Supp. Table S1: Estimates from previous studies of colorectal and endometrial cancer cumulative risks for carriers of *MLH1* and *MSH2* mutations. The current study is included here for ease of comparison. Abbreviations: CI, confidence interval; CRC, colorectal cancer; EC, endometrial cancer;

hyphen (-) or NA, not available.

|  |  |  | Percentage cumulative risks to age 70 years (95% CI) for | | |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Gene(s) | Correctly adjusted for ascertainment? | Setting | CRC  (male carriers) | CRC  (female carriers) | EC | Number of families | Reference |
| *MLH1* | yes | population and clinic | 34 (25-50) | 36 (25-51) | 18 (9-34) | 166 | Current study |
| population | 67 (27-89)a | 35 (10-59)a | - | 14 | ([Choi, et al., 2009](#_ENREF_10)) |
| clinic | 41 (25-70) | | 54 (20-80) | 248 | ([Bonadona, et al., 2011](#_ENREF_6)) |
| 20b | 14b | - | 17 | ([Borras, et al., 2010](#_ENREF_7)) |
| 6.8c | 7.3c | - | 12 | ([Borras, et al., 2010](#_ENREF_7)) |
| 97 | 53 | 33 | 55 | ([Stoffel, et al., 2009](#_ENREF_25)) |
| 22 (6.6-61) | 18 (5.4-52) | 66 (35-93) | 39 | ([Quehenberger, et al., 2005](#_ENREF_22)) |
| no | clinic | 57 (45-69)d | 50 (37-64)d | 20 (8.5-31)d | 26 | ([van der Post, et al., 2010](#_ENREF_27)) |
| 92e,f | | - | 17 | ([Stupart, et al., 2009](#_ENREF_26)) |
| 78 | 57 | 25 | 26 | ([Ramsoekh, et al., 2009](#_ENREF_23)) |
| 58 (52-63) | 49 (44-55)g | 28 (25-32)h | 51 | ([Barrow, et al., 2008](#_ENREF_4)) |
| - | - | 40i | NAj | ([Parc, et al., 2003](#_ENREF_21)) |
| 66i | 54i | 25i | 34 | ([Vasen, et al., 2001](#_ENREF_28)) |
| *MLH1* and *MSH2* | yes | population | 56 (37-75) | 48 (26-65) | - | 12 | ([Jenkins, et al., 2006](#_ENREF_16)) |
| 74 | 30 | 42 | 6 | ([Dunlop, et al., 1997](#_ENREF_12)) |
| clinic | 66 (59-76)h | 43 (37-53)h | 39 (31-47)h | 147 | ([Stoffel, et al., 2009](#_ENREF_25)) |
| 47 (12-98) | 33 (24-54) | 14 (6-20) | 36 | ([Alarcon, et al., 2007](#_ENREF_2)) |
| 27 (13-51) | 22 (11-44) | 32 (11-70) | 84 | ([Quehenberger, et al., 2005](#_ENREF_22)) |
| no | clinic | 69 (59-79)k | 52 (38-67)k | 54 (41-66)k | 70 | ([Hampel, et al., 2005](#_ENREF_15)) |
| 100i | 95i | - | NAj | ([Parc, et al., 2003](#_ENREF_21)) |
| 100l | 54l | 60l | 50 | ([Aarnio, et al., 1999](#_ENREF_1)) |
| *MSH2* | yes | population and clinic | 47 (36-60) |  |  | 224 | Current study |
| population | 55 (2-75) | 53 (2-70) | - | 17 | ([Choi, et al., 2009](#_ENREF_10)) |
| clinic | 48 (30-77) | | 21 (8-77) | 256 | ([Bonadona, et al., 2011](#_ENREF_6)) |
| 52 | 39 | 45 | 81 | ([Stoffel, et al., 2009](#_ENREF_25)) |
| 85 (68-91)m | 39 (24-62)m | 82m | 12 | ([Kopciuk, et al., 2009](#_ENREF_18)) |
| 30 (13-57) | 25 (12-50) | 22 (62-64)n | 45 | ([Quehenberger, et al., 2005](#_ENREF_22)) |
| no | clinic | 44 (35-52)d | 47 (37-58)d | 26 (17-35)d | 43 | ([van der Post, et al., 2010](#_ENREF_27)) |
| 57 | 52 | 49 | 20 | ([Ramsoekh, et al., 2009](#_ENREF_23)) |
| 54 (49-59) | 48 (42-53)g | 28 (25-32)h | 59 | ([Barrow, et al., 2008](#_ENREF_4)) |
| - | - | 60d | NAj | ([Parc, et al., 2003](#_ENREF_21)) |
| 92o | 64o | 79o | 12 | ([Green, et al., 2002](#_ENREF_14)) |
| 73d,i | 54d,i | 37d,i | 40 | ([Vasen, et al., 2001](#_ENREF_28)) |

Notes:

