Variation in the risk of colorectal cancer in families with Lynch syndrome: a retrospective cohort study

IMRC

acceptedVersion

Variation in the Risk of Colorectal Cancer for Lynch Syndrome: A retrospective family cohort study

The International Mismatch Repair Consortium[*]

[*] See the list of authors' names in Contributors section and in Appendix p1–6.

Corresponding author: Mark A. Jenkins, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, VIC 3010, Australia. E-mail: m.jenkins@unimelb.edu.au

Research in context

Evidence before this study

We searched PubMed Medline for peer-reviewed articles up to 31 December 2020, using the terms ("Lynch syndrome" OR "HNPCC" OR "mismatch repair") AND ("colorectal tumour" OR "colorectal neoplasm") AND ("risk variation" OR "risk difference" OR "penetrance variation" OR "penetrance difference"). References from relevant articles, letters, reviews and previous meta-analyses were reviewed to identify any additional studies that were not captured by the PubMed search. We only included prospective or retrospective studies that used rigorous methods to correct for ascertainment bias and reported age-specific risks of colorectal cancer for carriers of a pathogenic or likely pathogenic mutation in a specific DNA mismatch repair gene.

The current evidence shows that colorectal cancer risk for an individual carrier depends on their personal characteristic, lifestyle factors, the specific variant within the mismatch repair gene and other genetic factors. However, the current literature only reports, 'average' cumulative risk to age 70, which is estimated to be 20% to 60%, depending on the mismatch repair gene mutated and the sex of the carrier. Only one study provided evidence of the existence of a variation in penetrance estimates of colorectal cancer across carriers of pathogenic variants in the same gene, in addition to a variation by which gene has the pathogenic variant and the sex of the carrier.

Added value of this study

This large international study provides major novel findings and has important implications for colorectal cancer prevention in Lynch syndrome. Firstly, for families segregating any pathogenic variant in a DNA mismatch repair gene, the pathogenic variant does not account for all the observed family history of the disease. This observation is consistent with the existence of risk factors that modify Lynch syndrome colorectal cancer risk, that are yet to be identified but are shared by relatives, including polygenic factors. Secondly, these risk modifiers (or at least the ones modelled) are strong

and common enough to cause a wide variation in the risk of colorectal cancer across Lynch syndrome carriers—a majority of carriers are observed to be either at the lower end or the upper end of the risk distribution, showing that they are at the average population risk or almost certain to develop colorectal cancer in their lifetime, respectively. Thirdly, this observed variation in colorectal cancer risk for Lynch syndrome carriers exists internationally with similar findings across three continents: Europe, North America and Australasia.

Implications of all the available evidence

An implication of this wide variation in risk is that the average risk presented here for each country, and a standard metric reported for most studies of penetrance, applies to only a minority of carriers of pathogenic variants in mismatch repair genes. The average risks are not representative for a majority of carriers and, thus, current guidelines may not be applicable for a large proportion of carriers. Further work on identifying and characterising genetic and environmental modifiers of penetrance is critical to enable personalised risk assessment of colorectal cancer, which would have a profound impact on the development of precision prevention and early detection for Lynch syndrome clinical management.

Summary

Background: Current clinical practice guidelines for carriers of pathogenic variants of DNA mismatch repair genes (Lynch syndrome) are based on the average age-specific cumulative risk (penetrance) of colorectal cancer for all carriers of pathogenic variants in the same gene. We aimed to estimate how much penetrance varies between carriers of pathogenic variants in the same gene by sex and continent of residence of the carrier.

Methods: We studied 79,809 relatives from 5,255 families, of at least three relatives, in which at least one was a confirmed carrier of a pathogenic or likely pathogenic variant in a mismatch repair gene (1,829 *MLH1*, 2,179 *MSH2*, 798 *MSH6*, 449 *PMS2*), recruited in 15 countries from North America, Europe and Australasia by the collaborative centres of the International Mismatch Repair Consortium. We used modified segregation analysis conditioned on ascertainment to estimate the average penetrance and modelled unmeasured polygenic factors to estimate the variation in penetrance of colorectal cancer. The existence of familial risk factors modifying colorectal cancer risk for Lynch syndrome carriers was tested using a Wald p-value for the null hypothesis that the polygenic standard deviation is zero.

Findings: There was strong evidence of the existence of familial risk factors modifying colorectal cancer risk for Lynch syndrome carriers ($p<0.0001$ for all three continents). These resulted in a wide within-gene variation in the risk of colorectal cancer for males and females from each continent among carriers of all pathogenic variants combined of each gene, and among carriers of the *MSH2* c.942+3A>T variant. The variation was more prominent for *MLH1* and *MSH2* variant carriers; depending on gene, sex, and continent, with 7–56% of carriers having a risk of colorectal cancer to age 80 of less than 20%, and 9–44% having a risk of more than 80%, while only 10–19% had a risk of 40–60%.

Interpretation: Our study findings highlight the important role of risk modifiers, which could lead to personalised risk assessment for precision prevention and early detection of colorectal cancer for Lynch syndrome.

Keywords: Lynch syndrome, mismatch repair, penetrance, colorectal cancer, polygenic risk

Introduction

Lynch syndrome, caused by inherited pathogenic variants in one of four DNA mismatch repair genes, is the most common genetic cause of colorectal cancer,(1) accounting for approximately 3% of all cases(2) and 8–15% of cases diagnosed before age 50 years.(3) One in 279 of the population in Western countries is estimated to carry a pathogenic variant in a mismatch repair gene.(4) For carriers of a pathogenic variant in *MLH1*, *MSH2*, or *MSH6*, the cumulative risk to age 70 of colorectal cancer (penetrance) is estimated to be 20% to 60%, depending on the mismatch repair gene mutated and the sex of the carrier.(5-8) Based on these estimates, all current clinical practice guidelines from Europe(9), USA(10, 11), Canada(12), Australia(13) and New Zealand(14) unanimously recommend every Lynch syndrome carrier to undergo frequent colonoscopies (every 1, 2 or 3 years) beginning at a young age ranging from 25 to 35 years.

Penetrance for an individual carrier depends on their personal characteristic, lifestyle factors, the specific variant within the mismatch repair gene and other genetic factors.(15) Given a substantial variation in the risks of colorectal cancer for the general population around the globe,(16) colorectal cancer risk for Lynch syndrome carriers could also vary by geographic region but the evidence is not clear yet. Further, penetrance estimates of colorectal cancer have been found to vary substantially across carriers of pathogenic variants in the same gene, in addition to a variation by which gene has the pathogenic variant and the sex of the carrier. A study from the Colon Cancer Family Registry(5) has reported that, depending on the gene and sex, 16–23% of *MLH1* and *MSH2* pathogenic variant carriers had a lifetime colorectal cancer risk of less than 10% (i.e., their risk is close to the average risk for the general population); yet 10–17% of carriers had a lifetime risk of more than 90% (i.e., these carriers are almost certain to develop the disease). This finding is yet to be confirmed by a larger and more

comprehensive study because, if such wide variation in risk does exist, the current screening guidelines might not be optimal for a majority of carriers—they could be either over-screened (e.g., those with less than 20% lifetime risk) or under-screened (e.g., those with more than 80% lifetime risk).

As an initiative to address this critical clinical issue encountered in genetics clinics worldwide every day, we have established the International Mismatch Repair Consortium (IMRC), a collaborative international workforce of Lynch syndrome researchers and clinicians, with the facilitation of the International Society for Gastrointestinal Hereditary Tumours (InSiGHT), the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA) and the Colon Cancer Family Registry.(17) In the current study, we have amassed over 5,000 Lynch syndrome families to estimate the magnitude of variation in the risk of colorectal cancer across carriers of a pathogenic variant within the same gene, by different geographic regions of residence.

Methods

Data Source

This study data came from the International Mismatch Repair Consortium (IMRC), which currently comprises 273 members from 122 research centres or clinics in 32 countries throughout six continents (Africa, Asia, Australasia, Europe, North and South America), involved in research or treatment of Lynch syndrome – see http://www.sphinx.org.au/imrc.(17) The study has been approved by the institutional human ethics committees, institutional review boards or central national authorities of participating centres, where required.

Variation in the Risk of Colorectal Cancer for Lynch Syndrome

Data Collection

The following data was collected between 11 July 2014 and 31 December 2018. For each family: id number, mismatch repair gene with pathogenic variant; method of ascertainment of the family (population-based source such as cancer registry, or familial cancer clinic or genetics clinic); date the family was ascertained; and person in the family first identified as carrying the pathogenic variant (the proband). For each family member: personal ID, mother ID, father ID, sex, carrier status of pathogenic variant (carrier/non-carrier/untested), genetic testing date; cancer diagnoses (anatomical site and age of diagnosis); polypectomies and bowel surgery (ages); and ages at the time of pedigree collection and at last contact or death. Investigators at the Centre for Epidemiology and Biostatistics, The University of Melbourne, received data from IMRC members, checked data quality and consistency and liaised with contributor to redress incomplete or inconsistent data. Variants were classified for pathogenicity using the InSiGHT Variant Interpretation Committee Mismatch Repair Gene Variant Classification Criteria (http://www.insight-database.org/classifications).(18)

Eligibility Criteria

Analysis was restricted to families with at least three family members (because conditioning for ascertainment required non-singleton families i.e., at least one person and two parents) and at least one confirmed carrier of a variant in one of the DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6* and *PMS2* or loss of *EPCAM*, classified as likely pathogenic or pathogenic (LOVD class 4 or 5),(18) or if the variant was not previously submitted to the LOVD, reported to be pathogenic by the submitter and confirmed to be likely pathogenic by the curator of the LOVD; collectively referred to as pathogenic variants. The families of probands with known *de novo* pathogenic variants (both parents testing negative for the variant) were excluded from the analysis. Where possible, families who had family members in common were identified and combined with the youngest proband selected as the proband

for the combined family. Population-based families were defined as those for which the probands were ascertained from population-based studies or hospital-based series reported as being independent of family history of cancer. Clinic-based families were defined as those for which the probands were referred to genetic or familial cancer clinics/hospitals presumably because of a family history of cancer.

Statistical Methods

This was a retrospective family cohort study in which cancer incidences were observed in first- and second-degree relatives from birth to the earliest of the age at diagnosis of first cancer, age at first polypectomy or bowel resection, last known age alive or age at death. We conducted a segregation analysis[19, 20] fitted by maximum likelihood, using MENDEL version 3.2.[21] This method enables ungenotyped family members to be included in the analysis, based on their ages, cancer affected statuses, and relationships to known carriers and non-carriers. Analyses were adjusted for the population- and clinic-based ascertainment by conditioning each family's data either on the proband's genotype, cancer status and age (for population-based families) or on this proband data as well as the ages and affected statuses of all family members (for clinic-based families). Analyses were conducted for each gene (all pathogenic variants combined), and for a single gene variant *MSH2* c.942+3A>T, the most common pathogenic variant reported in the dataset.

Models that attribute all familial aggregation of disease to the major gene being studied can give biased estimates of risk,[22] so in addition to the mismatch repair genes, all models incorporated an unmeasured polygenic component, which models the combined effects of common colorectal cancer risk factors that are correlated within families. Hazard ratios (HRs; the sex-, age-, gene- and continent-specific cancer incidences for carriers, divided by those for non-carriers) and the polygenic standard deviation (SD, a measure of the variation in risk between individual carriers with the same sex, age and

mutated gene) were estimated for each continent. The HRs for colorectal cancer were allowed to vary as piece-wise linear functions of age that were constant before age 40 and after age 60, and linear in between, consistent with the results of a previous study.(5) This allows the HR to differ by age, but makes no assumptions on whether the HR was higher, lower or similar for those aged under 40 compared with those over 60. The polygenic SD was assumed to be the same for both clinic- and population-based settings, consistent with the results of a previous study,(5) and fit to be constant with age, since the models did not show a better fit when we allowed the polygenic SD to vary by age.

The colorectal cancer HRs and polygenic SDs were then used to calculate average age-specific cumulative risks (penetrance), and the corresponding distribution of carriers across deciles of lifetime penetrance, which is defined to be the cumulative risk to age 80 years, the limit set by the majority of previous studies. Due to much longer run-time required for more complex analyses, no attempt was made to test the HRs for age-dependence although age-constant HRs might be more appropriate in some settings and give more precise estimates. The existence of familial risk factors modifying colorectal cancer risk for carriers was tested using a Wald p-value for the null hypothesis that the polygenic SD is zero. The p-value threshold for significance was 0.05. See detailed statistical methods in Appendix p7–10.

Missing data

Age information for each family member was required for the pedigree analysis, so we imputed an age for each family member whose age was not reported (37% of total) using a defined protocol, as follows. If an exact age was unknown but an age range was provided, the age was estimated as the midpoint of the range. If the age at diagnosis was unknown, it was assumed to be the same as age at death (if the person was deceased) or the mean age at diagnosis for the specific cancer for their

continent (if the person was alive). For family members with an unknown last age, ages were censored

at the time they were last known to be alive (e.g., at the age of cancer diagnosis). In the absence of any

age information, it was assumed that both parents of the proband were born in the same year, that years

of birth differed by 25 years in each generation (e.g., at birth of proband, parents were aged 25 years

and grandparents were aged 50 years), and the ages of the siblings were the same.

