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## Original Article

# Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations

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Lynch syndrome or hereditary non-polyposis colorectal cancer is caused by mutations of DNA mismatch repair (MMR) genes. The extracolonic tumour spectrum includes endometrial, ovarian, gastric, small bowel, pancreatic, hepatobiliary, brain, and urothelial neoplasms. Families were referred on the basis of clinical criteria. Tumour immunohistochemistry and microsatellite testing were performed. Appropriate patients underwent sequencing of relevant exons of the MMR genes. Proven and obligate mutation carriers and first-degree relatives (FDRs) with a Lynch syndrome spectrum cancer were considered mutation carriers, as were a proportion of untested, unaffected FDRs based on the proportion of unaffected relatives testing positive in each age group. Kaplan–Meier analysis of risk to 70 years was calculated. One hundred and eighty-four Lynch syndrome spectrum extracolonic cancers in 839 proven, obligate, or assumed mutation carriers were analysed. Cumulative risk for females of an extracolonic tumour is 47.4% (95% CI 43.9–50.8). The risk to males is 26.5% (95% CI 22.6–30.4). There was no reduction in gynaecological malignancies due to gynaecological screening (examination, transvaginal ultrasound scan, hysteroscopy and endometrial biopsy). Males have a higher risk of gastric cancer than females ($p = 0.0003$). Gastric cancer risk in those born after 1935 does not justify surveillance. These penetrance estimates have been corrected for ascertainment bias and are appropriate for those referred to a high-risk clinic.

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Key words: DNA mismatch repair – hereditary non-polyposis colorectal cancer – Kaplan-Meiers analysis – Lynch syndrome – multiple primary neoplasms – statistical bias

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Lynch syndrome or hereditary non-polyposis colorectal cancer (CRC) is an inherited cancer predisposition syndrome accounting for around 4% of all incident CRCs (1). This autosomal dominant condition is characterized by early age of cancer onset (mean age 45 years), proximal predominance of CRC, excess of synchronous and metachronous tumours, and an extracolonic tumour spectrum that includes endometrial, ovarian, gastric, small bowel, pancreas, hepatobiliary, brain and urothelial neoplasms (2, 3).

Lynch syndrome is caused by inactivating mutations of DNA mismatch repair (MMR) genes, *MLH1*, *MSH2*, and *MSH6* (2). These mutations

result in the production of a faulty or truncated protein, which impairs the ability of the MMR system to recognize and repair DNA mismatches (4). In tumour tissue, DNA microsatellite instability reflects the impaired MMR function. *MLH1* and *MSH2* mutations account for almost 90% of all mutations, with *MSH6* mutations causing the remaining 10% (2).

In Lynch syndrome, the risks of developing CRC and extracolonic cancers within the disease spectrum are many orders of magnitude greater than that of the general population. The cumulative lifetime risks vary according to gender and gene mutation. Males have a significantly higher cumulative CRC risk than females (5–9). Dependent on the ascertainment criteria, the lifetime risks of CRC for men with known germline mutations vary between 28.5% and 100% (5–13). For women, there is a 23.7% to 63% cumulative lifetime risk of CRC (5–13).

A number of previous studies have examined the cumulative risks of extracolonic cancers in known mutation carriers (5–9, 11–15). There are a number of common findings:

(1) The cumulative risk of extracolonic cancer is higher for *MSH2* compared with *MLH1* mutation carriers (7, 8). This reaches significance in one study (7).
(2) In the majority of studies, for females, the cumulative lifetime risk of endometrial cancer is equal or greater to the cumulative risk of CRC (5, 6, 11, 12). The cumulative risk of endometrial cancer is particularly high in *MSH6* mutation carriers (71%) comparative to the CRC risk (30%) (9). In *MSH2* mutation carriers, the endometrial cancer risk remains high at 37% but is surpassed by the CRC risk (39–55%) (7, 8).

The majority of these previous studies examined known mutation carriers identified through cancer registries or high-risk clinics on the basis of Amsterdam and Bethesda criteria (3, 16). While these provide large numbers of mutation carriers for risk stratification, the mode of ascertainment can lead to bias. Analysis of this group with highly penetrant alleles results in an overestimation of the cumulative cancer risks. Families with small sibships, few cancer cases, non-paternity, adoption, and insufficient pedigree information may be excluded. Additionally, early analyses of cumulative cancer risks based on Amsterdam Criteria I (17) are biased against extracolonic tumours.