1. Based on part of the data used in the present study
2. *MLH1* c.306+5G>A
3. *MLH1* c.1865T>A
4. Estimates are for a mix of carriers and non-carriers
5. *MLH1* C1528T
6. Cumulative risks are to age 65 years
7. Cumulative risks are to age 69 years
8. Combined cumulative risks for carriers of mutations in *MLH1*, *MSH2* and *MSH6*
9. Cumulative risks read from graphs
10. 348 carriers
11. Based on a mixture of 45 clinic- and 25 population-based families
12. 47 of 50 families carried *MLH1* mutations
13. *MSH2* A>T nt942+
14. Confidence interval reported here as in the paper
15. *MSH2* nt943+3 A>T

Supp. Table S2: Estimates from previous studies of cumulative risks for non-colorectal, non-endometrial Lynch syndrome-associated cancers for carriers of *MLH1* and *MSH2* mutations.a The current study is included here for ease of comparison. Abbreviations: NCNE, non-colorectal, non-endometrial; CRC, colorectal cancer; EC, endometrial cancer; CI, confidence interval; M, male; F, female.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Percentage cumulative risks to age 70 years (95% CI) for cancer of the | | | | | | | | |  |
| Gene | Sex | Bladder | Brain | Ovary | Pancreas | Renal pelvis | Small bowel | Stomach | Urinary tract | All NCNE Lynch sites combined | Reference |
| *MLH1* | M&F | 0.2 (0-2.6)b | - | 20 (1-65) | - | 0.2 (0-2.6)b | 0.4 (0.1-3) | 6 (0.2-17) | 0.2 (0-2.6)b | - | ([Bonadona, et al., 2011](#_ENREF_6)) |
| - | 0.3 (0-0.6) | 5.5 (3.0-8.1) | 0 | - | 4.5 (2.7-6.4) | 11 (7.7-14) | 2.8 (1.2-4.4) | 39 (34-43) | ([Barrow, et al., 2009](#_ENREF_5)) |
| - | - | 3.4 (0-6.8)c | - | - | 7.2 (1.5-13)c | 2.1 (0-4.7)c | 1.3 (0-3.9)c | - | ([Vasen, et al., 2001](#_ENREF_28)) |
| M | - | - | - | - | - | - | 20 (10-35) | 1.2 (0.1-9.8) | - | Current study |
| 11 (0-25)c | - | - | - | 4.8 (0-14)c | - | - | 16 (0-39)c | - | ([van der Post, et al., 2010](#_ENREF_27)) |
| - | - | - | - | - | - | - | - | 19 (4.4-64) | ([Quehenberger, et al., 2005](#_ENREF_22)) |
| F | - | - | 13 (6.1-26) | - | - | - | 7.5 (2.6-20) | 2.9 (0.7-13) | - | Current study |
| 0 | - | - | - | 2.4 (0-7.2)c | - | - | 2.4 (0-7.2)c | - | ([van der Post, et al., 2010](#_ENREF_27)) |
| - | - | - | - | - | - | - | - | 16 (3.6-56) | ([Quehenberger, et al., 2005](#_ENREF_22)) |
| *MLH1* and *MSH2* | M&F | - | - | - | 3.7 (1.5-5.9)c | - | - | - | - | - | ([Kastrinos, et al., 2009](#_ENREF_17)) |
| - | 2.1 (1.5-2.9)c | 6.7 (5.4-9.1)c | 4.1 (2.8-5.9)c | - | 4.3 (3.1-5.9)c | 5.8 (4.4-7.7)c | 8.4 (6.6-11)c | - | ([Watson, et al., 2008](#_ENREF_29)) |
| - | 2 to 4e | 12e | - | 2 to 4e | - | 13e | 2 to 4e | - | ([Aarnio, et al., 1999](#_ENREF_1)) |
| M | - | - | - | - | - | - | 6.2 (3.2-9.2)d | - | - | ([Capelle, et al., 2010](#_ENREF_9)) |
| F | - | - | - | - | - | - | 2.0 (0.6-3.3)d | - | - | ([Capelle, et al., 2010](#_ENREF_9)) |
| *MSH2* | M&F | - | - | 24 (3-52) | - | - | 1.1 (0-5) | 0.2 (0-10) | - | - | ([Bonadona, et al., 2011](#_ENREF_6)) |
| - | 6.3 (4.0-8.7) | 7.5 (5.0-10) | 0.7 (0-1.4) | - | 1.3 (0.5-2.1) | 7.8 (5.4-10) | 4.1 (2.5-5.7) | 36 (32-39) | ([Barrow, et al., 2009](#_ENREF_5)) |
| - | 1.2 (0-2.6)c | 10 (3.2-18)c | - | - | 4.5 (0.5-8.5)c | 4.3 (0.5-8.1)c | 12 (3.5-20)c | - | ([Vasen, et al., 2001](#_ENREF_28)) |
| M | - | - | - | - | - | - | 2.2 (0.4-12) | 7.8 (3.2-19) | - | Current study |
| 12 (4.3-20)c | - | - | - | 5.9 (0.7-11)c | - | - | 18 (5.0-31)c | - | ([van der Post, et al., 2010](#_ENREF_27)) |
| - | - | - | - | - | - | - | - | 15 (5.2-39) | ([Quehenberger, et al., 2005](#_ENREF_22)) |
| F | - | - | 9.5 (4.2-21) | - | - | - | 9.3 (4.1-21) | 10 (4.2-23) | - | Current study |
| 2.6 (0-3.8)c | - | - | - | 5.8 (0-12)c | - | - | 8.4 (0-15)c | - | ([van der Post, et al., 2010](#_ENREF_27)) |
| - | - | - | - | - | - | - | - | 12 (4.2-33) | ([Quehenberger, et al., 2005](#_ENREF_22)) |

