 [61.6–69.3]	65.7 [NA]	62.0 [NA]	72.5 [NA]	NA
Kidney, ureter and/or urine bladder	62.9 [57.1–71.3]	67.5 [59.4–73.0]	62.5 [59.0–67.4]	64.3 [61.6–68.1]	70.6 [NA–74.2]	61.8 [NA–68.6]	72.5 [NA]	NA
Kidney, ureter and/or urine bladder/prostate	67.5 [62.5–71.4]		62.6 [59.8–65.5]		68.8 [59.2–73.0]		70.9 [NA]	
Stomach	68.1 [59.0–72.7]	65.7 [56.6–74.1]	64.3 [57.46–73.35]	61.9 [NA–73.7]	52.5 [NA]	62.5 [NA]	57.5 [NA]	NA
Small bowel	63.5 [54.0–70.1]	53.8 [NA–71.0]	59.8 [52.6–67.6]	54.2 [NA–66.2]	68.8 [NA]	57.5 [NA]	47.5 [NA]	62.5 [NA]
Pancreas	67.0 [NA]	64.7 [NA–74.8]	65.7 [NA]	66.8 [NA]	72.5 [NA]	66.4 [NA]	NA	NA
Bile duct/gall bladder	62.2 [48.0–68.7]	53.4 [NA]	69.9 [60.2–NA]	71.3 [NA]	NA	NA	NA	NA
Prostate	70.2 [63.7–72.6]		66.2 [62.0–70.0]		65.9 [NA–74.9]		47.5 [NA]	
Breast		57.7 [52.6–63.6]		60.7 [53.5–65.9]		62.7 [51.7–72.4]		70.2 [NA]
Brain	67.5 [NA]	49.9 [NA]	70.0 [43.0–74.6]	52.2 [NA]	62.5 [NA]	54.9 [NA]	NA	NA

NA: occurs for the median age of onset or the confidence limits if the corresponding conditional cumulative incidence estimates always are above or below 50%. ^aFollowing intervention with surveillance colonoscopy as described in text.

Table 3: Median age of onset for cancer in specific organs by age and gender for path_MMR carriers.

Table S3. Cumulative incidences with [95% confidence intervals] in respective organs by age and gender for *path_MLH1* carriers.