Published cancer registry data on cumulative extracolonic tumour risks in Lynch syndrome have to date been from the Netherlands, Finland, Germany and the USA (6–9, 11, 12, 14, 15). The cumulative tumour risks in Lynch syndrome in these populations may not be applicable worldwide due to founder effects. This is particularly noticeable in the Finnish population due to a single *MLH1* mutation in exon 16 [in frame 165-kb deletion (6, 18)]. To date, the only UK study into cumulative tumour risks was the population-based study by Dunlop et al. in 1997 with a total of 67 mutation carriers (5).

The Manchester Regional Genetics Service receives referrals of families with clustered CRC and extracolonic cancers from a population of 4.5 million within the North West of England. This study reports a large data set of Lynch syndrome families with proven pathogenic germline mutations in which cumulative extracolonic cancer risks have been assessed. This information is valuable in genetic counselling and in the assessment and development of screening protocols for the UK Lynch syndrome population.

## Materials and methods

Families from the North West of England fulfilling Amsterdam or Bethesda criteria were referred by their general practitioner, colorectal surgeon, gastroenterologist or oncologist to the Manchester Regional Genetics Service. Full pedigree information was obtained, and tumour site and diagnosis were confirmed from Cancer Registration data, hospital records or death certificate. Tumour tissue was acquired from family members with prior CRC or extracolonic tumours within the Lynch syndrome spectrum. The tumour samples were subjected to microsatellite instability (MSI) analysis and/or immunohistochemical screening for the MMR proteins as appropriate. From 1996 onwards, mutation analysis was performed for Amsterdam criteria-positive or Bethesda criteria-positive and MSI-high index patients. This involved screening of all exons of *MLH1*, *MSH2*, and more latterly *MSH6* with sequencing and multiple ligation-dependant probe amplification. In cases of proven germline MMR mutation in the index case, mutation analysis was offered to relatives.

Mutations were assessed for pathogenicity against the InSiGHT database (http://www.insight-group.org). Families with proven pathogenic mutations were entered on the Lynch syndrome database prospectively. Demographic data, dates and results of genetic testing, dates and results of screening (colonoscopic or gynaecological), and dates and details of colorectal and extracolonic cancers were entered for probands

and relatives. Age at diagnosis was assessed from Cancer Registration data, and age at follow up taken as 1 September 2007 or at date of death. Vital status and dates of death were obtained from Cancer Registration as of 1 September 2007, hospital records or from death certification. Surveillance was performed and documented from the time of diagnosis to 1 September 2007.

All mutation carriers were offered colonoscopic screening in line with British Society of Gastroenterology (BSG) guidelines (19). Females were offered gynaecological screening (examination, transvaginal ultrasound scan, hysteroscopy and endometrial biopsy) in line with recommendations from the International Collaborative Group for Hereditary Non-Polyposis CRC (20).

The following groups were regarded as mutation carriers:

(1) Proven mutation carriers: Individuals with a pathogenic mutation on germline mutation analysis.
(2) Obligate mutation carriers: Due to their position in the pedigree in relation to relatives testing positive for a mutation.
(3) Putative mutation carriers: First-degree relatives (FDRs) of a proven mutation carrier with a Lynch syndrome-related cancer were considered mutation carriers. The cancers included within the Lynch syndrome spectrum were colorectal (only 2/125 of tested FDRs with CRC were negative for the family gene mutation), endometrial, ovarian, gastric, brain [primary central nervous system (CNS) only, cerebral metastases excluded], biliary, small bowel, and sebaceous adenocarcinoma (only 1/60 tested FDRs with non-colorectal Lynch syndrome spectrum cancers were negative for the family mutation – gastric cancer aged 51 years).
(4) Assumed mutation carriers: half of the untested FDRs with non-Lynch syndrome spectrum cancers were assigned mutation carrier status on a 50:50 basis sequentially by familial gene mutation and age at diagnosis. Additionally, a proportion of untested, unaffected FDRs with no cancers were assigned mutation carrier status, based on the proportion of unaffected relatives who tested positive of the total number of individuals actually tested for each age group. The number of untested, unaffected FDRs assigned mutation carrier status is summarized in Table 1.

Data were transferred to SPSS 11.5 for analysis. The cumulative extracolonic tumour risk was ascertained by Kaplan–Meier analysis. Comparison between the cumulative incidence was made by the log rank test. A p-value $<0.05$ was considered to be significant. The cumulative tumour risk was calculated at age 70 years as this allowed direct comparison with the majority of the previous literature (5, 6, 8, 9, 11, 15). For the penetrance analysis of cumulative lifetime extracolonic cancer risk, index cases were excluded from the analysis.

