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

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## Summary

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Declaration of interests

We declare no competing interests.

Data sharing statement

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.

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**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.

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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.

### 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

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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

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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

The content of this manuscript does not necessarily reflect the views or policies of any of the sponsors or collaborating centres in the IMRC, nor does mention of trade names, commercial products, or organizations imply endorsement by the IMRC. Authors had full responsibility for study conceptualisation, data curation, investigation, methodology, writing and editing of the manuscript. The funders of the study had no role in study design, data collection, analysis, interpretation, or writing of the report. All authors had access, on request, to all the data reported in the study. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

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## 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

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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

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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.

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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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## 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.

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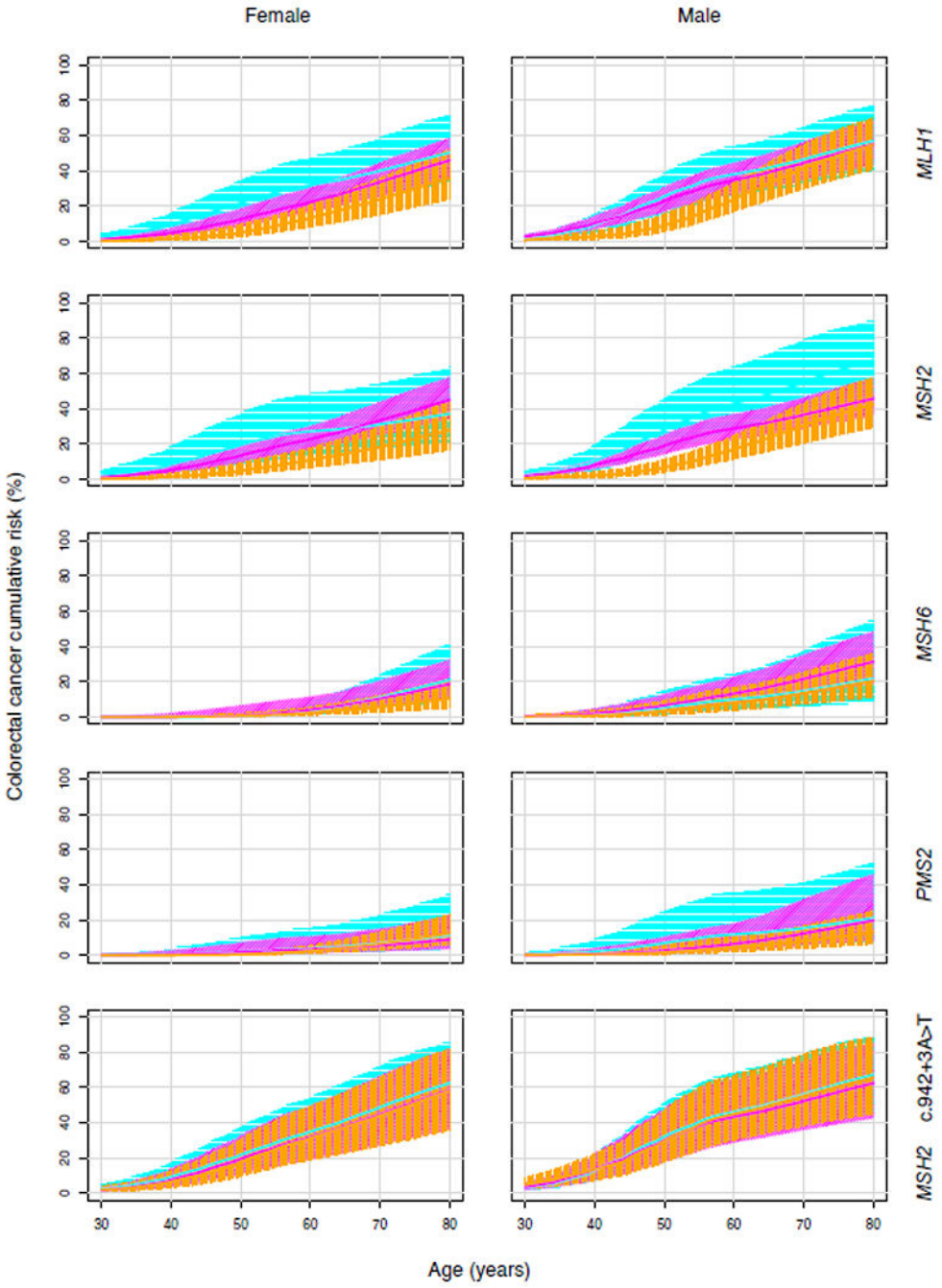


**Figure 1.**

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.