Site	Cumulative incidence 30 years		Cumulative incidence 40 years		Cumulative incidence 50 years		Cumulative incidence 60 years		Cumulative incidence 70 years		Cumulative incidence 75 years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Any organ	3.3 [1.5-7.1]	0 [-]	16.7 [12.7-21.9]	12.4 [9.1-16.7]	37.8 [32.5-43.7]	36.8 [31.9-42.3]	54.5 [48.5-60.7]	59.5 [53.9-65.1]	63.0 [56.1-69.8]	75.5 [69.4-81.3]	68.5 [60.8-76.0]	80.2 [73.5-86.1]
Colon*	2.7 [1.1-6.3]	0 [-]	14.0 [10.3-18.8]	8.1 [5.6-11.7]	32.0 [27.0-37.6]	16.3 [12.8-20.6]	45.4 [39.7-51.6]	28.6 [24.0-34.0]	53.0 [46.4-60.0]	40.0 [34.3-46.4]	55.9 [48.6-63.4]	46.2 [39.3-53.7]
Sigmoid/Rectum*	0.5 [0.1-3.5]	0 [-]	1.6 [0.6-3.9]	1.1 [0.4-3]	2.8 [1.5-5.3]	2.0 [1.0-4.0]	4.7 [2.9-7.6]	3.9 [2.4-6.4]	7.8 [5.1-11.8]	6.0 [3.8-9.3]	10.7 [6.9-16.3]	7.4 [4.7-11.4]
Colorectal*	3.3 [1.5-7.1]	0 [-]	14.9 [11.1-19.9]	9.0 [6.3-12.8]	32.5 [27.4-38.3]	18.2 [14.5-22.8]	45.9 [40.1-52.3]	30.6 [25.8-36.1]	52.8 [46.1-59.8]	42.1 [36.2-48.6]	56.0 [48.5-63.7]	48.3 [41.3-55.9]
Endometrium		0 [-]		2.0 [1.0-4.2]		14.9 [11.6-19.1]		28.4 [23.6-33.9]		35.8 [29.9-42.5]		37.2 [30.9-44.3]
Ovary		0 [-]		1.4 [0.6-3.5]		4.4 [2.7-7.2]		7.4 [4.9-11.1]		8.0 [5.3-12.0]		8.0 [5.3-12.0]
Endometrium/ ovary		0 [-]		3.4 [1.9-5.9]		18.8 [15.1-23.3]		34.5 [29.4-40.1]		41.9 [36.0-48.5]		43.2 [36.9-50.0]
CRC/Endometri um/ovary cancer		0 [-]		12.5 [9.3-16.8]		35.4 [30.4-41.1]		60.5 [54.4-66.6]		75.0 [68.4-81.1]		79.7 [72.7-85.9]
Urine bladder	0 [-]	0 [-]	0 [-]	0 [-]	0.5 [0.1-1.9]	0.2 [0-1.5]	2.1 [1.0-4.3]	1.0 [0.4-2.7]	3.8 [2.1-6.9]	2.7 [1.3-5.5]	5.6 [3.1-10.0]	4.8 [2.6-8.9]