## Results

One hundred and twenty-one Lynch syndrome families with proven pathogenic germline mutations (51 *MLH1*, 59 *MSH2*, and 11 *MSH6* families) were used in the analysis.

Table 2 shows the numbers of mutation carriers (proven, obligate, and assumed) used for analysis. In total, 282 extracolonic cancers occurred in the group analysed, and these are detailed in Table 3. One hundred and eighty-four of these cancers were within the Lynch syndrome spectrum (biliary, brain, endometrial, gastric, ovarian, pancreas, small bowel, or upper urothelial).

### Cumulative lifetime incidence of extracolonic tumours

The cumulative incidences at age 70 years are shown in Table 4; comparison is made with the previous literature. The Kaplan–Meier analyses are shown in Fig. 1.

Overall, the cumulative lifetime risk to a MMR mutation carrier of a Lynch syndrome spectrum extracolonic neoplasm is 37.5% (95% CI 34.9–40.1). The cumulative lifetime risk to women of an extracolonic tumour is 47.4% (95% CI 43.9–50.8). The cumulative risk to males of an extracolonic tumour is 26.5% (95% CI 22.6–30.4). This difference is significant (log rank $p < 0.0001$). There was no significant difference in the cumulative lifetime risk of Lynch syndrome spectrum extracolonic cancers for *MLH1*, *MSH2*, and *MSH6* mutation carriers.

Females with *MSH6* mutations have a higher cumulative lifetime incidence of endometrial cancer than *MLH1*/*MSH2* mutation carriers, but this did not reach significance. There was no significant difference in the cumulative incidence of ovarian cancer between the different mutation carriers.

All female mutation carriers were offered gynaecological screening (examination, transvaginal ultrasound scan, hysteroscopy and endometrial biopsy) in line with recommendations from the International Collaborative Group for Hereditary

Table 1. Proportion of unaffected first-degree relatives (FDRs) testing positive for specific gene mutations and number of untested unaffected FDRs assigned carrier status by decade

| | Number of unaffected FDRs testing positive for specific gene mutations as a proportion of the total tested (%) | | | Number of untested unaffected FDRs assigned mutation carrier status by decade (%) | | |
|---|---|---|---|---|---|---|
| Age (years) | *MLH1* | *MSH2* | *MSH6* | *MLH1* | *MSH2* | *MSH6* |
| 18–29 | 8/17 (47) | 11/20 (55) | None tested | 18/38 (47) | 24/43 (56) | 0/2 (0) |
| 30–39 | 13/28 (46) | 18/34 (53) | 1/1 (100) | 12/26 (46) | 19/36 (53) | 6/6 (100) |
| 40–49 | 7/33 (21) | 9/24 (38) | 0/1 (0) | 5/26 (19) | 14/36 (39) | 0/16 (0) |
| 50–59 | 1/10 (10) | 8/13 (62) | 0/1 (0) | 1/12 (8) | 18/29 (62) | 0/5 (0) |
| 60+ | 1/5 (20) | 1/16 (6) | 0/2 (0) | 11/55 (20) | 5/90 (6) | 0/6 (0) |
| Total | 30/93 (32) | 47/107 (44) | 1/5 (20) | 47/157 (30) | 80/234 (34) | 6/35 (17) |

Non-Polyposis CRC (20). Gynaecological screening after family ascertainment may have decreased the endometrial and ovarian cancer incidence in this series. Overall, female mutation carriers have a cumulative lifetime incidence of gynaecological cancers (endometrial and ovarian) of 32.5% (95% CI 29.1–35.9). To estimate the effect of surveillance on the cumulative risks quoted, the Kaplan–Meier analyses were recalculated, censoring at the date of family ascertainment. Prior to family ascertainment, the cumulative lifetime risk of gynaecological malignancies for female mutation carriers was essentially unchanged of 31.6% (95% CI 28.2–35.0). The annual incidence of gynaecological malignancies was also calculated for the two time periods: (i) 1 January 1980 to time of family ascertainment and (ii) time of family ascertainment to last follow up. This again confirmed that the annual incidence of gynaecological malignancies in mutation carriers was similar from 0.6% prior to family ascertainment to 0.7% after family ascertainment.