Role of Funding Sources

Results

Of the data from 32 countries submitted to the IMRC, data for 10 countries was either incomplete or

not submitted by the deadline for this analysis. Total 5,585 Lynch syndrome families (1,962 *MLH1*,

2,311*MSH2*, 827 *MSH6*, 457 *PMS2*, 28 *EPCAM*) from 22 countries in five continents (11 from Europe,

2 from North America, 2 from Australasia, 3 from Asia, 4 from South America) were eligible for the

analysis (Appendix p11). Of those, there were insufficient numbers of families to estimate penetrance

for Asia and South America, and for *EPCAM* variants. The analysis was restricted to 5,255 families

from 15 countries in Europe, North America and Australasia for the four DNA mismatch repair genes

(1,829 *MLH1*, 2,179 *MSH2*, 798 *MSH6*, 449 *PMS2*) (Table 1). Of them, 309 (5.9%) were ascertained via population-based resources (44 from Europe, 219 from North America, 46 from Australasia). The analysis included 79,809 relatives (31,944 first-degree relatives and 47,865 second-degree relatives), with an average 24.8 (SD 13.2) relatives per family (range, 3–106) of whom 8,087 (10%) were diagnosed with colorectal cancer at a mean age of 50.7 (SD 14.5) years and 10,114 (13%) were diagnosed with an extracolonic cancer.

The penetrance of colorectal cancer was, on average, observed to be highest for *MLH1* and *MSH2*, and lowest for *PMS2* variant carriers (Figure 1 and Appendix p12). There was strong evidence of the existence of familial risk factors modifying colorectal cancer risk for Lynch syndrome carriers (p<0.0001 for all three continents). The HR (95% CI) per one polygenic SD for carriers from Europe, North America and Australasia were observed to be 5.4 (2.9–9.9), 5.1 (3.5–7.4) and 3.5 (2.0–5.9), respectively (Table 2). That is, as an example, for Lynch syndrome carriers from Europe, there is an estimated 5.4-times increased risk of colorectal cancer for each standard deviation increment in polygenic factors.

This variation in risk was apparent in the estimated proportion of carriers across various deciles of lifetime penetrance (Figure 2 and Appendix p13). For example, 14% of European male *MLH1* carriers were estimated to have colorectal cancer penetrance to age 80 of 40–60% while 23% and 33% were estimated to have <20% penetrance and >80% penetrance, respectively. For *MSH6*, a majority of carriers were estimated to have <20% penetrance while a small fraction of carriers had >80% penetrance. Similar finding was observed for *PMS2* variant carriers (Table 3).

A wide variation in colorectal cancer risk was observed even when analysis was restricted to the 250 families carrying a specific *MSH2* pathogenic variant, c.942+3A>T. Depending on the sex and continent, approximately 9–15% of carriers had <20% penetrance while 33–45% of carriers had >80% penetrance (Figure 2 and Appendix p13).

When models with and without age imputation were compared, the results did not differ substantially, therefore results from the non-imputed analysis are not shown in detail.

Discussion

This large international cohort study of Lynch syndrome families from different continents has implications for colorectal cancer prevention in Lynch syndrome. Firstly, the pathogenic variant does not account for all the observed family history of the disease. This is consistent with the existence of risk factors shared by relatives, including polygenic factors, that modify colorectal cancer risk. Secondly, these risk modifiers (or at least the ones modelled) are strong and common enough to cause a wide variation in the risk of colorectal cancer across Lynch syndrome carriers. As a consequence a majority of carriers are observed to be either at the lower end (near average population risk) or the upper end (almost certain to develop colorectal cancer) of the risk distribution. Thirdly, variation in colorectal cancer risk exists internationally with similar findings for Europe, North America and Australasia. However, since a majority of data contributed to the IMRC was originally collected for clinical genetics purposes, screening and polypectomy history, important for penetrance estimation and interpretation, was often not available.

An implication of this wide variation in risk is that the *average* cumulative risk presented here, as well as reported by previous penetrance studies,(5-8) applies to only a minority of carriers, not the majority of carriers, and thus, current guidelines may not be applicable for a large proportion of carriers. Although the variation in risk is consistent with the existence of polygenic risk factors, it was based on only one of many possible models. In addition, as these are yet to be identified, it is not possible to directly determine where individual lie on the distribution of colorectal cancer risk. However, as family history is a proxy measure for this polygenic risk, in theory a detailed family history (acknowledging the challenges of collecting a detailed and accurate family history) could be used to approximate the risk of colorectal cancer for carriers, as has been done for breast and ovarian cancer risk for *BRCA1* and *BRCA2* mutation.(23) This has implications for determining risk-based screening towards precision prevention and early detection for Lynch syndrome.

Potential candidates for the polygenic factors include the more than 100 single nucleotide polymorphisms (SNPs) that, when combined into a polygenic risk score, can be used to identify people who are at elevated or decreased risk of colorectal cancer for the general population.(24) However, a study of 827 Lynch syndrome carriers found no evidence of association with a polygenic risk score comprising 107 SNPs reported to be associated with colorectal cancer.(25) Ten rare SNPs in candidate cell-cycle genes have been shown to be associated with colorectal cancer risk; with the 7% of Lynch syndrome carriers who were homozygous carriers for three or more of these SNPs having a 4.4-times increased colorectal cancer risk(26).

The actual cause for the wide variation in risk could be due to any risk-modifying factors correlated between relatives. Multiple environmental modifiers have been identified for colorectal cancer for Lynch syndrome, including body mass, smoking, alcohol consumption, aspirin and ibuprofen intake,

diabetes mellitus, increased cholesterol, multivitamin or calcium supplements, fruit and vegetable

intake, meat consumption, and physical activity.(9, 15) Mouse models suggest intestinal microbiome

and the exposure to dietary mutagens may have a carcinogenic role in Lynch syndrome.(27) To the

extent that any of these factors above aggregate within families, they may be an explanation, at least in

part, for variation in risk.

We did consider that the variation in colorectal cancer risk could be due to variant-specific effects on

risk. In other words, the risk of colorectal cancer is specific for the particular variant in the particular

gene. If this were the explanation for the observed variation in risk, we would expect there to be less

variation in colorectal cancer risk for carriers who all had the same specific pathogenic variant. We

were able to assess the variation in risk between carriers of the c.942+3A>T variant in *MSH2*, the most

common variant in the data provided, and observed a wide variation in risk, similar to all *MSH2*

pathogenic variants combined. Therefore, we cannot conclude that the variation in risk is due to

variant-specific risks. Future research should examine this issue further by estimating penetrance by

the predicted effect of variant on protein function.

Evidence for a polygenic modifier of similar magnitude has also been observed for the pathogenic

variants in *BRCA1* and *BRCA2* for the penetrance of breast cancer. Using methods similar to ours,

investigators of the family histories of 1,484 carriers of a pathogenic variants in *BRCA1* and *BRCA2*

estimated a polygenic SD of 1.4(19) compared with our estimates that ranged from 1.1 to 2.5.

Our observation of a variation in colorectal cancer penetrance by mismatch repair gene and by sex

(higher for men for *MLH1* and *MSH2*), is consistent with the findings from the large international

prospective analyses.(8) However, potential reasons for these differences were not identifiable from

this dataset. To our knowledge, we provide, for the first time, colorectal cancer risk for Lynch

syndrome carriers by continent. These risks reflect the role of environmental or genetic modifiers as

well as screening practices or health systems which may differ between these continents. If these

region-specific factors influencing penetrance can be identified, they will be of potential clinical

relevance as an avenue for more risk-appropriate clinical management specific for each region. These

data raise the question of variation in the risks of other Lynch syndrome-related cancers and the

potential clinical implications, a line of research we have already planned for future analyses.

A major strength of our study is the contribution of IMRC collaborators to this analysis, which makes

this the largest family study conducted to date for Lynch syndrome penetrance. Another major strength

is the modified segregation analysis method we used for this analysis properly adjusted for family

ascertainment (thereby minimising bias), and used data of all family members, whether genotyped or

not (thereby maximising statistical power), and included deceased individuals (thereby reducing

survival bias).

A limitation of our study is the incomplete validation of the reported history of colorectal cancer and

other cancers in relatives. We were unable to support linkages to cancer or death registries or validation

against medical records for every family. However, given the majority of families has been provided

from well-resourced family cohorts such as Colon Cancer Family Registry Cohort(28) and French-

nationwide ERISCAM study(7) and from clinical records from familial cancer clinics. Given that we

restricted analyses to first- and second-degree relatives, we think this issue would not have had a major

impact on our estimates. In addition, because we only used the colorectal cancer incidence rates for a

single country for each continent (Germany for Europe, USA for North America and Australia for

Australasia), the risk of colorectal cancer for carriers could be lower or higher than presented here if they live in a country with lower or higher colorectal cancer incidence rates than the country chosen.

Another limitation of this study is the quality of data pertaining to polypectomy. Accurate knowledge of which carriers had a polypectomy and at what age, is necessary to avoid the potential for underestimating the risk of colorectal cancer. Although we sought polypectomy data from each contributor of families, this information was not available for all families included in this study. It is also possible that some of the variation in risk might be due to differences in screening with relatives in some families being more likely to screen and relatives in other families being less likely to screen. A recent study suggested that the effect on colorectal cancer risk of annual versus triennial colonoscopy screening strategies is unlikely to be large,(29) but we cannot rule out the effect of widely disparate patterns of screening across families e.g., population-based vs. clinic-based families, causing some of this observed risk variation. A further limitation was our inability to analyse data by subsite within the bowel i.e., proximal colon vs. distal colon vs. rectum given that the majority of submitted data did not include the specific subsite of cancer in the affected family members.

Due to an insufficient number of families from Asia, South America and Africa, we were unable to estimate the penetrance or a variation in penetrance for Lynch syndrome carriers from these continents with a reasonable degree of precision although this remains a goal of the IMRC. Given genetic testing is becoming widespread in many Asian and South American countries,(30) we are actively engaging to expand collaborations for further contributions of families from these regions to achieve this goal.

In summary, this large international study provides clear evidence of a wide variation in colorectal cancer risk for Lynch syndrome carriers, particularly for *MLH1* and *MSH2,* consistent with the

existence of strong familial risk factors that modify colorectal cancer risk. Further work on identifying

and characterising genetic and environmental modifiers of penetrance is critical to enable personalised

risk assessment of colorectal cancer, which would have a profound impact on the development of

precision prevention and early detection for Lynch syndrome clinical management.

Contributors

AKW, RWH, FAM, GM and MAJ conceptualised the study investigation. AKW, RWH, FAM, GM and MAJ received the funding. JCR, GL, and AST contributed to data curation, project administration and resources under supervision of AKW and MAJ. AKW, JGD and MAJ conducted formal analysis using statistical software and methodology and drafted the manuscript. AKW, JCR, GL and MAJ accessed and verified data. All contributors participated in manuscript review and editing.

Manuscript Writing Group: Aung Ko Win, James G. Dowty, Mark A. Jenkins

Steering Committee: Mark A. Jenkins, Finlay A. Macrae, Gabriela Möslein, Robert W. Haile

Central Database Group: Jeanette C. Reece, Grant Lee, Allyson S. Templeton

Data Contributing Group: Kiwamu Akagi, Seçil Aksoy, Angel Alonso, Karin Alvarez, David J. Amor, Ravindran Ankathil, Stefan Aretz, Julie L. Arnold, Melyssa Aronson, Rachel Austin, Ann-Sofie Backman, Sanne W. Bajwa–ten Broeke, Verónica Barca-Tierno, Julian Barwell, Inge Bernstein, Pascaline Berthet, Beate Betz, Yves-Jean Bignon, Talya Boisjoli, Valérie Bonadona, Laurent Briollais, Joan Brunet, Daniel D. Buchanan, Karolin Bucksch, Bruno Buecher, Reinhard Buettner, John Burn, Trinidad Caldés, Gabriel Capella, Olivier Caron, Graham Casey, Min H. Chew, Yun-hee Choi, James Church, Mark Clendenning, Chrystelle Colas, Elisa J. Cops, Isabelle Coupier, Marcia Cruz-Correa, Albert de la Chapelle, Niels de Wind, Tadeusz Dębniak, Adriana Della Valle, Capuccine Delnatte, Marion Dhooge, Mev Dominguez-Valentin, Youenn Drouet, Floor A. Duijkers, Christoph Engel, Patricia Esperon, D. Gareth Evans, Aída Falcón de Vargas, Jane C Figueiredo, William Foulkes, Emmanuelle Fourme, Thierry Frebourg, Steven Gallinger, Pilar Garre, Maurizio Genuardi, Anne-Marie Gerdes, Lauren M. Gima, Sophie Giraud, Annabel Goodwin, Heike Görgens, Kate Green, Jose Guillem, Carmen Guillén-Ponce, Roselyne Guimbaud, Rodrigo S. C. Guindalini, Elizabeth E. Half, Michael J Hall, Heather Hampel, Thomas V. O. Hansen, Karl Heinimann, Frederik J. Hes, James Hill, Judy W.C. Ho, Elke Holinski-Feder, Nicoline Hoogerbrugge, John L. Hopper, Robert Hüneburg,

Vanessa Huntley, Paul A. James, Uffe B Jensen, Thomas John, Wan K.W. Juhari, Matthew Kalady, Fay Kastrinos, Matthias Kloor, Maija RJ Kohonen-Corish, Lotte N. Krogh, Sonia S. Kupfer, Uri Ladabaum, Kristina Lagerstedt-Robinson, Fiona Lalloo, Christine Lasset, Andrew Latchford, Pierre Laurent-Puig, Charlotte K. Lautrup, Barbara A. Leggett, Sophie Lejeune, Loic LeMarchand, Marjolijn Ligtenberg, Noralane Lindor, Markus Loeffler, Michel Longy, Francisco Lopez, Jan Lowery, Jan Lubiński, Anneke M Lucassen, Patrick M. Lynch, Karolina Malińska, Nagahide Matsubara, Jukka-Pekka Mecklin, Pål Møller, Kevin Monahan, Patrick J. Morrison, Jacob Nattermann, Matilde Navarro, Florencia Neffa, Deborah Neklason, Polly A. Newcomb, Joanne Ngeow, Cassandra Nichols, Maartje Nielsen, Dawn M. Nixon, Catherine Nogues, Henrik Okkels, Sylviane Olschwang, Nicholas Pachter, Rish K. Pai, Edenir I. Palmero, Mala Pande, Susan Parry, Swati G. Patel, Rachel Pearlman, Claudia Perne, Marta Pineda, John-Paul Plazzer, Nicola K Poplawski, Kirsi Pylvänäinen, Jay Qiu, Nils Rahner, Raj Ramesar, Lene J. Rasmussen, Silke Redler, Rui M. Reis, Luigi Ricciardiello, Emilia Rogoża-Janiszewska, Christophe Rosty, N. Jewel Samadder, Julian R. Sampson, Hans K. Schackert, Wolff Schmiegel, Karsten Schulmann, Helène Schuster, Rodney Scott, Leigha Senter, Toni T Seppälä, Rakefet Shtoyerman, Rolf H. Sijmons, Carrie Snyder, Ilana B. Solomon, Jose Luis Soto, Melissa C. Southey, Allan Spigelman, Florencia Spirandelli, Amanda B. Spurdle, Verena Steinke-Lange, Elena M. Stoffel, Christian P. Strassburg, Lone Sunde, Rachel Susman, Sapna Syngal, Kohji Tanakaya, Gülçin Tezcan, Christina Therkildsen, Steve Thibodeau, Naohiro Tomita, Katherine M. Tucker, Berrin Tunca, Daniela Turchetti, Nancy Uhrhammer, Joji Utsunomiya, Carlos Vaccaro, Fränzel J.B. van Duijnhoven, Meghan J. van Wanzeele, Deepak B. Vangala, Hans F.A. Vasen, Magnus von Knebel Doeberitz, Jenny von Salomé, Karin A. W. Wadt, Robyn L. Ward, Jürgen Weitz, Jeffrey N. Weitzel, Heinric Williams, Ingrid Winship, Paul E. Wise, Julie Wods, Michael O. Woods, Tatsuro Yamaguchi, Silke Zachariae, Mohd N. Zahary.