Ureter/kidney	0 [-]	0 [-]	0 [-]	0.3 [0-1.8]	0.7 [0.2-2.2]	0.5 [0.1-1.9]	1.3 [0.5-3.2]	0.7 [0.2-2.2]	3.7 [1.9-6.9]	2.2 [1.0-4.6]	4.5 [2.4-8.6]	2.9 [1.4-6.0]
Kidney, ureter and/or urine bladder	0 [-]	0 [-]	0 [-]	0.3 [0-1.8]	1.2 [0.5-2.9]	0.7 [0.2-2.1]	3.4 [1.9-5.9]	1.7 [0.8-3.6]	6.5 [4.1-10.3]	4.1 [2.4-7.1]	9.2 [5.8-14.2]	6.9 [4.1-11.3]
Kidney, ureter and/or urine bladder/prostate	0 [-]		0 [-]		1.4 [0.7-3.2]		6.0 [3.9-9.1]		13.3 [9.7-18.3]		23.9 [17.9-31.4]	
Gastric	0 [-]	0 [-]	0 [-]	0.3 [0-1.8]	0.7 [0.2-2.2]	0.5 [0.1-1.9]	2.4 [1.2-4.6]	1.0 [0.4-2.7]	5.5 [3.3-9.3]	2.9 [1.5-5.6]	8.9 [5.5-14.4]	4.3 [2.3-7.9]
Small bowel	0 [-]	0 [-]	0.3 [0-1.9]	0.9 [0.3-2.8]	1.5 [0.7-3.2]	1.6 [0.7-3.5]	3.6 [2.1-6.1]	2.5 [1.3-4.6]	6.6 [4.1-10.3]	3.8 [2.2-6.7]	8.3 [5.2-13.0]	4.5 [2.6-7.8]
Pancreas	0 [-]	0 [-]	0.3 [0-1.9]	0.3 [0-2.3]	0.5 [0.1-2.0]	0.8 [0.2-2.4]	1.1 [0.4-2.9]	1.2 [0.5-2.9]	2.2 [0.9-5.1]	2.3 [1.1-4.7]	3.1 [1.4-6.9]	3.7 [1.9-7.2]
Bile duct/gall bladder	0 [-]	0 [-]	0 [-]	0 [-]	0.7 [0.2-2.2]	0.4 [0.1-1.7]	1.3 [0.5-3.1]	1.2 [0.5-2.8]	4.0 [2.2-7.3]	1.5 [0.7-3.3]	4.0 [2.2-7.3]	1.5 [0.7-3.3]
Prostate	0 [-]		0 [-]		0.2 [0-1.7]		2.9 [1.5-5.4]		7.6 [4.8-11.8]		15.6 [10.7-22.6]	
Breast		0 [-]		0.6 [0.1-2.3]		3.0 [1.7-5.1]		7.4 [5.3-10.4]		10.4 [7.6-14.1]		12.4 [9.1-16.9]
Brain	0 [-]	0 [-]	0 [-]	0.3 [0-1.8]	0 [-]	0.7 [0.2-2.1]	0 [-]	0.9 [0.3-2.4]	0.6 [0.1-3.9]	1.4 [0.5-3.4]	0.6 [0.1-3.9]	1.4 [0.5-3.4]

Table S4. Cumulative incidences with [95% confidence intervals] in respective organs by age and gender for *path_MSH2* carriers.