CRC diagnoses were also recorded on the Lynch syndrome database. The full cumulative risk analyses for these have been reported (21). Males with Lynch syndrome had a cumulative incidence of CRC to age 70 years of 54.3% (95% CI 50.7–57.8). Females had a cumulative risk of CRC to age 70 years of 46.3% (95% CI 42.8–49.9) (log rank $p = 0.02$). To estimate the effects of competing CRC mortality on the extracolonic cancer incidence, the cases were censored at time of CRC diagnosis. The overall risk for both male and female mutation carriers to age 70 years of extracolonic malignancies of the Lynch syndrome spectrum dropped to 29.9% (95% CI 26.9–32.9). In female mutation carriers, when cases were censored at time of CRC diagnosis, the cumulative extracolonic cancer incidence dropped to 36.8% (95% CI 32.8–40.8). In male mutation carriers, the incidence dropped less markedly to 22.4% (95% CI 26.9–32.9).

Males with any germline mutation have a significantly higher cumulative risk of gastric cancer than females (log rank $p = 0.0003$; Fig. 1). However, on further analysis of the data, 23/25 of the gastric cancer cases were born prior to 1935. For those born subsequent to this, the cumulative incidence is significantly lower (Fig. 1).

Males compared with females and *MLH1* compared with *MSH2* mutation carriers had a higher cumulative lifetime incidence of small bowel cancers, but this did not reach significance in either case. *MSH2* mutation carriers had a significantly higher cumulative lifetime risk of brain tumours (primary CNS only, cerebral metastases excluded) (log rank $p = 0.05$; Fig. 1).

Twenty-five breast cancers occurred within our population group. The inclusion of breast cancer within the Lynch syndrome spectrum is controversial (22, 23). Assigning mutation carrier status to all FDRs with breast cancer (as with the other Lynch syndrome spectrum cancers in this study) would lead to an overestimation of cancer risk. Another method of calculating actuarial breast cancer risk must be employed, that is beyond the realms of this study. However, Kaplan–Meier analysis of cumulative risk of breast cancer in the proven female mutation carriers was estimated. For positive and obligate MLH1 mutation carriers, the cumulative risk to age 70 years was 18.2% (95% CI 11.9–24.5). For

Table 2. Lynch syndrome data set and mutation carriers for analysis

| | *MLH1* | *MSH2* | *MSH6* | Total |
|---|---|---|---|---|
| Total families on database | 51 | 59 | 11 | 121 |
| Total family members on database | 580 | 743 | 97 | 1420 |
| Proven mutation carriers | 105 | 133 | 11 | 249 |
| Obligate mutation carriers | 39 | 46 | 5 | 90 |
| Putative mutation carriers | 135 | 164 | 32 | 331 |
| Assumed mutation carriers | 61 | 100 | 8 | 169 |
| Total mutation carriers for analysis | 340 | 443 | 56 | 839 |

Table 3. Total extracolonic cancers diagnosed in cohort

| Cancer | Number of cases |
|---|---|
| Adrenal | 1 |
| Biliary | 4 |
| Bladder | 8 |
| Brain | 10 |
| Breast | 25 |
| Cervix | 5 |
| Endometrial | 86 |
| Gastric | 29 |
| Primary liver | 4 |
| Lung | 11 |
| Lymphoma | 1 |
| Myeloma | 1 |
| Oesophagus | 3 |
| Oropharyngeal | 2 |
| Ovarian | 24 |
| Pancreas | 2 |
| Prostate | 6 |
| Renal | 11 |
| Retinoblastoma | 1 |
| Sebaceous adenocarcinoma | 2 |
| Skin other | 11 |
| Small bowel | 15 |
| Spinal | 1 |
| Thyroid | 1 |
| Unknown | 3 |
| Upper urothelial | 15 |
| Total | 282 |

positive and obligate MSH2 mutation carriers, the cumulative risk to age 70 years was 1.5% (95% CI 0–3.0).

The Kaplan–Meier analyses for the other Lynch syndrome spectrum tumours are not illustrated due to the small numbers of tumours. Table 5 shows the cumulative risk to age 70 years as a multiple of population risk where this information is available (24).

### Mean age of onset of extracolonic cancers

The mean age of onset of endometrial, ovarian, breast, gastric and brain tumours is shown in Table 5. There were too few cases of the other Lynch syndrome spectrum tumours to make any conclusions regarding age of onset.