Declaration of interests

We declare no competing interests.

Acknowledgements

Data sharing statement

Variation in the Risk of Colorectal Cancer for Lynch Syndrome

Data collected for the study was contributed by the International Mismatch Repair Consortium (IMRC) investigators. Availability of this data will depend on the agreement of the investigators who contributed the data to the IMRC. Upon the agreement, de-identified individual participant data participant data that underlie the results reported in this publication will be made available, together with data dictionaries and the study protocol. The data will be available upon publication of all IMRC pre-specified manuscripts to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals can be submitted according to the instructions provided in https://sphinx.org.au/imrc. To gain access, data requestors will need to sign a data access agreement with The University of Melbourne and participating IMRC centres.

References

1.   Valle L, Vilar E, Tavtigian SV, Stoffel EM. Genetic predisposition to colorectal cancer: syndromes, genes, classification of genetic variants and implications for precision medicine. J Pathol. 2019;247(5):574-88.
2.   Yurgelun MB, Kulke MH, Fuchs CS, Allen BA, Uno H, Hornick JL, et al. Cancer Susceptibility Gene Mutations in Individuals With Colorectal Cancer. J Clin Oncol. 2017;35(10):1086-95.
3.   Stoffel EM, Koeppe E, Everett J, Ulintz P, Kiel M, Osborne J, et al. Germline Genetic Features of Young Individuals With Colorectal Cancer. Gastroenterology. 2018;154(4):897-905 e1.
4.   Win AK, Jenkins MA, Dowty JG, Antoniou AC, Lee A, Giles GG, et al. Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer. Cancer Epidemiol Biomarkers Prev. 2017;26(3):404-12.
5.   Dowty JG, Win AK, Buchanan DD, Lindor NM, Macrae FA, Clendenning M, et al. Cancer risks for MLH1 and MSH2 mutation carriers. Hum Mutat. 2013;34(3):490-7.
6.   Moller P, Seppala TT, Bernstein I, Holinski-Feder E, Sala P, Gareth Evans D, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut. 2018;67(7):1306-16.
7.   Bonadona V, Bonaiti B, Olschwang S, Grandjouan S, Huiart L, Longy M, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011;305(22):2304-10.
8.   Dominguez-Valentin M, Sampson JR, Seppala TT, Ten Broeke SW, Plazzer JP, Nakken S, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 2020;22(1):15-25.
9.   Seppala TT, Latchford A, Negoi I, Sampaio Soares A, Jimenez-Rodriguez R, Sanchez-Guillen L, et al. European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender. Br J Surg. 2020.
10.   U. S. Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, Jr., et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315(23):2564-75.
11.   National Comprehensive Cancer N. Guidelines for Detection, Prevention, & Risk Reduction. Genetic/Familial High Risk Assessment: Colorectal. 2017 15 April 2018 [cited 15 April 2018]. In: NCCN Clinical Practice Guidelines in Oncology Version 32017 [Internet]. [cited 15 April 2018]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.
12.   Leddin D, Lieberman DA, Tse F, Barkun AN, Abou-Setta AM, Marshall JK, et al. Clinical Practice Guideline on Screening for Colorectal Cancer in Individuals With a Family History of Nonhereditary Colorectal Cancer or Adenoma: The Canadian Association of Gastroenterology Banff Consensus. Gastroenterology. 2018;155(5):1325-47 e3.
13.   Cancer Council Australia Colorectal Cancer Guidelines Working Party. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer. Sydney: Cancer Council Australia; 2017.
14.   New Zealand Guidelines Group. Guidance on Surveillance for People at Increased Risk of Colorectal Cancer. Wellington: Ministry of Health; 2012.
15.   Win AK, Scott RJ. Genetic and Environmental Modifiers of Cancer Risk in Lynch Syndrome. In: Valle L, Gruber SB, Capellá G, editors. Hereditary Colorectal Cancer. Cham: Springer International Publishing; 2018. p. 67-89.
16.   Torre LA, Siegel RL, Ward EM, Jemal A. Global Cancer Incidence and Mortality Rates and Trends--An Update. Cancer Epidemiol Biomarkers Prev. 2016;25(1):16-27.
17.   Jenkins MA, Reece JC, Win AK. The International Mismatch Repair Consortium. In: Valle L, Gruber SB, Capellá G, editors. Hereditary Colorectal Cancer. Cham: Springer International Publishing; 2018. p. 479-95.
18.   Fokkema IF, Taschner PE, Schaafsma GC, Celli J, Laros JF, den Dunnen JT. LOVD v.2.0: the next generation in gene variant databases. Hum Mutat. 2011;32(5):557-63.
19.   Antoniou AC, Pharoah PD, McMullan G, Day NE, Ponder BA, Easton D. Evidence for further breast cancer susceptibility genes in addition to BRCA1 and BRCA2 in a population-based study. Genet Epidemiol. 2001;21(1):1-18.
20.   Lange K. Mathematical and statistical methods for genetic analysis. 2nd ed. New York: Springer; 2002. xvii, 361 p. p.
21.   Lange K, Weeks D, Boehnke M. Programs for Pedigree Analysis: MENDEL, FISHER, and dGENE. Genet Epidemiol. 1988;5(6):471-2.
22.   Gong G, Hannon N, Whittemore AS. Estimating gene penetrance from family data. Genet Epidemiol. 2010;34(4):373-81.
23.   Antoniou AC, Cunningham AP, Peto J, Evans DG, Lalloo F, Narod SA, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer. 2008;98(8):1457-66.
24.   Law PJ, Timofeeva M, Fernandez-Rozadilla C, Broderick P, Studd J, Fernandez-Tajes J, et al. Association analyses identify 31 new risk loci for colorectal cancer susceptibility. Nat Commun. 2019;10(1):2154.

25.   Jenkins MA, Buchanan DD, Lai J, Makalic E, Dite GS, Win AK, et al. Assessment of a Polygenic Risk Score for Colorectal Cancer to Predict Risk of Lynch Syndrome Colorectal Cancer. JNCI Cancer Spectrum. 2021.

26.   Chen J, Pande M, Huang YJ, Wei C, Amos CI, Talseth-Palmer BA, et al. Cell cycle-related genes as modifiers of age of onset of colorectal cancer in Lynch syndrome: a large-scale study in non-Hispanic white patients. Carcinogenesis. 2013;34(2):299-306.

27.   Wojciechowicz K, Cantelli E, Van Gerwen B, Plug M, Van Der Wal A, Delzenne-Goette E, et al. Temozolomide increases the number of mismatch repair-deficient intestinal crypts and accelerates tumorigenesis in a mouse model of Lynch syndrome. Gastroenterology. 2014;147(5):1064-72 e5.

28.   Jenkins MA, Win AK, Templeton AS, Angelakos MS, Buchanan DD, Cotterchio M, et al. Cohort Profile: The Colon Cancer Family Registry Cohort (CCFRC). Int J Epidemiol. 2018;47(2):387-8i.

29.   Engel C, Vasen HF, Seppala T, Aretz S, Bigirwamungu-Bargeman M, de Boer SY, et al. No Difference in Colorectal Cancer Incidence or Stage at Detection by Colonoscopy Among 3 Countries With Different Lynch Syndrome Surveillance Policies. Gastroenterology. 2018;155(5):1400-9 e2.

30.   Della Valle A, Rossi BM, Palmero EI, Antelo M, Vaccaro CA, Lopez-Kostner F, et al. A snapshot of current genetic testing practice in Lynch syndrome: The results of a representative survey of 33 Latin American existing centres/registries. Eur J Cancer. 2019;119:112-21.

Tables

Table 1. The numbers of Lynch syndrome families included in the current analysis by gene and continent

Region	MLH1	MSH2	MSH6	PMS2	Total
Europe	**1049**	**1245**	**392**	**154**	2840
Denmark	66	135	86	17	304
Finland	12	1	0	0	13
France	244	254	32	0	530
Germany	421	517	89	44	1071
Italy	3	11	3	0	17
Norway	15	44	31	11	101
Poland	6	1	0	0	7
Spain	118	73	49	16	256
Switzerland	5	3	2	0	10
The Netherlands	0	0	36	46	82
United Kingdom	159	206	64	20	449
North America	**526**	**637**	**242**	**199**	1604
Canada	69	77	16	11	173
USA	457	560	226	188	1431
Australasia	**254**	**297**	**164**	**96**	811
Australia	244	289	159	94	786
New Zealand	10	8	5	2	25
Total	**1829**	**2179**	**798**	**449**	**5255**

[*] Note: These are the number of families provided for this analysis and do not represent the numbers of families known in each of the countries.

Table 2. Hazard ratios (with corresponding 95% confidence intervals) of colorectal cancer for Lynch syndrome carriers, by their age, sex, gene and continent

Continent	Gene	Female		Male	
		Age 40	Age 60	Age 40	Age 60
Europe	MLH1	23.4 (9.0–61.0)	22.3 (8.7–57.3)	37.5 (15.7–89.7)	35.8 (15.0–85.7)
	MSH2	25.2 (10.3–61.6)	13.03 (4.10–41.3)	27.9 (12.8–60.4)	18.2 (6.67–49.6)
	MSH6	2.96 (0.79–11.04)	3.27 (1.18–9.06)	14.8 (4.35–50.2)	4.28 (1.28–14.29)
	PMS2	1.06 (0.17–6.62)	4.08 (1.64–10.15)	6.65 (1.65–26.7)	2.16 (0.73–6.39)
	Polygenic factors#	5.4 (2.9–9.9)			
North America	MLH1	72.1 (42.0–123.8)	32.9 (15.7–69.1)	165.3 (103–266)	32.2 (12.5–82.8)
	MSH2	81.0 (51.1–128.6)	30.45 (14.48–64.0)	126 (84.6–187)	18.4 (8.10–42.0)
	MSH6	2.56 (0.21–31.29)	7.16 (2.91–17.65)	29.3 (11.98–71.9)	10.23 (3.64–28.71)
	PMS2	8.23 (1.73–39.20)	1.99 (0.45–8.73)	9.75 (1.78–53.3)	4.90 (0.88–27.42)
	Polygenic factors#	5.1 (3.5–7.4)			
Australasia	MLH1	117 (59.2–232)	15.9 (4.4–57.7)	138 (71.0–267)	13.3 (3.4–52.9)
	MSH2	101.5 (37.0–279)	6.17 (1.33–28.6)	156 (68.9–351.2)	24.9 (5.16–120.2)
	MSH6	3.86 (0.89–16.8)^	3.86 (0.87–17.0)^	20.5 (6.22–67.8)	2.72 (0.44–16.65)
	PMS2	6.99 (1.07–45.66)	2.07 (0.40–10.69)	26.84 (5.68–127)	2.15 (0.34–13.49)
	Polygenic factors#	3.5 (2.0–5.9)			

*Hazard ratios were calculated as the incidence of colorectal cancer for carriers divided by that for non-carriers (assumed to be the same with age, sex, country-specific incidence for the general population). Estimates of the hazard ratios and polygenic standard deviation were assumed to constant before age 40 and after age 60 and linear in between.

#HR per one standard deviation of polygenic factors with estimates constrained to be constant over age and the same for all genes and both sexes in each continent.