Notes:

1. All studies were clinic-based (except the current one) and were adjusted for ascertainment, assuming recruitment of families depended on CRC and EC but not NCNE Lynch cancers.
2. Estimates were for the urothelium
3. Estimates are for a mix of carriers and non-carriers
4. Combined cumulative risks for carriers of mutations in *MLH1*, *MSH2* and *MSH6*
5. 47 of 50 families carried mutations in *MLH1*

Supp. Table S3: Estimated average cumulative risks (%) to various ages for *MLH1* and *MSH2* mutation carriers living in Australasia (Australia and New Zealand, combined). Abbreviations: CI, confidence interval; hyphen (-), not applicable.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Average cumulative risks (%), with 95% CIs in parentheses, for cancers of the | | | | |
| Sex | Gene | Age (years) | Colon and rectum (combined) | Endometrium | Ovary | Stomach | Urinary tracta |
| Males | MLH1 | 30 | 2.6 (1.5-4.5) | - | - | 0.1 (0.06-0.2) | 0.005 (5e-04-0.04) |
| 40 | 11 (6.4-17) | - | - | 0.8 (0.4-1.6) | 0.04 (0.005-0.4) |
| 50 | 25 (17-36) | - | - | 3.5 (1.8-6.9) | 0.2 (0.02-1.4) |
| 60 | 33 (24-47) | - | - | 9.7 (5.0-18) | 0.5 (0.05-4.0) |
| 70 | 37 (27-54) | - | - | 26 (14-44) | 1.0 (0.1-8.3) |
| 80 | 43 (30-64) | - | - | 48 (28-73) | 1.9 (0.2-15) |
| MSH2 | 30 | 2.0 (1.2-3.3) | - | - | 0.01 (0.002-0.07) | 0.03 (0.01-0.08) |
| 40 | 8.5 (5.4-13) | - | - | 0.08 (0.01-0.4) | 0.3 (0.1-0.7) |
| 50 | 25 (18-34) | - | - | 0.4 (0.06-2.0) | 1.1 (0.4-2.8) |
| 60 | 40 (30-52) | - | - | 1.0 (0.2-5.7) | 3.2 (1.3-7.8) |
| 70 | 50 (39-64) | - | - | 2.9 (0.5-15) | 6.7 (2.7-16) |
| 80 | 62 (48-76) | - | - | 6.4 (1.2-31) | 12 (5.1-28) |
| Females | MLH1 | 30 | 0.9 (0.4-2.1) | 0.2 (0.06-0.5) | 0.5 (0.2-1.0) | 0.07 (0.03-0.2) | 0.06 (0.01-0.3) |
| 40 | 3.8 (1.7-8.2) | 1.5 (0.5-4.3) | 0.9 (0.4-2.0) | 0.4 (0.1-1.2) | 0.2 (0.05-1.0) |
| 50 | 13 (8.0-23) | 4.1 (2.1-9.6) | 2.4 (1.1-5.1) | 1.6 (0.5-4.6) | 0.6 (0.1-2.6) |
| 60 | 26 (18-39) | 8.3 (4.2-18) | 5.5 (2.6-12) | 3.9 (1.3-11) | 1.5 (0.3-6.5) |
| 70 | 39 (27-55) | 13 (6.0-28) | 10 (4.8-21) | 9.1 (3.2-24) | 2.8 (0.6-12) |
| 80 | 52 (36-69) | 18 (7.8-36) | 17 (8.0-33) | 19 (7.0-47) | 4.9 (1.1-21) |
| MSH2 | 30 | 2.4 (1.3-4.2) | 0.2 (0.1-0.5) | 0.3 (0.1-0.8) | 0.09 (0.04-0.2) | 0.2 (0.09-0.6) |
| 40 | 8.7 (5.0-14) | 2.3 (1.1-4.8) | 0.7 (0.3-1.6) | 0.5 (0.2-1.3) | 0.7 (0.3-1.8) |
| 50 | 23 (17-33) | 9.7 (5.4-16) | 1.7 (0.7-4.0) | 2.0 (0.9-4.7) | 2.0 (0.8-5.0) |
| 60 | 35 (26-47) | 19 (11-31) | 4.1 (1.8-9.2) | 4.9 (2.1-11) | 5.1 (2.1-12) |
| 70 | 40 (30-54) | 23 (13-37) | 7.5 (3.3-17) | 11 (5.0-25) | 9.5 (4.0-22) |
| 80 | 47 (35-63) | 27 (14-43) | 12 (5.5-26) | 24 (11-47) | 16 (7.0-36) |

Notes:

1. Urinary tract means the bladder, ureter, renal pelvis and (due to limitations of the data) kidney other than renal pelvis.