## Discussion

This study reports the cumulative incidences of extracolonic cancers within the Lynch syndrome spectrum in the second largest data set of families with proven germline MMR mutations to date.

Gynaecological malignancies comprise the largest proportion of the Lynch syndrome spectrum tumours. It is therefore unsurprising that this study demonstrated that females have a significantly higher cumulative lifetime incidence of extracolonic cancers than males ($p < 0.0001$). A trend towards this has been noted by a previous smaller study (7) but reached significance only in *MSH2* mutation carriers. Our study demonstrated significance with mutations in all the three genes.

The higher cumulative incidence of extracolonic cancers in females is largely accounted for by the increased incidence of endometrial cancer and in part the increased incidence of ovarian cancer. The risk of endometrial cancer is particularly high in *MSH6* mutation carriers. Overall, these findings give a slightly lower risk of endometrial cancer than previously reported (5–9, 11, 12, 14). This may due to the method utilized for allocating mutation carrier status reducing ascertainment bias. However, in keeping with previous reports (9), this study demonstrates a particularly high cumulative endometrial cancer risk in *MSH6* mutation carriers. For females, the cumulative risk of CRC at age 70 years is 50.2% for *MLH1*, 47.7% for *MSH2* and 18.3% for *MSH6*. This can be compared with a cumulative incidence of endometrial cancer of 29.2%, 24.4% and 48.8%, respectively. These findings have implications for the surveillance and prophylaxis of endometrial cancer, particularly in MSH6 mutation carriers.

Gynaecological surveillance did not seem to alter the cumulative risks or annual incidence of gynaecological malignancies before and after family ascertainment. An almost equal number of gynaecological malignancies occurred before (60 years) and after (56 years) family ascertainment, so this should be a genuine finding. There is current limited evidence that gynaecological screening reduces morbidity (25).

Only two prior studies have assessed the cumulative incidence of all Lynch syndrome spectrum tumours in proven germline mutation carriers (6, 8). The findings are comparable to our results, particularly in relation to the risks of biliary and ovarian tumours. The risk of an upper urothelial tumour was lower in this study than previous reports (6, 8). We did not find any significantly greater increase in urothelial tumour risk in *MSH2* mutation carriers as has been previously reported (8). The risk of small bowel tumours in this study was lower than that has been previously reported (8). The specific cumulative incidence of pancreatic neoplasia in Lynch syndrome has not been previously reported. This study found a low cumulative risk across all gene mutations.

The cumulative incidence of gastric cancer to age 70 years of 9.4% (95% CI 7.5–11.3) was similar to that previously reported (6, 8). A higher risk in *MLH1* mutation carriers in this study was not significant, although the risk for males was

Table 4. Cumulative extracolonic tumour risk in Lynch syndrome: previous published literature and our report[a]