Site	Cumulative incidence 30 years		Cumulative incidence 40 years		Cumulative incidence 50 years		Cumulative incidence 60 years		Cumulative incidence 70 years		Cumulative incidence 75 years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Any organ	3.6 [1.5-8.4]	2.3 [0.9-6.1]	12.7 [8.7-18.3]	15.1 [11.0-20.7]	31.1 [25.5-37.8]	40.1 [34.2-46.6]	59.4 [52.4-66.5]	58.8 [52.6-65.2]	73.2 [65.5-80.4]	77.7 [71.0-83.8]	80.5 [72.3-87.5]	83.4 [76.8-89.1]
Colon*	3.4 [1.4-8.0]	1.7 [0.5-5.1]	8.4 [5.2-13.3]	7.1 [4.4-11.3]	19.9 [15.3-25.7]	14.9 [11.1-19.8]	34.2 [28.3-40.9]	22.1 [17.7-27.5]	47.3 [39.9-55.2]	36.5 [30.5-43.2]	52.7 [44.4-61.4]	38.4 [32.1-45.5]
Sigmoid/Rectum*	0 [-]	0 [-]	1.3 [0.4-3.9]	0.3 [0-2.5]	5.8 [3.7-9.1]	2.4 [1.2-4.8]	10.6 [7.6-14.8]	5.0 [3.2-8.0]	14.7 [10.8-20.0]	12.2 [8.7-16.9]	18.2 [13.1-24.9]	13.7 [9.9-19.0]
Colorectal*	3.6 [1.5-8.4]	1.7 [0.6-5.2]	10.3 [6.7-15.6]	7.3 [4.5-11.6]	21.7 [16.8-27.9]	15.8 [11.8-21.0]	38.6 [32.0-45.9]	24.2 [19.4-29.9]	51.0 [42.8-59.7]	39.8 [33.5-46.7]	55.8 [46.8-65.1]	42.6 [35.9-49.9]
Endometrium		0 [-]		2.0 [0.8-4.8]		18.1 [13.9-23.5]		33.9 [28.0-40.5]		42.1 [35.0-50.1]		44.1 [36.3-52.7]
Ovary		0 [-]		1.6 [0.6-4.2]		8.3 [5.5-12.4]		9.7 [6.6-14.2]		13.4 [8.9-20.1]		13.4 [8.9-20.1]
Endometrium/ ovary		0 [-]		3.6 [1.9-6.8]		25.7 [20.7-31.5]		41.6 [35.6-48.2]		51.5 [44.4-59.1]		53.3 [45.6-61.3]
CRC/Endometrium/ ovary cancer		1.7 [0.6-5.3]		10.9 [7.4-15.9]		37.6 [31.5-44.5]		55.8 [48.9-62.8]		75.1 [67.7-81.9]		80.4 [72.2-87.5]
Urine bladder	0 [-]	0 [-]	0 [-]	0.4 [0.1-3.1]	1.1 [0.4-3.0]	1.5 [0.6-3.7]	4.6 [2.7-7.6]	2.6 [1.3-4.9]	7.2 [4.6-11.3]	6.2 [3.9-9.8]	13.1 [8.3-20.3]	9.4 [6.0-14.5]
Ureter/kidney	0 [-]	0 [-]	0 [-]	0 [-]	1.7 [0.8-3.7]	1.9 [0.9-4.0]	6.8 [4.5-10.2]	5.1 [3.3-7.9]	13.4 [9.7-18.5]	13.9 [10.2-18.6]	15.8 [11.2-22.0]	19.5 [14.6-25.9]
Kidney, ureter and/or urine bladder	0 [-]	0 [-]	0 [-]	0.4 [0.1-3.1]	2.5 [1.3-4.8]	2.6 [1.4-5.1]	9.8 [7.0-13.7]	6.4 [4.3-9.4]	18.1 [13.7-23.6]	17.4 [13.3-22.6]	25.1 [18.9-33.0]	23.7 [18.4-30.3]
Kidney, ureter and/or urine bladder/prostate	0 [-]		0 [-]		3.1 [1.7-5.5]		15.6 [12.0-20.2]		31.7 [25.9-38.4]		39.7 [32.4-48.0]	
Gastric	0 [-]	0 [-]	0 [-]	0 [-]	0.3 [0-1.9]	0.5 [0.1-2.1]	3.0 [1.6-5.7]	1.6 [0.7-3.5]	5.0 [2.9-8.5]	3.1 [1.7-5.9]	8.3 [4.8-14.2]	4.0 [2.1-7.4]
Small bowel	0 [-]	0 [-]	0.7 [0.2-2.6]	0 [-]	0.9 [0.3-2.9]	1.4 [0.6-3.3]	3.6 [2.0-6.4]	2.5 [1.3-4.7]	7.0 [4.3-11.3]	3.7 [2.1-6.4]	7.0 [4.3-11.3]	3.7 [2.1-6.4]
Pancreas	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0.3 [0-1.9]	0.9 [0.3-2.9]	0.5 [0.1-2.1]	3.3 [1.5-7.1]	2.7 [1.3-5.8]	3.3 [1.5-7.1]	3.5 [1.7-7.3]
Bile duct/gall bladder	0 [-]	0 [-]	0 [-]	0 [-]	0.3 [0-1.9]	0 [-]	0.6 [0.1-2.2]	0.8 [0.3-2.4]	2.3 [0.9-5.7]	0.8 [0.3-2.4]	4.6 [2.0-10.2]	2.4 [0.9-6.5]
Prostate	0 [-]		0 [-]		0.8 [0.3-2.5]		6.6 [4.4-10.0]		16.4 [12.0-22.1]		24.0 [17.8-32.0]	
Breast		0 [-]		1.2 [0.4-3.7]		3.4 [1.9-6.1]		7.4 [5.1-10.7]		13.2 [9.7-17.7]		15.5 [11.5-20.9]
Brain	0 [-]	0 [-]	0.4 [0.1-3.0]	0.9 [0.2-3.5]	1.3 [0.5-3.5]	0.9 [0.2-3.5]	1.9 [0.9-4.3]	1.4 [0.5-3.8]	3.3 [1.7-6.3]	1.4 [0.5-3.8]	6.6 [3.4-12.4]	2.2 [0.8-5.7]