Supp. Table S4: Estimated average cumulative risks (%) to various ages for *MLH1* and *MSH2* mutation carriers living in Canada. Abbreviations: CI, confidence interval; hyphen (-), not applicable.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Average cumulative risks (%), with 95% CIs in parentheses, for cancers of the | | | | |
| Sex | Gene | Age (years) | Colon and rectum (combined) | Endometrium | Ovary | Stomach | Urinary tracta |
| Males | MLH1 | 30 | 2.7 (1.6-4.6) | - | - | 0.1 (0.06-0.2) | 0.01 (0.002-0.1) |
| 40 | 10 (6.1-16) | - | - | 0.6 (0.3-1.2) | 0.05 (0.006-0.5) |
| 50 | 23 (16-33) | - | - | 2.7 (1.4-5.4) | 0.2 (0.02-1.6) |
| 60 | 31 (22-45) | - | - | 8.8 (4.5-17) | 0.5 (0.06-4.2) |
| 70 | 35 (25-51) | - | - | 22 (12-39) | 1.0 (0.1-8.6) |
| 80 | 40 (28-60) | - | - | 40 (23-64) | 1.8 (0.2-14) |
| MSH2 | 30 | 2.1 (1.3-3.4) | - | - | 0.01 (0.002-0.06) | 0.1 (0.04-0.3) |
| 40 | 8.2 (5.2-13) | - | - | 0.06 (0.01-0.4) | 0.4 (0.1-0.9) |
| 50 | 23 (17-32) | - | - | 0.3 (0.05-1.6) | 1.2 (0.5-3.1) |
| 60 | 38 (29-50) | - | - | 0.9 (0.2-5.1) | 3.3 (1.3-8.2) |
| 70 | 49 (38-62) | - | - | 2.5 (0.4-13) | 6.9 (2.8-16) |
| 80 | 59 (46-74) | - | - | 5.0 (0.9-25) | 11 (4.7-26) |
| Females | MLH1 | 30 | 0.7 (0.3-1.5) | 0.3 (0.1-1.0) | 0.5 (0.2-1.1) | 0.1 (0.04-0.3) | 0.05 (0.01-0.2) |
| 40 | 3.1 (1.4-6.6) | 1.9 (0.7-5.5) | 1.2 (0.6-2.7) | 0.5 (0.2-1.3) | 0.2 (0.04-0.8) |
| 50 | 13 (7.5-21) | 5.2 (2.7-12) | 3.5 (1.6-7.5) | 1.4 (0.5-4.0) | 0.6 (0.1-2.7) |
| 60 | 25 (17-38) | 10 (5.3-21) | 7.6 (3.5-16) | 3.3 (1.1-9.4) | 1.4 (0.3-6.4) |
| 70 | 37 (25-53) | 17 (7.9-33) | 13 (6.2-27) | 7.6 (2.6-21) | 2.9 (0.6-12) |
| 80 | 50 (35-67) | 22 (9.9-41) | 20 (9.6-38) | 15 (5.5-39) | 4.8 (1.1-20) |
| MSH2 | 30 | 1.7 (1.0-3.1) | 0.5 (0.2-1.1) | 0.4 (0.2-0.8) | 0.1 (0.06-0.3) | 0.2 (0.08-0.5) |
| 40 | 7.1 (4.1-12) | 2.9 (1.3-5.9) | 0.9 (0.4-2.1) | 0.6 (0.2-1.3) | 0.6 (0.3-1.6) |
| 50 | 22 (15-32) | 12 (6.9-20) | 2.5 (1.1-5.8) | 1.7 (0.7-4.1) | 2.1 (0.9-5.2) |
| 60 | 34 (24-46) | 24 (13-37) | 5.5 (2.4-12) | 4.1 (1.8-9.5) | 5.0 (2.1-12) |
| 70 | 39 (28-52) | 28 (16-44) | 9.7 (4.3-21) | 9.5 (4.1-21) | 9.8 (4.1-23) |
| 80 | 45 (33-61) | 32 (18-50) | 15 (6.6-31) | 19 (8.5-39) | 16 (6.8-35) |

Notes:

1. Urinary tract means the bladder, ureter, renal pelvis and (due to limitations of the data) kidney other than renal pelvis.