| Study | Country | Selection criteria | CUM age | No families | No mutation carriers | Gene mutation | CUM extracolonic | CUM extracolonic male | CUM extracolonic female | CUM endometrial female | CUM gastric | CUM biliary tract | CUM urinary tract | CUM ovarian female | CUM brain | CUM small bowel | CUM Pancreas |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Aarnio et al. (14) | Finland | AC (cancer registry) | 80 | 40 | 293 putative | Combined | | | | 43% | 19% | 18% | 10% | 9% | | | |
| Dunlop et al. (5) | Scotland | Mutation carriers (population study CRC <35 years) | 70 | 6 (1 *MLH1*, 5 *MSH2*) | 67 positive | Combined | | | | 42% | | | | | | | |
| Lin et al. (7) | America | Mutation carriers (cancer registry) | 60 | | 105 positive/obligate (56 *MLH1*, 49 *MSH2*) | *MLH1*<br>*MSH2* | 11%<br>48% | 5%<br>34% | 19%<br>69% | 19%<br>36% | | | | | | | |
| Aarni et al. (6) | Finland | Mutation carriers (cancer registry) | 70 | 50 (47 *MLH1*, 3 *MSH2*) | 360 positive/obligate | | | | | 60% | 13% | 2% | 4% | 12% | 3.7% | | |
| Vasen et al. (8, 23) | Holland | Mutation carriers (cancer registry | 70 | 79 (34 *MLH1*, 40 *MSH2*, 5 *MSH6*) | | *MLH1*<br>*MSH2* | | | | 25%<br>37% | 2.1%<br>4.3% | | 1.3%<br>12% | 3.4%<br>10.4% | <br>1.2% | 7.2%<br>4.5% | |
| Hendriks et al. (9) | Holland | Mutation carriers (cancer registry) | 70 | 20 *MSH6* | 146 positive/obligate all *MSH6* | *MSH6* | | | | 71% | | | | | | | |
| Plaschke et al. (15) | Germany | Mutation carriers (cancer registry) | 70 | 183 (27 *MSH6*, 156 *MLH1*/*MSH2*) | 1974 carriers/FDRs/ SDRs (398 *MSH6*, 1578 *MLH1*/*MSH2*) | *MLH1*/*MSH2*<br>*MSH6* | 37%<br>33% | | | | | | | | | | |
| Hampel et al. (11) | Finland | Mutation carriers (cancer registry and population study) | 70 | 45 cancer registry, 25 population study | 277 cancer registry and 144 population study all positive/ obligate | Combined | | | | 54% | | | | 13.5% | | | |
| Quehenberger et al. (12) | Holland | Mutation carriers (cancer registry BUT corrected for ascertainment) | 80 | 84 (39 *MLH1*, 45 *MSH2*) | 397 positive | Combined | | 33% | 22% | 45.6% | | | | | | | |
| Carayol et al. (13) | | Simulated study | 79 | | | Combined | | 60% | 65% | | | | | | | | |
| This study | England | Mutation carriers (cancer registry) | 70 | 121(51 *MLH1*, 59 *MSH2*, 11 *MSH6*) | 839 positive, obligate, putative or assumed carriers | Combined | 37.5% (34.9–40.1) | 26.5% (22.6–30.4) | 47.4% (43.9–50.8) | 28.2% (24.9–31.5) | 9.4% (7.5–11.3) | 1.4% (0.6–2.2) | 3.2% (2.2–4.3) | 6.1% (4.5–7.8) | 3.4% (2.1–4.6) | 2.5% (1.6-3.3) | 0.4% (0–0.8) |
| | | | | | | *MLH1* | 38.5% (34.3–42.7) | 29.7% (22.7–36.7) | 44.8% (39.5–50.1) | 29.2% (24.0–34.5) | 10.9% (7.7–14.1) | 3.0% (1.2–4.9) | 2.8% (1.2–4.4) | 5.5% (3.0–8.1) | 0.3% (0–0.6) | 4.5% (2.7–6.4) | 0% |
| | | | | | | *MSH2* | 35.5% (32.0-39.0) | 23.8% (18.9–28.8) | 47.8% (43.0–52.6) | 24.4% (20.3–28.6) | 7.8% (5.4–10.1) | 0.4% (0–0.8) | 4.1% (2.5–5.7) | 7.5% (5.0–10.0) | 6.3% (4.0–8.7) | 1.3% (0.5–2.1) | 0.7% (0–1.4) |
| | | | | | | *MSH6* | 43.1% (33.7–52.6) | 28.4% (14.4–42.4) | 53.9% (41.7–65.9) | 48.8% (35.1–62.4) | 10.4% (3.4–17.3) | 0% | 0% | 0% | 0% | 0% | 0% |

CRC, colorectal cancer; CUM, cumulative lifetime risk; FDRs, first-degree relatives; SDRs, second-degree relatives.
[a]95% CI in parentheses.