^For Australasian female MSH6 carriers, hazard ratios were fixed to be age-independent

Table 3. Estimated proportions (with corresponding 95% confidence intervals) of Lynch syndrome carriers with less than 20%, between 40% and 60%, and more than 80% penetrance[*], by sex, gene and continent

Gene	Continent	Proportion of female carriers with			Proportion of male carriers with		
		<20% Penetrance	40–60% Penetrance	>80% Penetrance	<20% Penetrance	40–60% Penetrance	>80% Penetrance
MLH1	Europe	44% (20-64%)	12% (7-19%)	15% (6-28%)	23% (6-42%)	14% (10-20%)	33% (18-51%)
	North America	31% (16-46%)	14% (11-18%)	23% (14-36%)	22% (9-36%)	14% (11-18%)	33% (20-49%)
	Australasia	20% (2-45%)	19% (12-30%)	22% (6-48%)	14% (1-36%)	18% (11-28%)	30% (10-59%)
MSH2	Europe	56% (30-74%)	10% (6-17%)	9% (2-22%)	36% (15-55%)	13% (9-20%)	21% (9-35%)
	North America	32% (16-48%)	14% (10-18%)	22% (13-35%)	32% (17-46%)	14% (11-18%)	23% (14-34%)
	Australasia	36% (5-65%)	16% (8-29%)	11% (1-37%)	7% (0-28%)	16% (5-25%)	44% (17-82%)
MSH6	Europe	84% (65-94%)	4% (1-8%)	2% (0-5%)	67% (41-84%)	8% (3-14%)	5% (1-15%)
	North America	70% (46-85%)	7% (3-13%)	4% (1-12%)	50% (25-70%)	11% (7-17%)	11% (4-26%)
	Australasia	63% (23-86%)	9% (3-21%)	3% (0-12%)	61% (9-89%)	9% (2-24%)	3% (0-26%)
PMS2	Europe	72% (44-87%)	6% (3-13%)	4% (1-11%)	81% (57-92%)	4% (2-10%)	2% (0-7%)
	North America	83% (55-95%)	4% (1-10%)	2% (0-9%)	69% (29-88%)	7% (2-15%)	4% (1-24%)
	Australasia	74% (22-96%)	6% (0-20%)	1% (0-15%)	63% (14-92%)	9% (1-23%)	3% (0-24%)

[*] age-specific cumulative risk of colorectal cancer to age 80 years

Variation in the Risk of Colorectal Cancer for Lynch Syndrome

Figure Legends

Figure 1. Average age-specific cumulative risks (penetrance) of colorectal cancer for Lynch syndrome carriers from Australasia (blue lines), North America (pink lines) and Europe (orange lines), by sex and gene, with shaded areas representing the corresponding 95% confidence intervals. The overall estimates for *MSH2* include the variant *MSH2* c.942+3A>T, and the specific estimates for *MSH2* c.942+3A>T are based on hazard ratio estimates that were constrained to be the same across the three continents.

Figure 2. Estimated proportion of Lynch syndrome carriers in various risk groups (defined by deciles of colorectal cancer cumulative risks to age 80 years) for Australasia (blue rectangles), North America (pink rectangles) and Europe (orange rectangles), by sex and gene, with 95% confidence intervals represented as black error bars. The denominator being all carriers of a pathogenic mutation in the same gene and of the same sex and from the same continent. For example, in the top left panel (*MLH1* and Female), the left-most orange bar says that an estimated 28% of female *MLH1* variant carriers living in Europe have less than a 10% chance of developing colorectal cancer by age 80 years. The overall estimates for *MSH2* include the variant *MSH2* c.942+3A>T, and the specific estimates for *MSH2* c.942+3A>T are based on hazard ratio estimates that were constrained to be the same across the three continents.

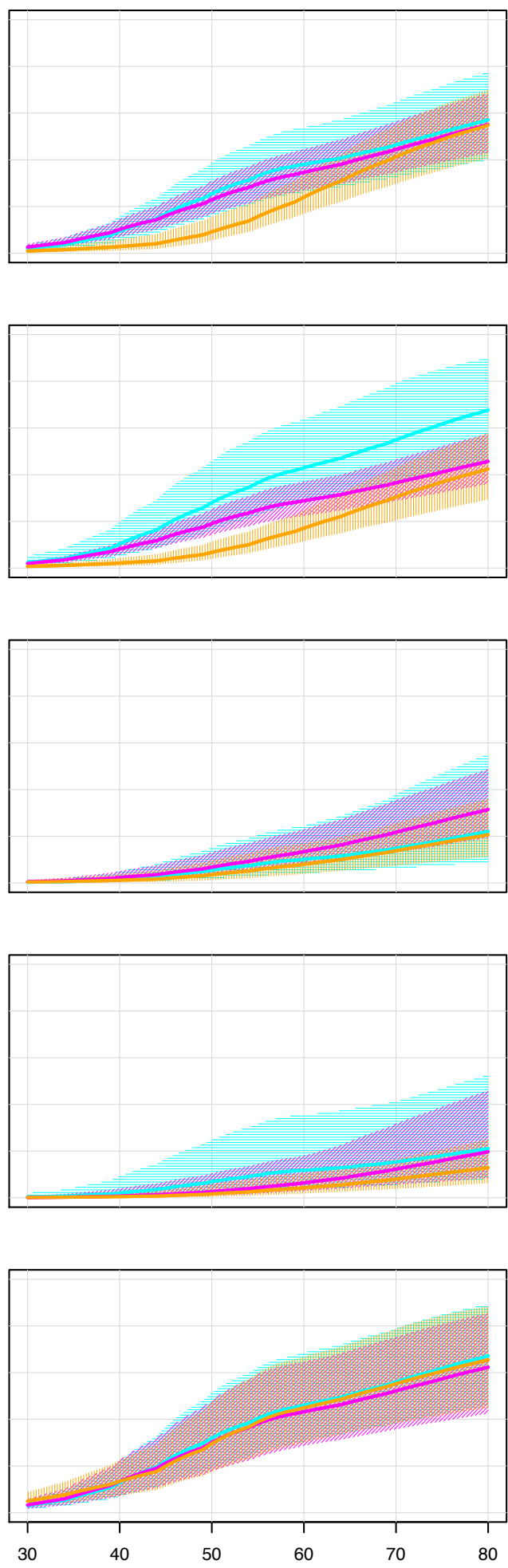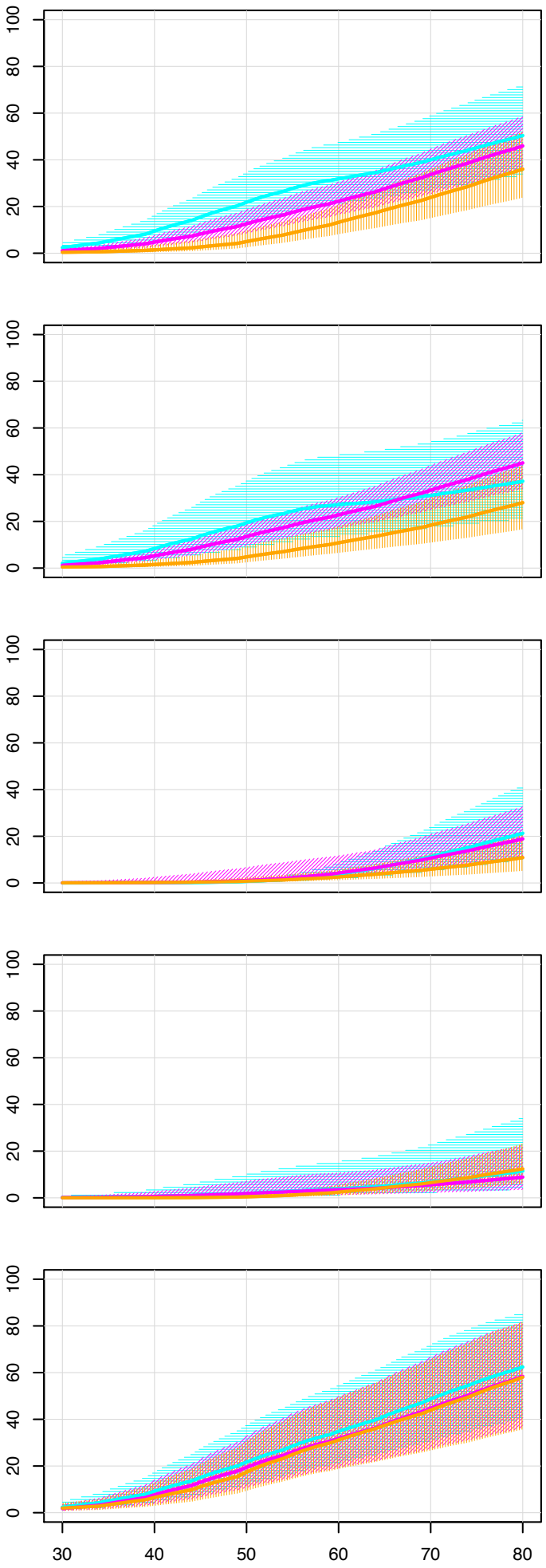Variation in the Risk of Colorectal Cancer for Lynch Syndrome
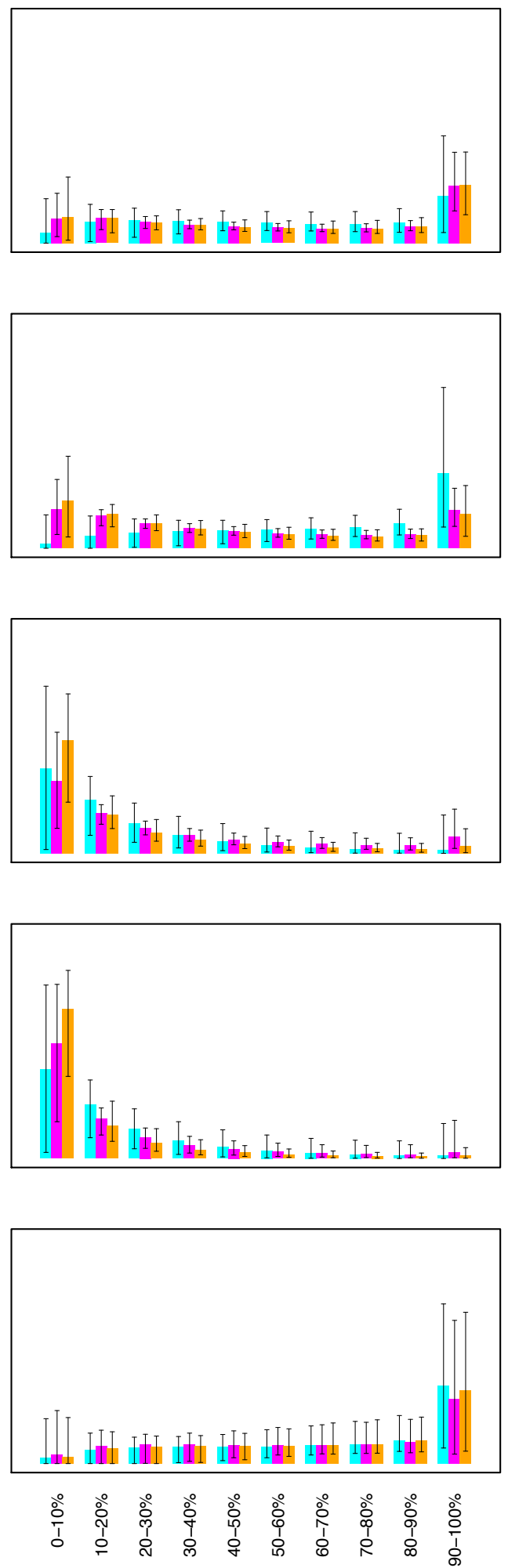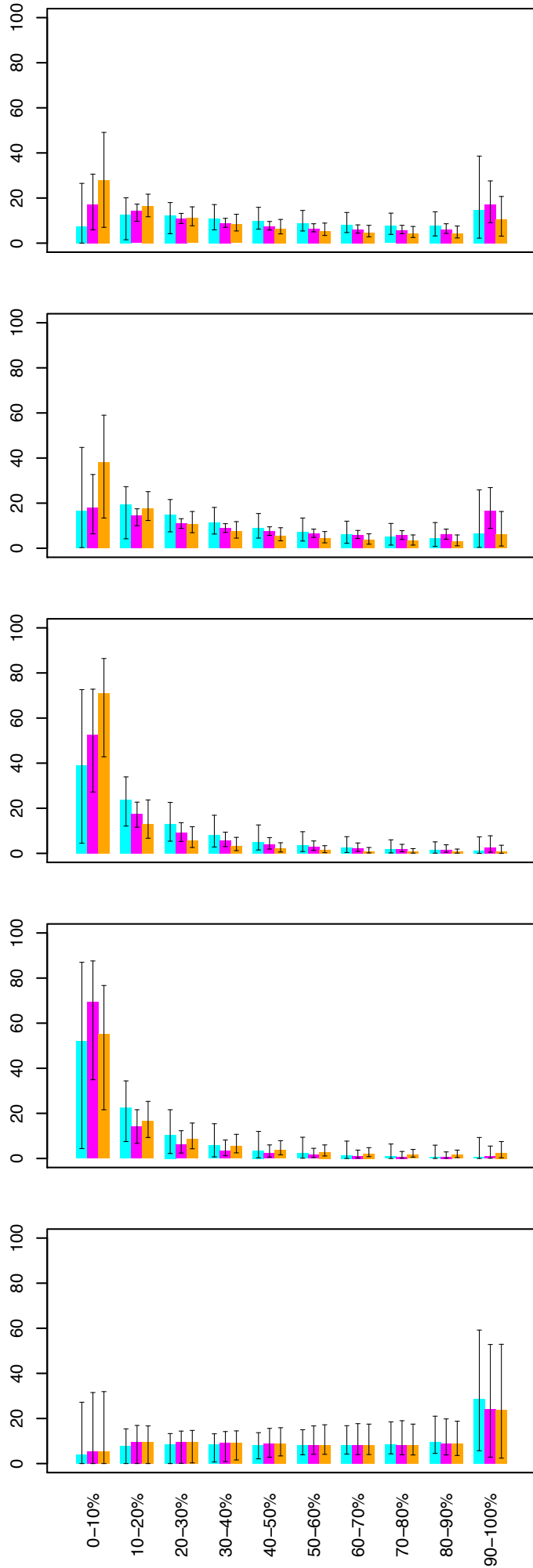
Female   Male

MLH1

MSH2

MSH6

PMS2

MSH2 c.942+3A>T

Estimated proportion (%) of carriers in each risk group

Colorectal cancer cumulative risk (%) to age 80 years

Appendix

Variation in the Risk of Colorectal Cancer for Lynch Syndrome:
A retrospective family cohort study