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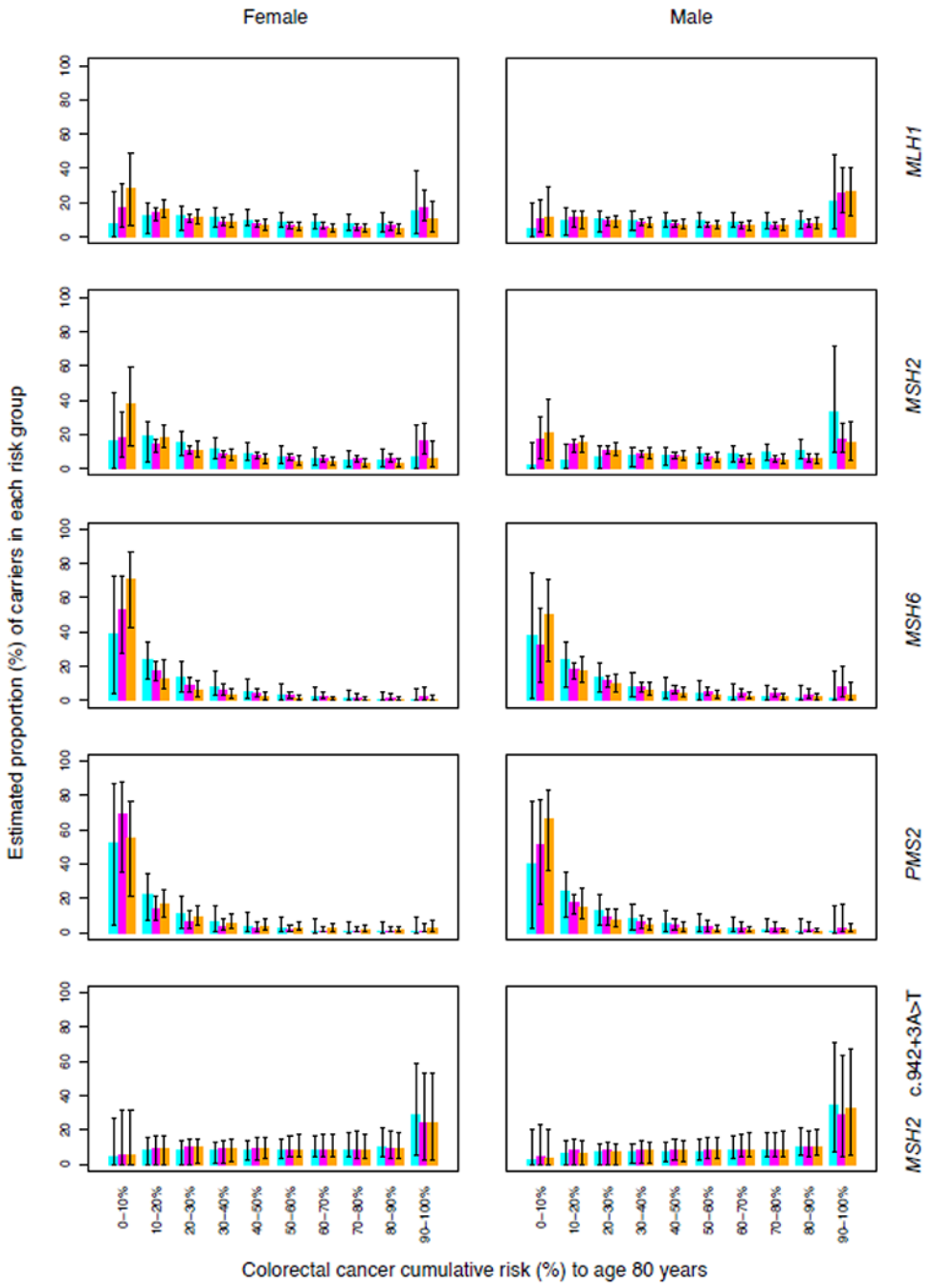


**Figure 2.**

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%

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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.

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**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.

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**Table 2.**

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

| | | Female | | Male | |
|---|---|---|---|---|---|
| **Continent** | **Gene** | **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

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**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

| | | Proportion of female carriers with | | | Proportion of male carriers with | | |
|---|---|---|---|---|---|---|---|
| **Gene** | **Continent** | **<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