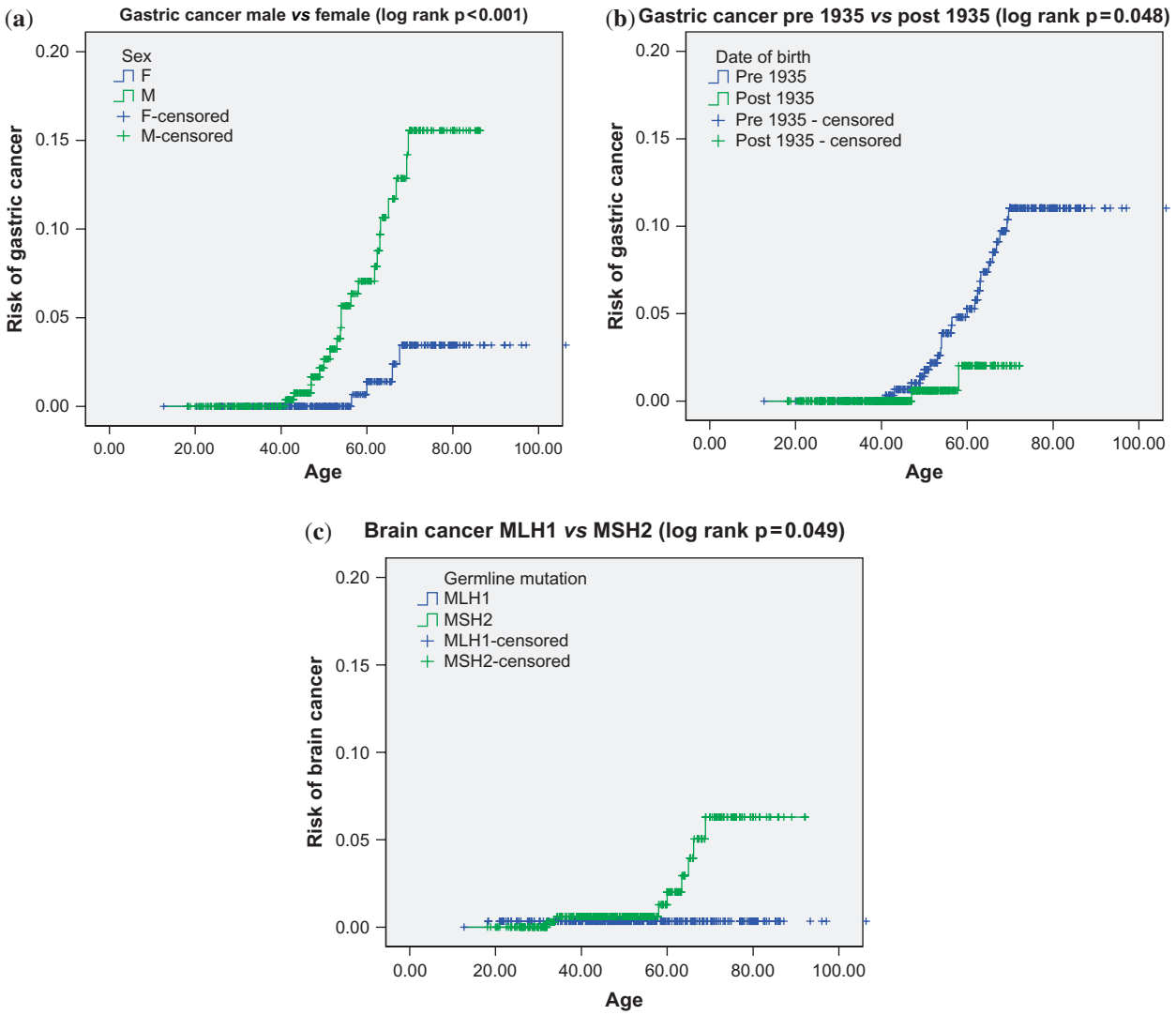


*Fig. 1.* (**a**–**c**) Kaplan–Meier graphs: cumulative incidence-specific extracolonic tumours.

significantly higher than that for females. However, further analysis of these cases revealed that less than 10% of the mutation carriers with gastric cancer were born after 1935. The cumulative risk for this latter group was only 2.0% to age 70 years (95% CI 0.5–3.6). This is only 0.5% above population risk (24). The decreasing incidence of gastric cancer over time may mean that the overall cumulative incidence and the difference between the sexes may not be applicable to the current population. It is therefore difficult to make recommendations for endoscopic surveillance for gastric neoplasms. Indeed, if other studies confirm this decrease in risk from 1935, then gastric screening is probably not now indicated.

The overall cumulative risk of CNS tumours in this study was similar to that found in the Finnish study by Aarnio et al. (6) and higher than that found by the Dutch group (8). This study found a significantly higher risk of CNS tumours in *MSH2* compared with *MLH1* mutation carriers. The higher proportion of *MSH2* mutation carriers suffering from CNS tumours in this study is unexpected, as in prior reports, and CNS tumours have been related to *MLH1* and *PMS2* mutations, particularly in recessive form (26, 27).