International Mismatch Repair Consortium authors

Aung Ko Win, James G. Dowty, Jeanette C. Reece, Grant Lee, Allyson S. Templeton, John-Paul Plazzer, Daniel D. Buchanan, Kiwamu Akagi, Seçil Aksoy, Angel Alonso, Karin Alvarez, David J. Amor, Ravindran Ankathil, Stefan Aretz, Julie L. Arnold, Melyssa Aronson, Rachel Austin, Ann-Sofie Backman, Sanne W. Bajwa–ten Broeke, Verónica Barca-Tierno, Julian Barwell, Inge Bernstein, Pascaline Berthet, Beate Betz, Yves-Jean Bignon, Talya Boisjoli, Valérie Bonadona, Laurent Briollais, Joan Brunet, Karolin Bucksch, Bruno Buecher, Reinhard Buettner, John Burn, Trinidad Caldés, Gabriel Capella, Olivier Caron, Graham Casey, Min H. Chew, Yun-hee Choi, James Church, Mark Clendenning, Chrystelle Colas, Elisa J. Cops, Isabelle Coupier, Marcia Cruz-Correa, Albert de la Chapelle, Niels de Wind, Tadeusz Dębniak, Adriana Della Valle, Capuccine Delnatte, Marion Dhooge, Mev Dominguez-Valentin, Youenn Drouet, Floor A. Duijkers, Christoph Engel, Patricia Esperon, D. Gareth Evans, Aída Falcón de Vargas, Jane C Figueiredo, William Foulkes, Emmanuelle Fourme, Thierry Frebourg, Steven Gallinger, Pilar Garre, Maurizio Genuardi, Anne-Marie Gerdes, Lauren M. Gima, Sophie Giraud, Annabel Goodwin, Heike Görgens, Kate Green, Jose Guillem, Carmen Guillén-Ponce, Roselyne Guimbaud, Rodrigo S. C. Guindalini, Elizabeth E. Half, Michael J Hall, Heather Hampel, Thomas V. O. Hansen, Karl Heinimann, Frederik J. Hes, James Hill, Judy W.C. Ho, Elke Holinski-Feder, Nicoline Hoogerbrugge, Robert Hüneburg, Vanessa Huntley, Paul A. James, Uffe B Jensen, Thomas John, Wan K.W. Juhari, Matthew Kalady, Fay Kastrinos, Matthias Kloor, Maija RJ Kohonen-Corish, Lotte N. Krogh, Sonia S. Kupfer, Uri Ladabaum, Kristina Lagerstedt-Robinson, Fiona Lalloo, Christine Lasset, Andrew Latchford, Pierre Laurent-Puig, Charlotte K. Lautrup, Barbara A. Leggett, Sophie Lejeune, Loic LeMarchand, Marjolijn Ligtenberg, Noralane Lindor, Markus Loeffler, Michel Longy, Francisco Lopez, Jan Lowery, Jan Lubiński, Anneke M Lucassen, Patrick M. Lynch, Karolina Malińska, Nagahide Matsubara, Jukka-Pekka Mecklin, Pål Møller, Kevin Monahan, Patrick J. Morrison, Jacob Nattermann, Matilde Navarro, Florencia Neffa, Deborah Neklason, Polly A. Newcomb, Joanne Ngeow, Cassandra Nichols, Maartje Nielsen, Dawn M. Nixon, Catherine Nogues, Henrik Okkels, Sylviane Olschwang, Nicholas Pachter, Rish K. Pai, Edenir I. Palmero, Mala Pande, Susan Parry, Swati G. Patel, Rachel Pearlman, Claudia Perne, Marta Pineda, Nicola K Poplawski, Kirsi Pylvänäinen, Jay Qiu, Nils Rahner, Raj Ramesar, Lene J. Rasmussen, Silke Redler, Rui M. Reis, Luigi Ricciardiello, Emilia Rogoża-Janiszewska, Christophe Rosty, N. Jewel Samadder, Julian R. Sampson, Hans K. Schackert, Wolff Schmiegel, Karsten Schulmann, Helène Schuster, Rodney Scott, Leigha Senter, Toni T Seppälä, Rakefet Shtoyerman, Rolf H. Sijmons, Carrie Snyder, Ilana B. Solomon, Jose Luis Soto, Melissa C. Southey, Allan Spigelman, Florencia Spirandelli, Amanda B. Spurdle, Verena Steinke-Lange, Elena M. Stoffel, Christian P. Strassburg, Lone Sunde, Rachel Susman, Sapna Syngal, Kohji Tanakaya, Gülçin Tezcan, Christina Therkildsen, Steve Thibodeau, Naohiro Tomita, Katherine M. Tucker, Berrin Tunca, Daniela Turchetti, Nancy Uhrhammer, Joji Utsunomiya, Carlos Vaccaro, Fränzel J.B. van Duijnhoven, Meghan J. van Wanzeele, Deepak B. Vangala, Hans F.A. Vasen, Magnus von Knebel Doeberitz, Jenny von Salomé, Karin A. W. Wadt, Robyn L. Ward, Jürgen Weitz, Jeffrey N. Weitzel, Heinric Williams, Ingrid Winship, Paul E. Wise, Julie Wods, Michael O. Woods, Tatsuro Yamaguchi, Silke Zachariae, Mohd N. Zahary, John L. Hopper, Robert W. Haile, Finlay A. Macrae, Gabriela Möslein, Mark A. Jenkins.

Manuscript Writing Group: Aung Ko Win, James G. Dowty, Mark A. Jenkins
Steering Committee: Mark A. Jenkins, Finlay A. Macrae, Gabriela Möslein, Robert W. Haile
Central Database Group: Jeanette C. Reece, Grant Lee, Allyson S. Templeton

Affiliations

Adelaide Medical School, University of Adelaide, Adelaide, SA 5000 Australia (N K Poplawski), Adult Genetics Unit, Royal Adelaide Hospital, Adelaide, SA 5000 Australia (N K Poplawski), Amsterdam University Medical Centers, University of Amsterdam, Department of Clinical Genetics, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands (F A Duijkers), APHP GHU Est Pitié-Salpétrière, Paris 13, France (C Colas), APHP GHU Ouest, Hopital Européen Georges Pompidou, Paris, France (M Dhooge, P Laurent-Puig), Ascension St. Vincent Hospital Cancer Care, Indianapolis, IN 46260, USA (D M Nixon), Ascension St. Vincent Hospital, Cancer Risk Assessment Program, Indianapolis, IN 46260, USA (M J van Wanzeele), Austin Health Familial Cancer Clinic, Heidelberg, VIC 3084, Australia (T John), Cancer Genetics Service, National Cancer Centre Singapore, Singapore (J Ngeow), Cancer Genetics Unit, St Vincent's Hospital; Sydney, Darlinghurst NSW 2010, Australia (A Spigelman), Cancer Genetics, Royal Prince Alfred Hospital, Sydney, NSW 2050 Australia (A Goodwin), Cedars-Sinai Cancer and Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA (R W Haile), Cedars-Sinai Medical Center, Los Angeles, CA 90048 USA (J C Figueiredo), Center for Genomic Medicine,Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark (T VO Hansen), Center for Hereditary Tumor Syndromes; University Hospital Bonn, Bonn, Germany (S Aretz, C Perne), Center for Hereditary Tumors, HELIOS Klinikum Wuppertal, University Witten-Herdecke, Wuppertal, Germany (G Möslein), Center for Personalized Medicine, University of Colorado School of Medicine, Aurora, CO 80045, USA (J Lowery), Center for Precision Medicine, City of Hope National Medical Center, Duarte, CA 91010, USA (I B Solomon), Center for Public Health Genomics, MSB Room 3238, Department of Public Health Sciences, University of Virginia (G Casey), Centre for cancer research and cell biology, Queens University of Belfast, Belfast, BT9 7AE, UK (P J Morrison), Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Parkville, VIC 3010 Australia (J L Hopper, A K Win, J G Dowty, J C Reece, M A Jenkins, G Lee), Centre for Healthy Aging, Department of Cellular and Molecular Medicine, University of Copenhagen, Denmark (L J Rasmussen), Centre François Baclesse, Caen, France (P Berthet), Centre Jean Perrin, Clermont-Ferrand, France (Y Bignon), Centre Léon Bérard, Département Prévention Santé Publique, 69373 Lyon, France (V Bonadona, Y Drouet), Centro de Investigação Translacional em Oncologia (CTO), Instituto do Cancer do Estado de Sao Paulo (ICESP), Hospital das Clínicas da Faculdade de Medicina da Universidade de Sao Paulo (HCFMUSP), São Paulo, Brazil (R SC Guindalini), CHRU, Hopital Jeanne de Flandres, Lille, France (S Lejeune), CHU de Rouen, Rouen, France (T Frebourg), Ciber Oncología (CIBERONC) Instituto Salud Carlos III, L'Hospitalet de Llobregat, Barcelona, Spain (J Brunet), City of Hope Comprehensive Cancer Center, Duarte, CA 91010, USA (J N Weitzel), Clinical Genetics, Faculty of Medicine, University of Southampton, Southampton SO17 1BJ, UK (A M Lucassen), Colon and Rectal Surgery Division, The Ohio State University College of Medicine, Columbus, OH 43210, USA (M Kalady), Coloproctology, Asesoria Genetica Oncologica Sanatorio Parque G.O. Rosario, Argentina (F Spirandelli), Colorectal Medicine and Genetics, The Royal Melbourne Hospital, Parkville VIC 3050 Australia (F A Macrae, J Plazzer), Colorectal Oncogenomics Group, Department of Clinical Pathology, The University of Melbourne, Parkville, VIC 3010, Australia (M Clendenning, D D Buchanan), Columbia University Medical Center, New York, NY 10019 USA (J Guillem), Complejo Hospitalario de Navarra, Navarrabiomed, Universidad Pública de Navarra (UPNA), IdiSNA, Pamplona, Spain (A Alonso), Cooperation Unit Applied Tumour Biology, German Cancer Research Center (DKFZ), Heidelberg, Germany (M Kloor, M von Knebel Doeberitz), Danish HNPCC register, Clinical Research Department, Copenhagen University Hospital, Hvidovre, Denmark (C Therkildsen), Department of Applied Tumour Biology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany (M Kloor, M von Knebel Doeberitz), Department of Cancer Biology and Genetics, The Ohio State University Comprehensive Cancer Center, Columbus, OH 43210

USA (A de la Chapelle), Department of Clinical Genetics, Aalborg University Hospital, Aalborg, Denmark (L Sunde, C K Lautrup, U B Jensen), Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, PA 19111 USA (M J Hall), Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands (F J Hes, M Nielsen), Department of Clinical Genetics, Odense University Hospital, Odense, Denmark (L N Krogh), Department of Clinical Genetics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark (T VO Hansen, K AW Wadt), Department of Clinical Genetics, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan (T Yamaguchi), Department of Epidemiology and Biostatistics, Western University, London, ON N6A 5C1, Canada (Y Choi), Department of Gastroenterology & Hepatology, Leiden University Medical Center, Leiden, The Netherlands (H FA Vasen), Department of Gastroenterology, Hepatology & Nutrition, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA (P M Lynch, M Pande), Department of Genetics, University Medical Center Groningen, Groningen, The Netherlands (S W Bajwa–ten Broeke), Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (R H Sijmons), Department of Health Science Research, Mayo Clinic Arizona, Scottsdale, AZ 85259, USA (N Lindor), Department of Hematology and Oncology, Klinikum Hochsauerland, Meschede, Germany (K Schulmann), Department of Human Genetics and Department of Pathology, Radboud university medical center, Nijmegen, The Netherlands (M Ligtenberg), Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands (N de Wind), Department of Human Genetics, McGill University, Montreal, QC H3A 0C7, Canada (W Foulkes), Department of Human Genetics, Radboud university medical center, Nijmegen, The Netherlands (N Hoogerbrugge), Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany (C P Strassburg, R Hüneburg, J Nattermann), Department of Internal Medicine, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA (D Neklason), Department of Internal Medicine, Knappschaftskrankenhaus, Ruhr-University Bochum, Bochum, Germany (D B Vangala, W Schmiegel), Department of Internal Medicine, University of Michigan, Ann Arbor, MI 48109, USA (E M Stoffel), Department of Laboratory Medicine and Pathology, Mayo Clinic Arizona, Scottsdale, AZ 85259, USA (R K Pai), Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55902 USA (S Thibodeau), Department of Medicine, The University of Melbourne, Parkville, VIC 3010, Australia (I Winship), Department of Molecular Diagnosis & Cancer Prevention, Saitama Cancer Center, Saitama, Japan (K Akagi), Department of Molecular Diagnostics, Aalborg University Hospital, Aalborg Denmark (H Okkels), Department of Molecular Medicine and Surgery, Karolinska Institutet, Department of Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden (J von Salomé, K Lagerstedt-Robinson), Department of Pathology, University of Melbourne, Melbourne, VIC 3010 Australia (C Rosty, M C Southey), Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland (T T Seppälä), Department of Surgery, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan (N Matsubara), Department of Surgery, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, M13 9WL UK (J Hill), Department of Surgery, National Hospital Organization Iwakuni Clinical Center, Iwakuni, Yamaguchi, Japan (K Tanakaya), Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong (J WC Ho), Department of Surgery, University of Toronto, Toronto, ON M5S 1A8, Canada (S Gallinger), Department of Surgical Research, Technische Universität Dresden, Dresden, Germany (H K Schackert, H Görgens), Department of the clinical genetics, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain (V Barca-Tierno), Department of Tumor Biology, Institute of Cancer Research, The Norwegian Radium Hospital, Oslo, Norway (M Dominguez-Valentin), Department of Urology, Geisinger Medical Center, Danville, PA 17822, USA (H Williams), Department of Visceral, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus of the Technical University Dresden, Fetscherstr. 74D-01307 Dresden, Germany (J Weitz), Dept. of Clinical Genetics, Rigshospitalet, Copenhagen University hospital, Copenhagen, Denmark (A Gerdes), Dept. Surgical Gastroenterology,