Supp.Table S5: Estimated average 10-year risks (%) at various ages for *MLH1* and *MSH2* mutation carriers living in Australasia (Australia and New Zealand, combined).a Abbreviations: CI, confidence interval; hyphen (-), not applicable.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Average 10-year risks (%), with 95% CIs in parentheses, for cancers of the | | | | |
| Sex | Gene | Age (years) | Colon and rectum (combined) | Endometrium | Ovary | Stomach | Urinary tractb |
| Males | MLH1 | 30 | 8.1 (5.0-13) | - | - | 0.7 (0.3-1.3) | 0.04 (0.004-0.4) |
| 40 | 16 (11-24) | - | - | 2.8 (1.4-5.4) | 0.1 (0.01-1.1) |
| 50 | 11 (6.4-20) | - | - | 6.4 (3.2-12) | 0.3 (0.03-2.8) |
| 60 | 5.6 (1.3-19) | - | - | 17 (9.0-32) | 0.5 (0.06-4.8) |
| 70 | 8.9 (2.3-24) | - | - | 31 (16-51) | 0.9 (0.1-7.8) |
| MSH2 | 30 | 6.6 (4.1-10) | - | - | 0.07 (0.01-0.4) | 0.3 (0.1-0.7) |
| 40 | 18 (13-26) | - | - | 0.3 (0.05-1.6) | 0.8 (0.3-2.0) |
| 50 | 20 (13-28) | - | - | 0.7 (0.1-3.7) | 2.1 (0.8-5.2) |
| 60 | 18 (9.0-30) | - | - | 1.9 (0.4-10) | 3.6 (1.5-8.8) |
| 70 | 23 (13-35) | - | - | 3.6 (0.7-19) | 5.9 (2.4-14) |
| Females | MLH1 | 30 | 2.9 (1.3-6.0) | 1.4 (0.5-3.9) | 0.5 (0.2-1.0) | 0.4 (0.1-1.0) | 0.1 (0.03-0.7) |
| 40 | 9.9 (5.6-18) | 2.6 (1.4-5.9) | 1.5 (0.7-3.1) | 1.2 (0.4-3.3) | 0.4 (0.08-1.7) |
| 50 | 15 (9.1-24) | 4.3 (1.0-12) | 3.2 (1.5-6.8) | 2.3 (0.8-6.5) | 0.9 (0.2-3.9) |
| 60 | 17 (8.8-30) | 5.4 (1.4-13) | 5.0 (2.4-10) | 5.4 (2.0-15) | 1.3 (0.3-5.9) |
| 70 | 21 (12-33) | 5.2 (1.4-11) | 7.1 (3.4-15) | 11 (4.2-29) | 2.2 (0.5-9.6) |
| MSH2 | 30 | 6.5 (3.8-11) | 2.1 (0.9-4.3) | 0.3 (0.1-0.8) | 0.4 (0.2-1.0) | 0.5 (0.2-1.3) |
| 40 | 16 (11-24) | 7.6 (4.0-13) | 1.1 (0.5-2.5) | 1.5 (0.6-3.4) | 1.3 (0.5-3.2) |
| 50 | 15 (9.4-22) | 11 (4.7-19) | 2.4 (1.0-5.4) | 2.9 (1.3-6.7) | 3.1 (1.3-7.6) |
| 60 | 8.0 (3.0-18) | 4.6 (1.0-13) | 3.6 (1.6-8.2) | 6.8 (2.9-15) | 4.7 (1.9-11) |
| 70 | 12 (4.9-23) | 4.5 (1.1-12) | 5.2 (2.3-12) | 14 (6.2-29) | 7.6 (3.2-18) |

Notes:

1. For example, male *MSH2* mutation carriers who are unaffected at age 70 years are estimated to have a 23% (95% CI: 13-35) chance of developing CRC before the age of 80 years.
2. Urinary tract means the bladder, ureter, renal pelvis and (due to limitations of the data) kidney other than renal pelvis.