Table S5. Cumulative incidences with [95% confidence intervals] in respective organs by age and gender for *path_MSH6* carriers.

Site	Cumulative incidence 30 years		Cumulative incidence 40 years		Cumulative incidence 50 years		Cumulative incidence 60 years		Cumulative incidence 70 years		Cumulative incidence 75 years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Any organ	2.7 [0.4-17.7]	0 [-]	5.9 [1.9-17.7]	1.3 [0.2-8.7]	9.4 [4.2-20.5]	13.7 [8.4-22.1]	20.7 [12.9-32.3]	33.0 [24.8-43.1]	22.6 [14.3-34.5]	52.1 [40.6-64.7]	28.5 [18.3-42.6]	55.2 [43.0-68.2]
Colon*	2.6 [0.4-17.1]	0 [-]	5.5 [1.7-16.8]	1.1 [0.2-7.5]	6.5 [2.3-17.3]	4.5 [1.9-10.5]	11.5 [5.9-21.7]	7.4 [3.9-13.7]	12.7 [6.8-23.1]	15.5 [9.9-24]	17.1 [9.7-29.2]	15.5 [9.9-24]
Sigmoid/Rectum*	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	2.4 [0.8-7.3]	1.9 [0.6-5.6]	6.2 [3.0-12.7]	4.7 [2.3-9.7]	6.2 [3.0-12.7]	4.7 [2.3-9.7]
Colorectal*	2.7 [0.4-17.7]	0 [-]	5.8 [1.8-17.6]	1.2 [0.2-8.1]	6.9 [2.5-18.3]	4.0 [1.5-10.3]	11.8 [5.9-22.8]	8.6 [4.7-15.5]	13.5 [7.1-24.8]	17.3 [11.2-26.3]	16.4 [8.8-29.4]	17.3 [11.2-26.3]
Endometrium		0 [-]		1.1 [0.2-7.4]		8.6 [4.7-15.4]		22.8 [16.3-31.5]		41.4 [32.3-52.0]		45.7 [35.6-57.0]
Ovary		0 [-]		1.1 [0.2-7.4]		1.9 [0.5-7.5]		2.9 [0.9-8.7]		6.3 [2.6-15.2]		6.3 [2.6-15.2]
Endometrium/ ovary		0 [-]		2.2 [0.5-8.3]		10.3 [6.0-17.5]		25.1 [18.2-33.9]		45.7 [36.3-56.1]		49.6 [39.5-60.6]
CRC/Endometrium/ ovary cancer		0 [-]		3.7 [1.2-10.9]		15.6 [9.7-24.6]		29.2 [21.2-39.5]		50.4 [39.1-62.9]		50.4 [39.1-62.9]
Urine bladder	0 [-]	0 [-]	0 [-]	0 [-]	0.8 [0.1-5.6]	0 [-]	1.5 [0.4-5.8]	1.2 [0.3-4.5]	3.0 [1.1-7.9]	2.6 [1.0-6.8]	9.0 [4.7-16.9]	2.6 [1.0-6.8]
Ureter/kidney	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	1.4 [0.3-5.4]	1.2 [0.3-4.6]	3.3 [1.2-8.7]	3.9 [1.8-8.6]	3.3 [1.2-8.7]	3.9 [1.8-8.6]
Kidney, ureter and/or urine bladder	0 [-]	0 [-]	0 [-]	0 [-]	0.8 [0.1-5.6]	0 [-]	2.2 [0.7-6.6]	2.3 [0.9-6.1]	4.7 [2.1-10.2]	6.5 [3.5-11.8]	10.9 [6.0-19.1]	6.5 [3.5-11.8]
Kidney, ureter and/or urine bladder/prostate	0 [-]		0 [-]		0.8 [0.1-5.6]		3.6 [1.5-8.5]		8.9 [5.0-15.7]		16.4 [10.4-25.4]	
Gastric	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0.7 [0.1-4.9]	0 [-]	0.7 [0.1-4.9]	0.7 [0.1-4.7]	0.7 [0.1-4.9]	0.7 [0.1-4.7]
Small bowel	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0.7 [0.1-4.8]	0.6 [0.1-4.0]	1.6 [0.4-6.5]	0.6 [0.1-4.0]	2.8 [0.9-8.7]	0.6 [0.1-4.0]
Pancreas	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0.7 [0.1-4.8]	0 [-]	0.7 [0.1-4.8]	0 [-]	2.2 [0.7-6.8]	1.2 [0.2-8.1]	2.2 [0.7-6.8]
Bile duct/gall bladder	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]
Prostate	0 [-]		0 [-]		0 [-]		1.4 [0.4-5.5]		5.8 [2.8-11.8]		7.0 [3.5-13.7]	
Breast		0 [-]		0 [-]		2.3 [0.8-7.1]		6.5 [3.5-11.7]		9.3 [5.6-15.3]		15.1 [9.7-23.1]
Brain	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	1.2 [0.3-4.6]	0.8 [0.1-5.3]	1.2 [0.3-4.6]	0.8 [0.1-5.3]	1.2 [0.3-4.6]

Table S6. Cumulative incidences with [95% confidence intervals] in respective organs by age and gender for *path_PMS2* carriers.