Aalborg University Hospital, Aalborg, Denmark (I Bernstein), Digestive Diseases Institute, Cleveland Clinic, Cleveland, OH 44106 USA (J Church), Dipartimento di Scienze della Vita e Sanità Pubblica, Università Cattolica del Sacro Cuore, Rome, Italy (M Genuardi), Division of Biomedical Sciences, Memorial University of Newfoundland, St. John's, NL A1C 5S7, Canada (M O Woods), Division of Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Brigham and Women's Hospital; Boston, MA 02215, USA (S Syngal), Division of Clinical Cancer Genomics, City of Hope National Medical Center, Duarte, CA 91010 USA (L M Gima), Division of Digestive and Liver Diseases, Columbia University Irving Medical Center, New York, NY 10032, USA (F Kastrinos), Division of Gastroenterology & Hepatology, University of Colorado Anschutz Medical Center, Aurora, CO 80045, USA (S G Patel), Division of Gastroenterology and Hepatology, Mayo Clinic, Phoenix, AZ 85054, USA (N J Samadder), Division of Gastroenterology and Heptaology, Stanford University School of Medicine, Stanford, CA, USA (U Ladabaum), Division of Human Genetics, The Ohio State University Comprehensive Cancer Center, Columbus, OH 43210 USA (H Hampel, R Pearlman), Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, The Netherlands (F JB van Duijnhoven), Division of Lower GI Surgery, Department of Surgery, Hyogo College of Medicine; Nishinomiya, Hyogo, Japan (N Tomita), Division of Molecular Medicine, NSW Health Pathology, Newcastle, NSW 2300, Australia (R Scott), Education & Research, Central Finland Health Care District, Jyväskylä, Finland (K Pylvänäinen), Emory University School of Medicine, Atlanta, GA 30322, USA (J Qiu), Envoi Specialist Pathologists, Brisbane, QLD 4059 Australia (C Rosty), Facultad de Medicina, Universidad Central de Venezuela, Caracas, Venezuela (A Falcón de Vargas), Faculty of Health and Medical Sciences, University of Western Australia; WA 6009, Australia (N Pachter), Faculty of Medicine and Health, University of Sydney, NSW 2006, Australia (R L Ward), Faculty of Medicine, Department of Medical Biology & Faculty of Dentistry, Department of Fundamental Sciences, Bursa Uludag University, Bursa, Turkey (G Tezcan), Faculty of Medicine, Department of Medical Biology, Bursa Uludag University, Bursa, Turkey (S Aksoy, B Tunca), Faculty of Medicine, The University of Queensland, Brisbane, QLD 4072 Australia (C Rosty), Familial Cancer Centre and Adult Genetics, Department of Genetic Medicine, The Royal Melbourne Hospital, Parkville, VIC 3050, Australia (A K Win, D D Buchanan, I Winship), Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC Genetica Medica, Rome, Italy (M Genuardi), Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA (A S Templeton), Geisinger Health System, Danville, PA 17821, USA (J Wods), Genetic Health Queensland, Herston, QLD 4006, Australia (R Austin), Genetic Services of Western Australia, King Edward Memorial Hospital, Subiaco WA 6008, Australia (N Pachter), Genetics and Computational Biology Division, QIMR Berghofer Medical Research Institution, Herston QLD 4006 Australia (A B Spurdle), Genetics Unit. Hospital Vargas de Caracas, Caracas, Venezuela; Escuela de Medicina Jose Maria Vargas, Caracas, Venezuela (A Falcón de Vargas), GI Malignancy Unit ,Familial Cancer Syndromes, Institute of Gastroenterology, Rambam Health Care Campus, Haifa, Israel (E E Half), Grupo Colaborativo Uruguayo, Hospital Central de las Fuerzas Armadas, Montevideo, Uruguay (P Esperon), Gustave Roussy, Villejuif, France (O Caron), Harvard Medical School, Boston, MA 02115, USA (S Syngal), HCL, Hopital Edouard Herriot, Lyon, France (S Giraud), Heinrich-Heine-University, Medical Faculty, Institute of Human Genetics, Düsseldorf, Germany (B Betz, N Rahner, S Redler), Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY 10032, USA (F Kastrinos), Hereditary Cancer Center, Department of Preventive Medicine, Creighton University, Omaha, NE 68178 USA (C Snyder), Hereditary Cancer Centre, Prince of Wales Hospital, Randwick, NSW 2031 Australia (K M Tucker), Hereditary Cancer Program (ProCanHe), IMTIB, Hospital Italiano, Buenos Aires, Argentina (C Vaccaro), Hereditary Cancer Program Valencian Region, Molecular Genetics Laboratory, Elche University Hospital, Elche, Alicante, Spain (J L Soto), Hereditary Cancer Program, Catalan Institute of Oncology - ICO, Hereditary Cancer Group, Molecular Mechanisms and Experimental Therapy in Oncology Program, Institut d'Investigació Biomèdica de Bellvitge – IDIBELL, Ciber Oncología (CIBERONC) Instituto

Salud Carlos III, L'Hospitalet de Llobregat, Barcelona, Spain (G Capella, M Pineda), Hereditary Cancer Program, Catalan Institute of Oncology-IDIBELL, ONCOBELL, Hospitalet de Llobregat, 08908 Barcelona, Spain (M Navarro, J Brunet), Hereditary Cancer Research Center, Department of Medical and Surgical Sciences, University of Bologna, Italy (L Ricciardiello, D Turchetti), Hereditary cancer, Theme Cancer, Karolinska University hospital, Stockholm, Sweden (A Backman), Hereditary Gastrointestinal Cancer Registry, Hong Kong (J WC Ho), Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia (R Ankathil), Hunter Family Cancer Service, Gateshead, NSW 2290, Australia (A Spigelman), Hunter Medical Research Insitute, University of Newcaste, Newcastle, NSW 2305 Australia (R Scott), Hyogo College of Medicine, Nishinomiya, Hyōgo, Japan (J Utsunomiya), Inherited Cancer Connect Partnership, Genetic Services of Western Australia,WA 6008 Australia (C Nichols), Institut Bergonié, Bordeaux, France (M Longy), Institut Claudius Regaud, Toulouse, France (R Guimbaud), Institut Curie, Paris, France (B Buecher), Institut de Cancérologie de l'Ouest, Nantes, France (C Delnatte), Institut de Cancérologie de Montpellier, Montpellier, France (I Coupier), Institut de cancérologie Strasbourg Europe, Strasbourg, France (H Schuster), Institut Paoli-Calmettes, Marseille, France (C Nogues), Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany (K Bucksch, C Engel, M Loeffler, S Zachariae), Institute for Pathology, University Hospital Cologne, Cologne, Germany (R Buettner), Institute of Human Genetics, Medical Faculty, University of Bonn, Bonn, Germany (S Aretz, C Perne), Institute of Medical Genetics, Cardiff University School of Medicine, Cardiff CF144XN, UK (J R Sampson), International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University in Szczecin, Szczecin, Poland (T Dębniak, J Lubiński, K Malińska, E Rogoża-Janiszewska), Jewish General Hospital, Montréal, QC H3T 1E2, Canada (T Boisjoli), Karolinska Gut group, Unit of Internal medicine, Department of Internal medicine Solna, Karolinska institutet, Stockholm, Sweden (A Backman), Laboratoire OncoGenAuvergne, Centre Jean Perrin, Clermont-Ferrand, France (N Uhrhammer), Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore (J Ngeow), Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Joseph & Wolf Lebovic Health Complex, Toronto, ON M5G 1X5, Canada (S Gallinger), Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, ON M5G 1X5, Canada (L Briollais), Lynch Syndrome and Family Cancer Clinic, St Mark's Hospital, Harrow HA1 3UJ, UK (A Latchford, K Monahan), Lyon 1 University, UMR CNRS 5558 LBBE,69622 Villeurbanne, France (C Lasset), Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester, M13 9WL UK (D G Evans, K Green, F Lalloo), Medical Genetics, University Hospital Basel, and Research Group Human Genomics, Department of Biomedicine, University of Basel, Basel, Switzerland (K Heinimann), Medical Oncology Department, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain (C Guillén-Ponce), Medizinisch Genetisches Zentrum, Munich, Germany (E Holinski-Feder, V Steinke-Lange), Medizinische Klinik und Poliklinik IV, Campus Innenstadt, Klinikum der Universität München, Munich, Germany (E Holinski-Feder, V Steinke-Lange), Member of the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS)—Project ID No 739547 (R H Sijmons, D G Evans, K AW Wadt, S Aretz, J Brunet, G Capella, M Genuardi, E Holinski-Feder, N Hoogerbrugge, M Ligtenberg, J Lubiński, V Steinke-Lange), Molecular Diagnostic Unit. Hospital Clinico San Carlos IdISSC. Madrid, Spain (P Garre), Molecular genetic Laboratory. School of Chemistry Universidad de la Republica Uruguay (P Esperon), Molecular Oncology Laboratory. Hospital Clinico San Carlos IdISSC. Ciber Oncología (CIBERONC) Instituto Salud Carlos III, Madrid, Spain (T Caldés), Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, São Paulo, Brazil (E I Palmero, R M Reis), Monash Health Translation Precinct, Monash University, Clayton South, VIC 3169 Australia (M C Southey), Murdoch Children's Research Institute and University of Melbourne Department of Paediatrics, Royal Children's Hospital, Parkville, VIC 3052, Australia (D J Amor), National Center for Hereditary Tumor Syndromes, University Hospital Bonn, Bonn, Germany (C P

Strassburg, R Hüneburg, J Nattermann), New Zealand Familial Gastrointestinal Cancer Service, Auckland, New Zealand (J L Arnold, S Parry), Newcastle University Translational and Clinical Research Institute, UK (J Burn), Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway (P Møller), Ohio State University Comprehensive Cancer Center, Columbus, OH 43210, USA (L Senter), Oncologia D'or, Rede D'or São Luiz, Brazil (R SC Guindalini), Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC 3000 Australia (P A James, E J Cops), Pele Little Prince Research Institute, Curitiba, Brazil and Faculdades Pequeno Príncipe, Curitiba, Brazil (E I Palmero), Prince of Wales Clinical School, University of New South Wales, Sydney, NSW 2052 Australia (K M Tucker), Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, 98109, USA (P A Newcomb), Ramsay Santé, Hôpital Clairval & INSERM UMR1251, MMG, Marseille, France (S Olschwang), Royal Brisbane and Women's Hospital, Herston, QLD 4029, Australia (R Susman), Royal Brisbane and Womens Hospital; University of Queensland; Herston, QLD 4006, Australia (B A Leggett), SA Clinical Genetics Service, Adult Genetics Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia (V Huntley), Saint-Cloud, Institut Curie, Saint-Cloud, France (E Fourme), School of Biomedicine, Faculty of Health Sciences, Universiti Sultan Zainal Abidin, Gong Badak Campus, Kuala Nerus, Terengganu, Malaysia (M N Zahary), School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia (W KW Juhari), School of Public Health, University of Washington, Seattle, WA, 98195, USA (P A Newcomb), Section of Gastroenterology, Hepatology and Nutrition, University of Chicago, Chicago, IL (S S Kupfer), Sengkang General Hospital, Singapore (M H Chew), Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, VIC 3010 Australia (P A James), South African Medical Research Council/University of Cape Town Precision and Genomic Medicine Research Unit, Division of Human Genetics, Department of Pathology, Institute for Infectious Diseases and Molecular Medicine, University of Cape Town, South Africa (R Ramesar), Sport and HealthSciences, Univ of Jyväskylä, Education & Research, Central Finland Health Care District, Jyväskylä, Finland (J Mecklin), St Vincent's Clinical School; The University of New South Wales, Sydney NSW 2052, Australia (A Spigelman), The Kaplan Medical Center, Rehovot, Israel (R Shtoyerman), The University of Auckland, New Zealand (S Parry), Unidad de Coloproctología, Clinica Las Condes, Santiago, Chile (K Alvarez, F Lopez), University Hospitals of Leicester, Leicester LE5 4PW, UK (J Barwell), University of Hawaii Cancer Center, Honolulu, HI 96813, USA (L LeMarchand), University of Helsinki, Helsinki, Finland (T T Seppälä), University of Melbourne Centre for Cancer Research, Victorian Comprehensive Cancer Centre, Melbourne, VIC 3000, Australia (A K Win, D D Buchanan, M A Jenkins), University of Puerto Rico School of Medicine, San Juan, 00921, Puerto Rico (M Cruz-Correa), Uruguayan Collaborative Group: Investigation of Hereditary Oncological Conditions. Hospital Militar, Montevideo, Uruguay (A Della Valle), Uruguayan Collaborative Group. Hereditary Cancer. Hospital Militar. Montevideo, Uruguay (F Neffa), Washington University, St. Louis, MO 63130, USA (P E Wise), Woolcock Institute of Medical Research; School of Medicine, Western Sydney University; University of Technology Sydney; St George & Sutherland Clinical School, University of New South Wales, Sydney, Australia (M RJ Kohonen-Corish), Zane Cohen Centre, Sinai Health System, Toronto, Ontario, Canada (M Aronson).

Supplementary Statistical Methods

Our main analytical method was segregation analysis[1,2] fitted by maximum likelihood, as implemented in the statistical package MENDEL version 3.2.(3) This method enables the inclusion of ungenotyped family by using their relationships to known carriers and non-carriers. Full mathematical details of a very similar approach are given in a previous report,[4] so an overview of our approach is given here.

Estimates were appropriately adjusted for the clinic- and population-based ascertainment of families using a combination of retrospective likelihood and ascertainment-corrected joint likelihood,[5-8] in which each pedigree's data was conditioned on either the proband's genotype, cancer status and age of onset (for population-based families) or on the proband's genotype and the ages and affected statuses of all family members (for clinic-based families).