Supp.Table S6: Estimated average 10-year risks (%) at various ages for *MLH1* and *MSH2* mutation carriers living in Canada.a Abbreviations: CI, confidence interval; hyphen (-), not applicable.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Average 10-year risks (%), with 95% CIs in parentheses, for cancers of the | | | | |
| Sex | Gene | Age (years) | Colon and rectum (combined) | Endometrium | Ovary | Stomach | Urinary tractb |
| Males | MLH1 | 30 | 7.7 (4.6-12) | - | - | 0.5 (0.3-1.0) | 0.04 (0.004-0.3) |
| 40 | 14 (9.3-22) | - | - | 2.1 (1.1-4.2) | 0.1 (0.01-1.1) |
| 50 | 11 (6.5-20) | - | - | 6.2 (3.2-12) | 0.3 (0.04-2.6) |
| 60 | 5.5 (1.2-18) | - | - | 15 (7.7-27) | 0.5 (0.06-4.5) |
| 70 | 7.9 (1.9-22) | - | - | 23 (12-40) | 0.7 (0.08-6.1) |
| MSH2 | 30 | 6.2 (3.9-9.7) | - | - | 0.05 (0.009-0.3) | 0.3 (0.1-0.6) |
| 40 | 16 (11-24) | - | - | 0.2 (0.04-1.2) | 0.9 (0.4-2.2) |
| 50 | 19 (13-28) | - | - | 0.6 (0.1-3.6) | 2.1 (0.9-5.2) |
| 60 | 17 (8.6-29) | - | - | 1.6 (0.3-8.8) | 3.7 (1.5-8.9) |
| 70 | 20 (12-32) | - | - | 2.6 (0.4-14) | 4.9 (2.0-12) |
| Females | MLH1 | 30 | 2.4 (1.0-5.2) | 1.6 (0.6-4.3) | 0.7 (0.3-1.6) | 0.3 (0.1-1.0) | 0.1 (0.03-0.6) |
| 40 | 9.8 (5.6-17) | 3.4 (1.8-7.3) | 2.3 (1.0-5.0) | 0.9 (0.3-2.8) | 0.4 (0.09-1.9) |
| 50 | 15 (9.1-23) | 5.5 (1.4-14) | 4.2 (1.9-9.1) | 1.9 (0.7-5.7) | 0.8 (0.2-3.8) |
| 60 | 16 (8.1-27) | 6.9 (1.9-15) | 6.0 (2.8-13) | 4.4 (1.5-13) | 1.5 (0.3-6.6) |
| 70 | 20 (12-31) | 6.4 (2.0-13) | 7.6 (3.5-16) | 8.4 (3.0-23) | 2.0 (0.4-8.9) |
| MSH2 | 30 | 5.5 (3.1-9.2) | 2.4 (1.1-4.9) | 0.5 (0.2-1.2) | 0.4 (0.2-1.0) | 0.5 (0.2-1.1) |
| 40 | 16 (11-24) | 9.6 (5.2-16) | 1.7 (0.7-3.8) | 1.2 (0.5-2.8) | 1.5 (0.6-3.6) |
| 50 | 15 (9.6-23) | 13 (6.2-22) | 3.1 (1.3-6.9) | 2.4 (1.1-5.7) | 2.9 (1.2-7.1) |
| 60 | 7.2 (2.7-17) | 5.7 (1.4-16) | 4.4 (1.9-9.8) | 5.6 (2.4-13) | 5.1 (2.1-12) |
| 70 | 11 (4.5-22) | 5.5 (1.4-14) | 5.6 (2.4-12) | 10 (4.6-23) | 6.9 (2.8-16) |

Notes:

1. For example, male *MSH2* mutation carriers who are unaffected at age 70 years are estimated to have a 20% (95% CI: 12-32) chance of developing CRC before the age of 80 years.
2. Urinary tract means the bladder, ureter, renal pelvis and (due to limitations of the data) kidney other than renal pelvis.

**Supplementary statistical methods**

Ott’s form([Lange, 2002](#_ENREF_19); [Ott, 1974](#_ENREF_20)) for the (unconditional) likelihood



for each pedigree  was assumed, where: ** is the vector of parameters to be estimated; *g* is a vector specifying genotypes for all family members; the sum is over all genotypes consistent with the observed genotypes; *P(g)* is the joint probability of the genotypes *g*, as determined by Mendelian transmission probabilities, assumed allele frequencies and Hardy-Weinberg equilibrium([Lange, 2002](#_ENREF_19)); the product is over all individuals *i* in the family; *xi* is a vector specifying all phenotypic data for person *i*, consisting of affected statuses and ages; *gi* is the genotype of person *i* according to the vector *g*; *P(xi|gi)* specifies a parametric survival model for each person so that either *P(xi|gi)* = *Sd(xi|gi)* if individual *i* is unaffected or *P(xi|gi)* = *dk(tik|gi)Sd(xi|gi)* if individual *i* is affected and his or her first cancer diagnosis was at age *tik* years and site *k*; *d* represents demographic data for individual *i*, consisting of the individual’s sex and country of recruitment (though with Australia and New Zealand combined); *Sd(xi|gi)* is the product of *Sdk(tik|gi)* over all sites *k*; *tik* is the earliest age in years at which individual *i* either died, was last followed up, had prophylactic surgery at site *k* or was diagnosed with cancer at any site; *Sdk(tik|gi)* is the survival function for site *k,* demographic variables *d* and genotype *gi* evaluated at age *tik* years, equal to *exp(-∫dk(t|gi) dt)* where the terminals of integration are 0 and *tik; dk(tik|gi)* is the hazard for site *k,* demographic variables *d* and genotype *gi*, evaluated at age *tik*years;*dk(tik|gi) = HRdk(tik|gi)* *dk(tik)* where *dk(tik)* is the age-standardized and age-, sex- and country-specific population incidence rates([Curado MP, et al., 2007](#_ENREF_11)) for cancers at site *k* and appropriate for a person with demographic variables *d* and age *tik* years; and *HRdk(tik|gi)* is the hazard ratio at age *tik* years for genotype *gi*, site *k* and demographic variables *d*.

Families were assumed to be independent so estimates were obtained by maximizing a weighted sum of the conditional log-likelihoods of all families. The weight assigned to each family was 1 for clinic-based families and the reciprocal of the sampling probability for population-based families. Estimates obtained by maximizing such a weighted likelihood are design unbiased and are asymptotically model unbiased([Skinner, et al., 1989](#_ENREF_24)).