Site	Cumulative incidence 30 years		Cumulative incidence 40 years		Cumulative incidence 50 years		Cumulative incidence 60 years		Cumulative incidence 70 years		Cumulative incidence 75 years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Any organ	0 [-]	0 [-]	0 [-]	0 [-]	6.7 [1.0-38.7]	4.3 [0.6-26.8]	30.1 [14.8-55.1]	17.4 [7.6-36.9]	30.1 [14.8-55.1]	20.9 [10.0-40.7]	57.3 [33.4-83.1]	40.1 [19.9-69.3]
Colon*	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	9.5 [2.5-32.9]	0 [-]	15.9 [5.3-42.2]	7.7 [1.9-28.9]	35.4 [15.5-67.7]	7.7 [1.9-28.9]
Sigmoid/Rectum*	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	2.2 [0.3-14.6]	0 [-]	2.2 [0.3-14.6]
Colorectal*	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	10.5 [2.7-36.0]	0 [-]	10.5 [2.7-36.0]	8.5 [2.1-31.5]	32.8 [12.7-68.6]	8.5 [2.1-31.5]
Endometrium		0 [-]		0 [-]		0 [-]		9.9 [3.8-24.3]		12.7 [5.5-27.9]		21.2 [8.5-46.9]
Ovary		0 [-]		0 [-]		0 [-]		2.5 [0.4-16.3]		2.5 [0.4-16.3]		2.5 [0.4-16.3]
Endometrium/ ovary		0 [-]		0 [-]		0 [-]		12.4 [5.3-27.2]		15.1 [7.1-30.5]		23.3 [10.2-48.0]
CRC/Endometrium/ ovary cancer		0 [-]		0 [-]		0 [-]		10.3 [3.4-28.6]		14.5 [5.7-34.3]		28.0 [10.1-63.9]
Urine bladder	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]
Ureter/kidney	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	5.1 [0.7-30.9]	0 [-]
Kidney, ureter and/or urine bladder	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	5.1 [0.7-30.9]	0 [-]
Kidney, ureter and/or urine bladder/prostate	0 [-]		0 [-]		3.3 [0.5-21.5]		3.3 [0.5-21.5]		3.3 [0.5-21.5]		8.6 [2.1-31.1]	
Gastric	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	2.7 [0.4-17.5]	0 [-]	2.7 [0.4-17.5]	0 [-]	2.7 [0.4-17.5]	0 [-]
Small bowel	0 [-]	0 [-]	0 [-]	0 [-]	3.3 [0.5-21.3]	0 [-]	3.3 [0.5-21.3]	0 [-]	3.3 [0.5-21.3]	2.1 [0.3-14.0]	3.3 [0.5-21.3]	2.1 [0.3-14.0]
Pancreas	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]
Bile duct/gall bladder	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]
Prostate	0 [-]		0 [-]		3.3 [0.5-21.5]		3.3 [0.5-21.5]		3.3 [0.5-21.5]		3.3 [0.5-21.5]	
Breast		0 [-]		0 [-]		0 [-]		6.0 [2.0-17.5]		6.0 [2.0-17.5]		12.4 [4.0-34.7]
Brain	0 [-]	7.3 [1.1-41.6]	0 [-]	7.3 [1.1-41.6]	0 [-]	7.3 [1.1-41.6]	0 [-]	7.3 [1.1-41.6]	0 [-]	7.3 [1.1-41.6]	0 [-]	7.3 [1.1-41.6]

Incidence at when 25 years set to zero. Cumulative incidences during age periods given.

*Following intervention with surveillance colonoscopy and gynecological examinations as described in text.

Table S8. Median age of onset and cumulative incidences with [95% confidence intervals] of *path_MMR* carriers not having had previous or prevalent cancers at inclusion by group of organs, age, and gender.