Our main measures of risk were hazard ratios (HRs), which were defined to be the sex-, age-, gene- and continent-specific cancer incidences for carriers divided by those for non-carriers. Incidences for non-carriers were set equal to the age-, sex- and country-specific annual population incidences reported in *Cancer Incidence in Five Continents* for the combined period 1998-2002.(9) Here, we assumed that the incidences for Germany, USA, Australia, Hong Kong and Brazil (the countries that gave the most data for each continent) represent the incidences for their respective continents, and the period 1998–2002 was selected because it was closest to the mean calendar year of cancer diagnoses in the entire dataset. The age at cancer diagnosis for carriers of pathogenic variants was modelled as a random variable (time-to-event outcome) whose hazard function was the population incidence of the relevant continent multiplied by the relevant HR. For each anatomical site, the observation time for each subject started at birth and ended at the earliest of the age at diagnosis of first cancer, age at first polypectomy or bowel resection, last known age alive or age at death. Therefore, the study's estimates describe the risk of first colorectal cancer for those who have not undergone prophylactic surgery, regardless of whether they are undergoing screening. Cancers at different anatomical sites within the same person were assumed to be conditionally independent, given the person's genotype (i.e., the person's major gene and polygenic genotypes, see below). HRs were assumed to be constant in age for all cancers except colorectal cancer. To allow colorectal cancer HRs to depend on age, and to provide stability to the estimates for younger and older cases, the HRs for colorectal cancer were modelled as continuous, piece-wise linear functions of age that are constant before age 40 years and after age 60 years, and linear in between (similar to our previous approach[4]).

Major gene models, which attribute all familial aggregation of disease to the gene being studied, can lead to biased estimates of risk if other sources of familial aggregation exist.(7) A genetic mixed model that incorporated unmeasured polygenic factors in addition to the major gene[5,10] was therefore used in the segregation analyses to account for unexplained familial aggregation of colorectal cancer risk (see the detailed methods in a previous report[4]). The polygenic factors capture the combined effect of a large number of genes and other heritable risk factors that individually have small, additive effects on the log HR (similar to a polygenic risk score). We implemented the polygenic factor as a hypergeometric polygenic model with four loci,[5,10] since this model is computationally feasible and it gives a polygenic factor that is approximately normally distributed (on the log HR scale) and correlated within families, with correlation coefficients between relatives equal to the kinship coefficients.(11) The standard deviation of the polygenic factor is a measure of the combined strength of the unmeasured polygenic factors, so it is a measure of the variation in risk between individual carriers with the same sex, age and mutated gene. The existence of familial risk factors modifying colorectal cancer risk for Lynch syndrome carriers was tested using a Wald p-value for the null hypothesis that the polygenic standard deviation is zero. The polygenic standard deviation was constant in age for the main analyses,

but we tested for an age-dependence by allowing the polygenic standard deviation to be a piece-wise linear function of age (of the same form as described above for the colorectal cancer HRs). The mean of the polygenic factor at each age was chosen so that the average HR due to the polygenic factors was 1.

For each combination of gene, sex and continent, the age-specific cumulative risk (penetrance) of colorectal cancer to age t years was calculated from the estimated HRs as the average over the polygenic factor of

$$1 - \exp\left(-\int_0^t \lambda(s)ds\right),$$

where $\lambda(s)$ is the product of the polygenic HR, the HR at age s for the relevant MMR gene, and the relevant population incidence at age s. Confidence intervals (CIs) for these cumulative risks were calculated using a parametric bootstrap, in which: a sample of 5,000 draws was taken from the multivariate normal distribution that the maximum likelihood estimates are expected to follow under asymptotic likelihood theory; for each age, a corresponding sample of 5,000 cumulative risks to that age were calculated as above; then the 95% CI for the cumulative risks to that age were taken to be the 2.5th and 97.5th percentiles of this sample.

HRs for colorectal cancer, endometrial cancer, and other Lynch syndrome cancers were estimated simultaneously, since this allows proper adjustment for largely colorectal cancer-based ascertainment schemes when estimating the risks of non-colorectal cancers, and it increases statistical power by helping the model to identify likely carriers from the placement of all Lynch syndrome-associated cancers within each family. For all segregation analyses except single-variant analyses (see below), HRs for all mismatch repair genes (i.e., *MLH1*, *MSH2*, *MSH6*, *PMS2*) were estimated simultaneously to allow the polygenic standard deviation parameters to be the same across all mismatch repair genes, though separate estimates were produced for each continent.

To examine whether any observed polygenic effect might be due to variant-specific colorectal cancer risks, we conducted a separate analysis on a single variant, namely the founder pathogenic variant *MSH2* c.942+3A>T variant, which was the most common variant in the families provided. For this analysis, because there was only one gene involved and there were relatively few families, the HRs were constrained to be the same across the three continents and the polygenic standard deviation parameters were the same for all continents to increase the stability of the estimates.

Lifetime cumulative risks will follow a U-shaped curve whenever the polygenic standard deviation is large enough, essentially because the transformation from the normally distributed polygenic factor to lifetime cumulative risk is non-linear. Under the above genetic mixed model, each value of the polygenic factor corresponds (monotonically) to a different value of the lifetime cumulative risk (different even for carriers of a pathogenic MMR gene variant with the same sex, age and mutated gene). So all values of the polygenic factor below some threshold correspond to lifetime risks of less than 10%, and all values above a given threshold correspond to risks of 90% or more. Therefore, for any mean risk and for any large-enough polygenic standard deviation, most lifetime cumulative risks will fall into one of these two extreme categories, giving a U-shaped distribution of lifetime cumulative risks. Note that this U-shaped distribution could be caused by any strong multifactor modifier of risk shared by family members.

Based on the estimated HRs and polygenic standard deviation, the distribution of lifetime cumulative risk (i.e., cumulative risk to age 80 years) due to the polygenic factor was calculated for each combination of sex, continent and MMR gene, as follows. On the log HR scale, the polygenic factor is normally distributed with mean μ and standard deviation σ, and σ was set equal to the estimated polygenic standard deviation. The mean μ was taken to be $\mu = -\sigma^2/2$ so that, on the HR scale, the polygenic factor has a mean of 1, and is log-normally distributed. To each of the 1000 equally-spaced percentages 0.05, 0.15, 0.25, …, 99.95, a corresponding polygenic HR was calculated using the quantile function of the normal distribution (with the above values of μ and σ). To each of these percentages, a corresponding cumulative risk at age 80 years was then calculated as above, with $\lambda(s)$ in the cumulative risk formula being the product of the polygenic HR (described in the previous sentence), the HR at age s for the relevant MMR gene, and the relevant population incidence at age s. The proportion of carriers with lifetime cumulative risks within a given range was then calculated as the difference in the percentages corresponding to the end-points of the range. CIs for the proportion of people in such a risk category were calculated using a parametric bootstrap procedure, similar to the CI calculation for the cumulative risks described above.

Age information for each family member was required for the pedigree analysis, so we imputed an age for each family member whose age was not reported (37% of total) using a defined protocol, as follows. If an exact age was unknown but an age range was provided, the age was estimated as the midpoint of the range. If the age at diagnosis was unknown, it was assumed to be the same as age at death (if the person was deceased) or the mean age at diagnosis for the specific cancer for their continent (if the person was alive). For family members with an unknown last age, ages were censored at the time they were last known to be alive (e.g., at the age of cancer diagnosis). In the absence of any age information, it was assumed that both parents of the proband were born in the same year, that years of birth differed by 25 years in each generation (e.g., at birth of proband, parents were aged 25 years and grandparents were aged 50 years), and the ages of the siblings were the same. As a sensitivity analysis, we compared the results of analysis after imputing missing age with the analysis by censoring at birth for those with missing ages. The median, range, mean and standard deviation of the age at colorectal cancer diagnosis were calculated using Stata 15.1.(12)

All p-values for the segregation analyses were two-sided and based on the likelihood ratio test, and a p-value threshold of 0.05 was used to define statistical significance.

References

1.	Antoniou AC, Pharoah PD, McMullan G, Day NE, Ponder BA, Easton D. Evidence for further breast cancer susceptibility genes in addition to *BRCA1* and *BRCA2* in a population-based study. *Genet Epidemiol* 2001; **21**(1): 1-18.
2.	Lange K. Mathematical and statistical methods for genetic analysis. 2nd ed. New York: Springer; 2002.
3.	Lange K, Weeks D, Boehnke M. Programs for pedigree analysis: MENDEL, FISHER, and dGENE. *Genet Epidemiol* 1988; **5**(6): 471-2.
4.	Dowty JG, Win AK, Buchanan DD, et al. Cancer risks for MLH1 and MSH2 mutation carriers. *Hum Mutat* 2013; **34**(3): 490-7.
5.	Antoniou AC, Pharoah PDP, McMullan G, Day NE, Ponder BAJ, Easton D. Evidence for further breast cancer susceptibility genes in addition to *BRCA1* and *BRCA2* in a population-based study. *Genet Epidemiol* 2001; **21**(1): 1-18.
6.	Quehenberger F, Vasen HF, van Houwelingen HC. Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: correction for ascertainment. *J Med Genet* 2005; **42**(6): 491-6.
7.	Gong G, Hannon N, Whittemore AS. Estimating gene penetrance from family data. *Genet Epidemiol* 2010; **34**(4): 373-81.
8.	Kraft P, Thomas DC. Bias and efficiency in family-based gene-characterization studies: conditional, prospective, retrospective, and joint likelihoods. *Am J Hum Genet* 2000; **66**(3): 1119-31.
9.	Ferlay J BF, Steliarova-Foucher E and Forman D. (2014). Cancer Incidence in Five Continents, CI5plus. IARC CancerBase No. 9. 20142017).
10.	Cannings C, Thompson EA, Skolnick MH. Probability Functions on Complex Pedigrees. *Advances in Applied Probability* 1978; **10**(1): 26-61.
11.	Lange K. Mathematical and statistical methods for genetic analysis: Springer; 2002.
12.	StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC; 2019.

Supplementary Table 1. The numbers of Lynch syndrome families that inclusion criteria for analyses, by gene and continent

Region	MLH1	MSH2	MSH6	PMS2	EPCAM	Total
Europe	**1049**	**1245**	**392**	**154**	**10**	**2850**
Denmark	66	135	86	17	1	305
Finland	12	1	0	0	0	13
France	244	254	32	0	0	530
Germany	421	517	89	44	0	1071
Italy	3	11	3	0	0	17
Norway	15	44	31	11	1	102
Poland	6	1	0	0	0	7
Spain	118	73	49	16	4	260
Switzerland	5	3	2	0	0	10
The Netherlands	0	0	36	46	0	82
United Kingdom	159	206	64	20	4	453
North America	**526**	**637**	**242**	**199**	**15**	**1619**
Canada	69	77	16	11	3	176
USA	457	560	226	188	12	1443
Australasia	**254**	**297**	**164**	**96**	**2**	**813**
Australia	244	289	159	94	1	787
New Zealand	10	8	5	2	1	26
Asia	**66**	**83**	**14**	**1**	**1**	**165**
Hong Kong	28	57	3	0	1	89
Japan	34	21	8	1	0	64
Singapore	4	5	3	0	0	12
South America	**67**	**49**	**15**	**7**	**0**	**138**
Argentina	10	12	1	1	0	24
Brazil	22	23	11	3	0	59
Chile	17	5	0	2	0	24
Uruguay	18	9	3	1	0	31
Total	**1962**	**2311**	**827**	**457**	**28**	**5585**

Note: These are the number of families provided for this analysis and do not represent the numbers of families known in each of the countries.

Supplementary Table 2. Average age-specific cumulative risks % (penetrance) of colorectal cancer for Lynch syndrome carriers, by sex, gene and continent