To model any residual familial aggregation of CRC risk, a mixed model was employed which incorporates an unmeasured polygenic factor in addition to the MMR genes. This was necessary since models which attribute all familial aggregation to the major gene being studied are subject to bias([Gong, et al., 2010](#_ENREF_13)). The polygenic part of this model, which models the cumulative effect of a large number of biallelic genes that individually have small effects on cancer susceptibility, was implemented as a hypergeometric polygenic model with four loci([Antoniou, et al., 2001](#_ENREF_3); [Cannings, et al., 1978](#_ENREF_8)). Under this model, the number of disease alleles for each person is approximately normally distributed and is correlated within families with correlation coefficients equal to the kinship coefficients([Lange, 2002](#_ENREF_19)). If *G* is the number of MMR gene mutations that individual *i* has and *P* is his or her number of disease alleles at the loci which contribute to the polygenic component of risk then *gi = (G,P)* represents the overall genotype of individual *i*. The hazard ratio *HRdk(tik|gi)* was modelled as *HRdk(ti|gi) = exp(dkP- dk) HRdk(ti|G)* where *dk* is a positive factor that was estimated, *dk* is a constant which was chosen so that the average hazard for MMR non-carriers equals the appropriate population incidence rates and *HRdk(tik|G)* is a HR corresponding purely to the MMR gene. The hazard ratios *HRdk(tik|G=0)* for non-carriers of MMR mutations were chosen so that the average hazard (averaged over the major gene) was equal to the population incidence. For CRC and EC, hazard ratios *HRdk(tik|G=1)* for carriers were assumed to be continuous, piece-wise linear functions of age *tik* which are constant before age 40 years, linear in the intervals 40-50, 50-60, 60-70 and constant after age 70 years. For all other cancer sites, HRs were assumed to be independent of age. HRs for non-Lynch cancers were estimated using models which included sex-, gene- and age-specific HRs for CRC, EC and all NCNE Lynch cancers combined. Similarly, separate HRs for NCNE Lynch cancers were estimated using models which included sex-, gene- and age-specific HRs for CRC, EC and all other NCNE Lynch cancers combined.

Age-specific cumulative risk estimates at age *t* years for site *k*, demographic variables *d* and genotype *g* were estimated from the HR estimates as *1 - Sdk(t|g)* where *Sdk(t|g)* is the survival function described above. Corresponding confidence intervals (CIs) were calculated using a parametric bootstrap as follows. Five thousand draws were taken from the multivariate normal distribution that the maximum likelihood estimates would be expected to follow from asymptotic likelihood theory.  For each age, corresponding values of the cumulative risk were calculated and the 95% CI for the cumulative risks to that age were taken to be the 2.5th and 97.5th percentile of this sample.  Ten-year risks of cancer at age t years were calculated as (*Sdk(t|g) - Sdk(t+10|g)*)/*Sdk(t|g)* and CIs were calculated by a parametric bootstrap as for the cumulative risks.

All MMR genes were modelled using a single locus, effectively assuming that each family carries MMR gene mutations for at most one gene (this is consistent with observation, since no families with mutations in more than one MMR gene were found). Allele frequencies of 0.001 were assumed for mutations in each MMR gene though sensitivity analyses were conducted in which this frequency was varied. Further modelling assumptions were that Hardy-Weinberg equilibrium held at each MMR gene and that MMR gene mutations were dominant to non-mutations in their effect on cancer risk.  All p-values were two-sided and for the modified segregation analyses were based on likelihood ratio tests.

**References for all supplementary material**

Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, Peltomaki P, Mecklin JP, Jarvinen HJ. 1999. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 81:214-8.

Alarcon F, Lasset C, Carayol J, Bonadona V, Perdry H, Desseigne F, Wang Q, Bonaiti-Pellie C. 2007. Estimating cancer risk in HNPCC by the GRL method. Eur J Hum Genet 15:831-6.

Antoniou AC, Pharoah PD, McMullan G, Day NE, Ponder BA, Easton D. 2001. Evidence for further breast cancer susceptibility genes in addition to BRCA1 and BRCA2 in a population-based study. Genet Epidemiol 21:1-18.

Barrow E, Alduaij W, Robinson L, Shenton A, Clancy T, Lalloo F, Hill J, Evans DG. 2008. Colorectal cancer in HNPCC: cumulative lifetime incidence, survival and tumour distribution. A report of 121 families with proven mutations. Clin Genet 74:233-42.

Barrow E, Robinson L, Alduaij W, Shenton A, Clancy T, Lalloo F, Hill J, Evans DG. 2009. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. Clin Genet 75:141-9.

Bonadona V, Bonaiti B, Olschwang S, Grandjouan S, Huiart L, Longy M, Guimbaud R, Buecher B, Bignon YJ, Caron O and others. 2011. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 305:2304-10.

Borras E, Pineda M, Blanco I, Jewett EM, Wang F, Teule A, Caldes T, Urioste M, Martinez-Bouzas C, Brunet J and others. 2010. MLH1 founder mutations with moderate penetrance in Spanish Lynch syndrome families. Cancer Res 70:7379-91.