The inclusion of breast cancer within the Lynch syndrome spectrum of tumours is controversial, including the relative risk in *MLH1* and *MSH2* mutation carriers. Scott et al. found that breast cancer incidence was higher in *MLH1* mutation carriers but not in *MSH2* mutation carriers (22). This was contradicted by Vasen et al. who did not found an increased risk (23). In our study group, the proven and obligate *MLH1* mutation carriers have double the population risk (the UK population risk is 7.5–8% at age 70 years), while the risk for *MSH2* mutation carriers is low. However,

Table 5. Multiple of population risk for mutation carriers for Lynch syndrome spectrum cancers and mean age of onset of tumours[a]

| Cancer type | Females | | | | | Males | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Population cumulative lifetime risk | Multiple of population risk | | | Mean age of onset of tumours in mutation carriers (years) | Population cumulative lifetime risk | Multiple of population risk | | | Mean age of onset of tumours in mutation carriers (years) |
| | | *MLH1* | *MSH2* | *MSH6* | | | *MLH1* | *MSH2* | *MSH6* | |
| Endometrial | 1.4% to age 74 (24) | 21× risk | 17× risk | 35× risk | 49.1 (47.2–51.0) | | | | | |
| Ovarian | 1.0% to age 74 (24) | 6.1× risk | 7.5× risk | 7.5× risk | 43.3 (38.4–48.2) | | | | | |
| Gastric | 0.6% to age 74 (24) | 8.8× risk | 4.0× risk | n/a | 61.4 (57.9–64.8) | 1.5% to age 74 (24) | 12× risk | 8.1× risk | 16× risk | 56.1 (52.3–60.0) |
| Brain | 0.5% to age 74 (24) | 1.4× risk | 16× risk | n/a | 49.9 (28.9–70.8) | 0.7% to age 74 (24) | n/a | 7.1× risk | n/a | 55.5 (9.1–101.9) |
| Biliary | 0.2% to age 74 (24) | 13× risk | 4.5× risk | n/a | 49.7 (31.7–67.7) | 0.2% to age 74 (24) | n/a | n/a | n/a | n/a |

n/a, ≤1 reported cancers in study group.
[a]95% CI in parentheses.

including only positive and obligate mutation carriers in the analysis may lead to an overestimation of the breast cancer risk, and these figures should be interpreted with caution. More rigorous methods of assessing breast cancer risk for mutation carriers must be employed before breast screening protocols are considered for this group.

As an aid to the assessment and development of screening protocols, Table 5 illustrates the cumulative cancer risks to age 70 years as a multiple of population risk [where these data are available (24)]. The mean age of onset of the different tumour types is also shown. These data show the relative risks of different tumour types for each of the MMR genes, stratified for gender. While the confidence intervals for the less common tumour types are large due to the size of the data set, for endometrial, ovarian, breast and gastric tumours, the standard error is smaller and the findings in keeping with previous published reports. These data, in combination with past and future reports, may enable the development of specific screening regimens dependent on gene mutation and gender.

Guidelines for the screening of extracolonic malignancies in Lynch syndrome were established at a European Workshop in 2006 (28). The available evidence on surveillance for endometrial cancer in Lynch syndrome was reviewed. It was concluded that surveillance by annual gynaecological examination, transvaginal ultrasound and aspiration biopsy commencing at age 30–35 years may result in the detection of premalignant lesions and early endometrial cancers (28), although the evidence for this is limited (25).

There is poor evidence that transvaginal ultrasound and CA-125 estimation detect early ovarian tumours (25).

Prophylactic hysterectomy and bilateral salpingo-oopherectomy after the completion of childbearing for females with Lynch syndrome prevent all ovarian and endometrial cancers developing (29). Due to the failure of detection of ovarian cancers by surveillance, and the high risk of endometrial cancers, particularly for *MSH6* mutation carriers, this may be an appropriate option for women after the completion of childbearing as it substantially reduces site-specific cancers (28).

Current screening recommendations for extracolonic tumours from the International Collaborative Group for Hereditary Non-Polyposis CRC (20) and the European Workshop (28) are as follows:

(1) Gynaecologic examination, transvaginal ultrasound scan, hysteroscopy and endometrial biopsy and CA-125 from age 30–35 years performed every 1–2 years (20, 28).

(2) If familial gastric cancers are present (20) or in a country with a high incidence of gastric cancer (28), gastroscopy from age 30–35 years performed every 1–2 years.
(3) If familial cancers of the kidney, ureter, and bladder are present, screening should be performed every 1–2 years with ultrasound, cystoscopy, urine cytology, and urinalysis (20, 28).
(4) If familial biliary tract cancers are present, transabdominal hepatobiliary ultrasound and liver function tests should be performed every 1–2 years, beginning at age 30 years (20).

On the basis of the cumulative cancer risks found in this study, for the UK population, these screening guidelines and ages of intervention are appropriate. Due to the low cumulative incidence of gastric cancer in mutation carriers born after 1935, gastric screening is probably not now indicated.

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