Sex	Gene	Continent	Average age-specific cumulative risks % (penetrance) to age					
			30 years	40 years	50 years	60 years	70 years	80 years
Female	*MLH1*	Australasia	2.4 (1.3–4.5)	9.5 (5.3–16)	22 (13–35)	32 (21–48)	40 (27–59)	50 (33–72)
		North America	1.1 (0.7–1.9)	4.8 (2.9–7.7)	13 (8.6–19)	22 (17–30)	34 (25–45)	46 (35–59)
		Europe	0.4 (0.2–1.1)	1.4 (0.6–3.5)	5.0 (2.7–9.7)	13 (8.3–21)	24 (15–36)	36 (24–52)
	MSH2	Australasia	2.1 (0.8–5.3)	8.4 (3.3–19)	19 (8.3–37)	27 (14–49)	31 (17–54)	37 (21–63)
		North America	1.3 (0.8–1.9)	5.3 (3.5–7.8)	14 (9.6–19)	23 (17–30)	33 (25–44)	45 (34–58)
		Europe	0.4 (0.2–1.0)	1.5 (0.7–3.5)	4.8 (2.6–9.3)	11 (6.6–18)	18 (11–30)	28 (17–44)
	MSH6	Australasia	0.1 (0.02–0.9)	0.7 (0.1–4.0)	1.9 (0.4–10)	3.9 (1.1–16)	6.8 (2.2–23)	11 (3.6–34)
		North America	0.04 (0.003–0.5)	0.2 (0.02–2.5)	1.0 (0.4–6.7)	4.2 (2.1–12)	11 (5.6–21)	19 (10–33)
		Europe	0.05 (0.01–0.2)	0.2 (0.05–0.7)	0.8 (0.3–2.2)	2.6 (1.3–5.7)	5.9 (2.9–12)	11 (5.3–22)
	PMS2	Australasia	0.02 (0.02–0.02)	0.09 (0.09–0.09)	0.7 (0.4–1.4)	3.8 (1.7–8.7)	11 (5.0–24)	21 (9.9–42)
		North America	0.1 (0.03–0.6)	0.6 (0.1–2.8)	1.9 (0.5–7.2)	3.5 (1.3–11)	5.6 (2.3–15)	8.9 (3.6–23)
		Europe	0.02 (0.003–0.1)	0.07 (0.01–0.4)	0.5 (0.2–1.6)	2.5 (1.2–5.5)	6.5 (3.1–13)	12 (6.1–23)
	MSH2 c.942+3A>T	Australasia	2.4 (1.1–4.8)	9.2 (4.5–17)	22 (12–38)	35 (21–55)	49 (31–72)	62 (40–86)
		North America	1.8 (0.8–3.5)	7.7 (3.7–14)	19 (11–33)	32 (19–50)	45 (27–67)	58 (37–82)
		Europe	2.0 (0.9–4.1)	6.6 (3.1–13)	17 (9.5–31)	31 (19–49)	44 (27–66)	58 (36–82)
Male	*MLH1*	Australasia	2.1 (1.1–3.9)	9.4 (5.1–16)	25 (16–39)	38 (26–54)	46 (33–65)	57 (40–78)
		North America	2.6 (1.6–3.9)	10 (7.0–15)	23 (17–31)	35 (27–45)	44 (35–56)	55 (43–68)
		Europe	0.9 (0.4–2.1)	2.9 (1.3–6.0)	9.2 (5.6–16)	24 (17–34)	41 (30–55)	55 (41–70)
	MSH2	Australasia	2.3 (1.0–5.0)	10 (5.0–20)	28 (16–46)	43 (28–64)	55 (37–79)	68 (46–90)
		North America	2.0 (1.4–2.8)	8.2 (5.8–11)	19 (14–25)	29 (22–37)	37 (29–46)	46 (36–58)
		Europe	0.7 (0.3–1.5)	2.2 (1.0–4.3)	6.7 (4.1–11)	17 (12–25)	30 (21–43)	42 (29–58)
	MSH6	Australasia	0.3 (0.09–1.0)	1.6 (0.5–4.9)	5.5 (1.9–15)	10 (4.2–25)	15 (6.2–38)	22 (8.8–55)
		North America	0.5 (0.2–1.1)	2.3 (1.0–5.0)	6.7 (3.3–13)	13 (7.9–23)	22 (13–35)	31 (19–49)
		Europe	0.4 (0.1–1.3)	1.2 (0.4–3.7)	3.6 (1.3–9.5)	8.0 (4.0–17)	14 (7.5–26)	21 (11–36)
	PMS2	Australasia	0.4 (0.09–2.0)	2.1 (0.5–9.1)	6.9 (1.8–25)	12 (3.7–36)	15 (5.6–41)	21 (8.1–53)
		North America	0.2 (0.03–0.9)	0.8 (0.2–4.0)	2.7 (1.0–10)	6.4 (3.1–18)	12 (5.7–32)	20 (8.5–46)
		Europe	0.2 (0.04–0.7)	0.5 (0.1–2.1)	1.7 (0.6–5.8)	4.3 (2.0–11)	8.1 (3.9–17)	13 (6.4–25)
	MSH2 c.942+3A>T	Australasia	3.1 (1.6–5.6)	13 (7.0–22)	32 (19–51)	46 (31–69)	56 (38–79)	67 (46–89)
		North America	3.3 (1.8–5.8)	13 (7.3–22)	30 (18–48)	43 (29–65)	52 (36–75)	62 (43–85)
		Europe	5.0 (2.6–8.7)	13 (7.3–22)	30 (18–47)	45 (30–67)	55 (38–79)	65 (45–88)

Supplementary Table 3. Estimated proportions of Lynch syndrome carriers with various risk groups (defined by deciles of colorectal cancer cumulative risks, penetrance, to age 80 years), by sex, gene and continent

Sex	Gene	Continent	Proportion of Lynch syndrome carriers with									
			0–10% penetrance	10–20% penetrance	20–30% penetrance	30–40% penetrance	40–50% penetrance	50–60% penetrance	60–70% penetrance	70–80% penetrance	80–90% penetrance	90–100% penetrance
Female	MLH1	Australasia	7.3 (0–26.5)	12.6 (1.5–20.1)	12.2 (4.2–18)	11 (5.9–17.1)	9.8 (6.2–15.9)	8.8 (5.4–14.5)	8.1 (4.7–13.6)	7.6 (3.9–13.3)	7.7 (3.2–13.9)	14.8 (2.2–38.6)
		North America	17.1 (5.9–30.6)	14.2 (9.7–17.3)	10.8 (8.7–13.2)	8.8 (7–11)	7.4 (5.8–9.6)	6.5 (5–8.6)	6 (4.4–8.1)	5.8 (4.2–7.9)	6.2 (4.3–8.6)	17.1 (9.1–27.6)
		Europe	27.8 (7–49.1)	16.5 (11.7–21.7)	11.1 (7.7–16.1)	8.3 (5.4–12.8)	6.5 (4.1–10.5)	5.5 (3.4–8.9)	4.8 (2.8–7.9)	4.4 (2.5–7.4)	4.4 (2.3–7.6)	10.6 (3.1–20.7)
	MSH2	Australasia	16.5 (0.3–44.7)	19.2 (4.2–27.3)	14.8 (7.3–21.6)	11.4 (6.3–18.1)	8.9 (4.5–15.4)	7.2 (3.2–13.4)	6 (2.2–12)	5 (1.4–11)	4.5 (0.8–11.4)	6.4 (0.4–25.9)
		North America	17.9 (6.4–32.7)	14.4 (10–17.5)	10.9 (8.8–13.1)	8.8 (7–10.9)	7.4 (5.7–9.5)	6.5 (4.8–8.5)	5.9 (4.3–7.9)	5.7 (3.9–7.8)	6 (4–8.5)	16.4 (8.8–26.9)
		Europe	38.1 (13.4–59)	17.6 (12.3–25.1)	10.7 (6.9–16.3)	7.4 (4.5–11.8)	5.5 (3.3–9.1)	4.4 (2.4–7.4)	3.7 (1.8–6.4)	3.2 (1.4–5.9)	3.1 (1.1–5.9)	6.2 (1–16.3)
	MSH6	Australasia	39.1 (4.5–72.6)	23.8 (12.1–33.9)	13.1 (5.4–22.6)	8.1 (2.8–16.9)	5.2 (1.5–12.6)	3.6 (0.8–9.6)	2.5 (0.4–7.4)	1.8 (0.2–6)	1.4 (0.1–5.1)	1.3 (0–7.3)
		North America	52.6 (27.2–72.8)	17.5 (11.6–22.7)	9.1 (5.3–13.6)	5.8 (3–9.4)	3.9 (1.9–7)	2.9 (1.3–5.5)	2.2 (0.9–4.6)	1.8 (0.7–4)	1.6 (0.5–3.8)	2.5 (0.5–7.8)
		Europe	71.2 (42.8–86.4)	13 (6.7–23.7)	5.8 (2.6–11.8)	3.2 (1.2–7.1)	2.1 (0.6–4.7)	1.4 (0.3–3.4)	1 (0.2–2.6)	0.7 (0.1–2.1)	0.7 (0.1–1.9)	0.8 (0–3.6)
	PMS2	Australasia	51.9 (4.4–87)	22.4 (7.5–34.4)	10.5 (2.2–21.6)	5.8 (0.7–15.4)	3.5 (0.3–12)	2.2 (0.1–9.4)	1.4 (0–7.7)	1 (0–6.4)	0.6 (0–5.9)	0.6 (0–9.3)
		North America	69.3 (34.9–87.6)	14 (6.7–21.6)	6.2 (2.4–12.3)	3.4 (1.2–8.2)	2.2 (0.6–6)	1.5 (0.4–4.5)	1.1 (0.2–3.7)	0.7 (0.1–3.1)	0.7 (0.1–2.9)	0.8 (0.1–5.5)
		Europe	55.1 (21.6–76.7)	16.6 (9.3–25.3)	8.6 (4.3–15.7)	5.3 (2.5–10.7)	3.7 (1.6–7.9)	2.8 (1.1–6)	2.1 (0.8–4.8)	1.7 (0.6–4)	1.5 (0.4–3.7)	2.5 (0.3–7.5)
	MSH2 c.942+3A>T	North America	4 (0–27.2)	7.8 (0–15.4)	8.5 (0–13.3)	8.4 (0.7–13.2)	8.2 (2.1–13.7)	8.1 (3.9–15)	8.1 (4.2–16.8)	8.5 (4.3–18.5)	9.7 (4.5–21)	28.6 (5.7–59.2)
		Europe	5.5 (0–31.9)	9.5 (0–16.7)	9.2 (0.3–14.7)	9.2 (1.6–14.5)	8.7 (3.4–15.9)	8.3 (4.1–17.2)	8 (4–17.5)	8.2 (3.8–17.5)	9 (3.6–18.8)	23.8 (2.4–52.9)
Male	MLH1	Australasia	4.6 (0–19.7)	9.5 (0.7–17.2)	10.2 (2.6–15.5)	9.9 (4.1–14.8)	9.4 (5.5–14.3)	9 (5.6–14)	8.6 (5.4–13.8)	8.6 (5.1–14)	9.2 (4.8–15.3)	20.9 (4.7–47.6)
		North America	10.8 (2.9–22.1)	11.1 (6–14.9)	9.4 (6.5–11.8)	8.2 (6.4–10.2)	7.4 (5.9–9.3)	6.9 (5.4–8.7)	6.5 (5.1–8.4)	6.7 (5–8.6)	7.5 (5.5–10)	25.4 (14.3–40.3)
		Europe	11.7 (1.3–29.3)	11.1 (4.6–14.9)	9.3 (5.9–12.1)	8 (5.9–10.9)	7.1 (5.2–10.3)	6.6 (4.6–9.9)	6.4 (4.3–9.8)	6.5 (4.3–10.1)	7.3 (4.7–11.3)	25.9 (12.6–40.4)
	MSH2	Australasia	1.9 (0–14.8)	5.3 (0–14.3)	6.9 (0.4–13)	7.5 (1.1–12.4)	7.9 (2–12.4)	8.2 (3–12.7)	8.6 (4.1–13.5)	9.3 (5.2–14.6)	11 (5.9–17.3)	33.3 (9.4–71.3)
		North America	17.3 (6.1–30.5)	14.3 (10–17.1)	10.8 (8.8–13)	8.8 (7–10.9)	7.4 (5.8–9.6)	6.5 (4.9–8.7)	6 (4.4–8.1)	5.8 (4.2–7.9)	6.1 (4.3–8.5)	16.9 (9.7–26.6)
		Europe	21.1 (5–40.8)	15 (9.5–19.4)	10.8 (7.8–14.8)	8.5 (5.9–12.3)	7.1 (4.7–10.6)	6.1 (4–9.3)	5.5 (3.5–8.4)	5.2 (3.2–8.2)	5.6 (3.2–8.6)	15 (5.3–27.8)
	MSH6	Australasia	37.6 (1.7–74.1)	23.8 (8–34.1)	13.4 (4.9–22.3)	8.3 (2.4–16.4)	5.5 (1.2–13.2)	3.7 (0.6–11.2)	2.7 (0.3–9.8)	1.9 (0.1–9.1)	1.5 (0.1–8.9)	1.5 (0–17)
		North America	32.3 (11.1–53.7)	17.8 (12.9–21.6)	11.3 (8.2–14.3)	8.1 (5.4–11)	6.2 (3.8–9)	5.1 (2.9–7.7)	4.2 (2.2–7)	3.8 (1.8–6.7)	3.6 (1.5–6.9)	7.5 (2.2–19.6)
		Europe	50.1 (22.7–70.7)	17.2 (11–25.5)	9.3 (5.4–15)	6 (3.2–10.3)	4.3 (2.1–7.5)	3.2 (1.4–5.9)	2.5 (0.9–4.9)	2.1 (0.7–4.4)	1.9 (0.5–4.4)	3.3 (0.3–10.9)
	PMS2	Australasia	39.5 (2.7–76.9)	23.8 (9.2–34.8)	13.1 (4.3–22)	7.9 (1.8–16.3)	5.2 (0.7–12.7)	3.5 (0.3–10.4)	2.5 (0.1–8.9)	1.8 (0.1–8.1)	1.3 (0–7.8)	1.3 (0–15.5)
		North America	50.9 (16.3–77.2)	17.7 (10.4–22.4)	9.4 (4.5–13.5)	5.9 (2.4–9.8)	4.2 (1.5–7.8)	3 (0.9–6.8)	2.4 (0.6–6.1)	2 (0.4–5.8)	1.7 (0.3–6.1)	2.7 (0.3–16.9)
		Europe	66.3 (36.4–83.4)	14.4 (7.6–25.4)	6.7 (3.2–13.2)	3.8 (1.6–8.3)	2.6 (0.9–5.7)	1.7 (0.5–4.2)	1.3 (0.3–3.3)	1.1 (0.2–2.7)	0.8 (0.1–2.4)	1.2 (0.1–4.8)
	MSH2 c.942+3A>T	Australasia	2.7 (0–19.9)	6.1 (0–13.5)	7.1 (0–11.7)	7.3 (0.4–12)	7.6 (1.3–12.9)	7.6 (2.6–15)	8 (3.8–16.7)	8.6 (4.5–18.7)	10.3 (5.4–21.3)	34.6 (6.9–70.8)
		North America	4 (0–23.5)	7.9 (0–14.8)	8.4 (0.1–13)	8.3 (1–13.5)	8.1 (2.6–14.5)	8.4 (3.8–16)	8.1 (4.3–17.2)	8.4 (4.5–18.3)	9.7 (4.8–19.6)	28.6 (4.2–63.5)
		Europe	3.1 (0–20.4)	6.7 (0–14.1)	7.5 (0–12.2)	7.8 (0.5–12.4)	7.8 (1.7–13.4)	7.8 (3.2–15.4)	8.1 (4.2–18)	8.6 (4.2–18)	10.1 (5.2–20.6)	32.4 (5.5–67.1)