Cannings C, Thompson E, Skolnick M. 1978. Probability functions on complex pedigrees. Adv Appl Prob 10:26-61.

Capelle LG, Van Grieken NC, Lingsma HF, Steyerberg EW, Klokman WJ, Bruno MJ, Vasen HF, Kuipers EJ. 2010. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterology 138:487-92.

Choi YH, Cotterchio M, McKeown-Eyssen G, Neerav M, Bapat B, Boyd K, Gallinger S, McLaughlin J, Aronson M, Briollais L. 2009. Penetrance of colorectal cancer among MLH1/MSH2 carriers participating in the colorectal cancer familial registry in Ontario. Hered Cancer Clin Pract 7:14.

Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, P B, editors. 2007. Cancer Incidence in Five Continents, Vol. IX. Lyon, France

Dunlop MG, Farrington SM, Carothers AD, Wyllie AH, Sharp L, Burn J, Liu B, Kinzler KW, Vogelstein B. 1997. Cancer risk associated with germline DNA mismatch repair gene mutations. Hum Mol Genet 6:105-10.

Gong G, Hannon N, Whittemore AS. 2010. Estimating gene penetrance from family data. Genet Epidemiol 34:373-81.

Green J, O'Driscoll M, Barnes A, Maher ER, Bridge P, Shields K, Parfrey PS. 2002. Impact of gender and parent of origin on the phenotypic expression of hereditary nonpolyposis colorectal cancer in a large Newfoundland kindred with a common MSH2 mutation. Dis Colon Rectum 45:1223-32.

Hampel H, Stephens JA, Pukkala E, Sankila R, Aaltonen LA, Mecklin JP, de la Chapelle A. 2005. Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: later age of onset. Gastroenterology 129:415-21.

Jenkins MA, Baglietto L, Dowty JG, Van Vliet CM, Smith L, Mead LJ, Macrae FA, St John DJ, Jass JR, Giles GG and others. 2006. Cancer risks for mismatch repair gene mutation carriers: a population-based early onset case-family study. Clin Gastroenterol Hepatol 4:489-98.

Kastrinos F, Mukherjee B, Tayob N, Wang F, Sparr J, Raymond VM, Bandipalliam P, Stoffel EM, Gruber SB, Syngal S. 2009. Risk of pancreatic cancer in families with Lynch syndrome. JAMA 302:1790-5.

Kopciuk KA, Choi YH, Parkhomenko E, Parfrey P, McLaughlin J, Green J, Briollais L. 2009. Penetrance of HNPCC-related cancers in a retrolective cohort of 12 large Newfoundland families carrying a MSH2 founder mutation: an evaluation using modified segregation models. Hered Cancer Clin Pract 7:16.

Lange K. 2002. Mathematical and statistical methods for genetic analysis. New York: Springer.

Ott J. 1974. Estimation of the recombination fraction in human pedigrees: efficient computation of the likelihood for human linkage studies. Am J Hum Genet 26:588-97.

Parc Y, Boisson C, Thomas G, Olschwang S. 2003. Cancer risk in 348 French MSH2 or MLH1 gene carriers. J Med Genet 40:208-13.

Quehenberger F, Vasen HF, van Houwelingen HC. 2005. Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: correction for ascertainment. J Med Genet 42:491-6.

Ramsoekh D, Wagner A, van Leerdam ME, Dooijes D, Tops CM, Steyerberg EW, Kuipers EJ. 2009. Cancer risk in MLH1, MSH2 and MSH6 mutation carriers; different risk profiles may influence clinical management. Hered Cancer Clin Pract 7:17.

Skinner CJ, Holt D, Smith TMF. 1989. Analysis of complex surveys. Chichester ; New York: Wiley.

Stoffel E, Mukherjee B, Raymond VM, Tayob N, Kastrinos F, Sparr J, Wang F, Bandipalliam P, Syngal S, Gruber SB. 2009. Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. Gastroenterology 137:1621-7.

Stupart DA, Goldberg PA, Algar U, Ramesar R. 2009. Cancer risk in a cohort of subjects carrying a single mismatch repair gene mutation. Fam Cancer 8:519-23.

van der Post RS, Kiemeney LA, Ligtenberg MJ, Witjes JA, Hulsbergen-van de Kaa CA, Bodmer D, Schaap L, Kets CM, van Krieken JH, Hoogerbrugge N. 2010. Risk of urothelial bladder cancer in Lynch syndrome is increased, in particular among MSH2 mutation carriers. J Med Genet 47:464-70.

Vasen HF, Stormorken A, Menko FH, Nagengast FM, Kleibeuker JH, Griffioen G, Taal BG, Moller P, Wijnen JT. 2001. MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. J Clin Oncol 19:4074-80.

Watson P, Vasen HF, Mecklin JP, Bernstein I, Aarnio M, Jarvinen HJ, Myrhoj T, Sunde L, Wijnen JT, Lynch HT. 2008. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer 123:444-9.