Path_MLH1														
Site	Median age of onset		Cumulative incidence 30 years		Cumulative incidence 40 years		Cumulative incidence 50 years		Cumulative incidence 60 years		Cumulative incidence 70 years		Cumulative incidence 75 years	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Colorectal*	46.9 [43.9-49.8]	56.9 [53.0-60.9]	3.3 [1.5-7.1]	0 [-]	15.0 [11.2-20.0]	9.0 [6.3-12.9]	32.8 [27.7-38.7]	17.7 [13.9-22.4]	46.8 [40.8-53.2]	30.6 [25.4-36.6]	52.9 [46.0-60.1]	44.1 [36.9-52.1]	54.8 [47.3-62.6]	53.2 [43.3-63.8]
Endometrium /ovary		51.3 [48.9-53.5]		0 [-]		3.4 [1.9-6.3]		19.3 [15.0-24.6]		35.4 [29.1-42.7]		41.2 [33.4-50.1]		45.1 [35.2-56.5]
Kidney, ureter and/or urine bladder	70.9 [NA]	66.5 [NA]	0 [-]	0 [-]	0 [-]	0.3 [0-2.2]	1.3 [0.4-3.9]	0.7 [0.2-2.6]	1.3 [0.4-3.9]	0.7 [0.2-2.6]	2.3 [0.8-6.7]	2.3 [0.5-9.2]	6.0 [1.7-19.9]	2.3 [0.5-9.2]
Path_MSH2														
Colorectal*	53.0 [47.8-56.8]	59.4 [50.1-63.4]	3.6 [1.5-8.4]	1.7 [0.6-5.3]	10.0 [6.4-15.3]	7.5 [4.7-12.0]	22.1 [17.0-28.4]	16.9 [12.5-22.5]	38.6 [31.7-46.4]	22.9 [17.6-29.4]	46.9 [38.7-55.9]	40.8 [32.2-50.8]	52.4 [42.3-63.3]	45.2 [35.5-56.2]
Endometrium /ovary		51.5 [49.0-54.0]		0 [-]		3.3 [1.6-6.8]		23.3 [17.7-30.3]		40.4 [32.9-48.8]		50.3 [40.9-60.7]		54.7 [43.1-67.2]
Kidney, ureter and/or urine bladder	62.5 [57.8-70.7]	66.8 [61.5-72.4]	0 [-]	0 [-]	0 [-]	0.5 [0.1-3.4]	0.5 [0.1-3.3]	1.8 [0.7-4.8]	9.3 [5.2-16.3]	4.5 [2.2-8.8]	19.0 [11.3-31.0]	15.4 [8.9-26.1]	23.2 [13.5-38.2]	21.1 [12.4-34.6]
Path_MSH6														
Colorectal*	55.6 [NA-73.4]	62.6 [NA]	2.7 [0.4-17.7]	0 [-]	5.9 [1.9-17.7]	1.3 [0.2-8.7]	7.0 [2.6-18.5]	3.4 [1.1-10.1]	12.3 [6.2-23.5]	5.8 [2.4-13.4]	14.2 [7.5-26.0]	13.6 [6.6-27.2]	17.5 [9.4-31.3]	13.6 [6.6-27.2]
Endometrium /ovary		56.9 [49.8-63.1]		0 [-]		1.3 [0.2-8.8]		11.0 [6.0-19.4]		24.0 [16.3-34.6]		38.1 [26.9-52.1]		38.1 [26.9-52.1]
Kidney, ureter and/or urine bladder	70.7 [NA]	61.3 [NA]	0 [-]	0 [-]	0 [-]	0 [-]	1.3 [0.2-8.6]	0 [-]	2.6 [0.7-10.2]	0.9 [0.1-6.4]	2.6 [0.7-10.2]	3.0 [0.7-12.5]	6.4 [1.8-21.5]	3.0 [0.7-12.5]
Path_PMS2														
Colorectal*	71.6 [NA]	62.5 [NA]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	0 [-]	10.5 [2.7-36.0]	0 [-]	10.5 [2.7-36.0]	3.7 [0.5-23.7]	38.2 [14.6-76.9]	3.7 [0.5-23.7]
Endometrium /ovary		70. [NA]		0 [-]		0 [-]		0 [-]		10.9 [3.7-30.1]		10.9 [3.7-30.1]		26.0 [8.0-66.2]
Kidney, ureter and/or urine bladder	NA	NA	NA	0 [-]	NA	0 [-]	NA	0 [-]	NA	0 [-]	NA	0 [-]	NA	0 [-]

* Following intervention with surveillance colonoscopy and gynecological examinations as described in text.; NA: occurs for the median age of onset or the confidence limits if the corresponding conditional cumulative incidence estimates always are above or below 50%.