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Risk of Colorectal Cancer for Carriers of Mutations in *MUTYH*, with and without a Family History of Cancer

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Abstract

We studied 2332 individuals with monoallelic mutations in *MUTYH* among 9504 relatives of 264 colorectal cancer (CRC) cases with a *MUTYH* mutation. We estimated CRC risks, through 70 y of age, of 7.2% for male carriers of monoallelic mutations (95% confidence interval [CI], 4.6%–11.3%) and 5.6% for female carriers of monoallelic mutations (95% CI, 3.6%–8.8%), irrespective of family history. For monoallelic *MUTYH* mutation carriers with a first-degree relative with CRC, diagnosed by 50 y of age who does not have the *MUTYH* mutation, risks of CRC were 12.5% for men and (95% CI, 8.6%–17.7%) and 10% for women (95% CI, 6.7%–14.4%). Risks of

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CRC for carriers of monoallelic mutations in *MUTYH* with a first-degree relative with CRC are

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DISCLOSURE

The authors have no conflict of interest to declare with respect to this manuscript.

Authors' Contributions

Aung Ko Win: study concept and design; acquisition of data; statistical analysis; interpretation of data; drafting and critical review of the manuscript for important intellectual content; approval of the final version of the manuscript

James G. Dowty: study concept and design; statistical analysis; interpretation of data; drafting and critical review of the manuscript for important intellectual content; approval of the final version of the manuscript

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sufficiently high to warrant more intensive screening than for the general population.

Keywords

colon cancer; genetics; base excision repair gene; DNA damage response

MUTYH is a base excision repair gene that detects and protects against oxidative DNA damage.[1] Individuals with germline mutations in both alleles (biallelic mutation carriers), whether they are homozygotes or compound heterozygotes, develop *MUTYH*-associated polyposis, an autosomal recessive disorder with substantially increased risk of CRC.[2] Individuals with germline mutations in one allele (monoallelic mutation carriers) have a small increased risk of CRC[3–5]. Due to the rarity of these mutations,[4, 6] previous studies have had limited ability to provide precise estimates of age- and sex-specific CRC risks for *MUTYH* mutation carriers. Further, the variability in CRC risk between carriers has not been quantified. Modelling of this variability can indicate a potential role for modifiers of risk.

RESULTS

We identified 9504 relatives (4613 females) from the families of the 264 (236 population-based and 28 clinic-based) probands with a monoallelic or biallelic *MUTYH* mutation from the Colon Cancer Family Registry; 138 (52%) from USA, 81 (31%) from Canada, and 45 (17%) from Australia and New Zealand. In the relatives, we observed 261 CRCs (114 females) whose ages at diagnosis had a median of 65 (range 26–98) years. *MUTYH* mutation status was known for 340 relatives (13 biallelic mutation carriers, 142 monoallelic mutation carriers, and 185 non-carriers). We estimated an additional 43 biallelic and 2190 monoallelic mutation carriers among non-genotyped relatives, giving a total estimated number of 56 biallelic and 2332 monoallelic mutation-carrying relatives in our sample.

Our methods allowed for CRC risk estimation in mutation families to be due to the *MUTYH* mutation as well as polygenic factors (combination of a large number of CRC-associated genetic susceptibility loci).[7] We estimated CRC risks, through 70y of age, for male and female to be: 75.4% (95%CI, 41.2%–96.6%) and 71.7% (95%CI, 44.5%–92.1%), respectively, for biallelic mutation carriers, and 7.2% (95%CI, 4.6%– 11.3%) and 5.6% (95%CI, 3.6%–8.8%), respectively, for monoallelic mutation carriers (Figure 1). The estimated CRC risks, through 70y of age, for monoallelic mutation carriers with a first-degree relative with CRC were similar whether the relative was untested or a non-carrier or a monoallelic mutation carrier: approximately 12% (95%CI, 9%–18%) and 10% (95%CI, 7%–14%) respectively for males and females in comparison with males and females from the general population (2.9% and 2.1% respectively). However, if their affected first-degree relative was a biallelic mutation carrier then risks of CRC, through 70y of age, for monoallelic mutation carriers was estimated to be 10.4% (95%CI, 7.0%–15.0%) and 8.2% (95%CI, 5.4%–12.0%) respectively for males and females (Table 1). In addition, we estimated CRC risks for six other scenarios (Supplementary Figure 1). The highest risk of CRC for a monoallelic mutation carrier corresponded to having two affected first-degree relatives: one is a biallelic mutation carrier and one is a noncarrier (Supplementary Figure 1C).

We found no evidence for a difference in hazard ratios of CRC for biallelic mutation carriers between males and females (108 (95%CI, 25.9–454) vs 129 (95%CI, 43.7–380); p=0.85), nor for monoallelic mutation carriers between males and females (2.46 (95%CI, 1.54–3.93) vs 2.67 (95%CI, 1.67–4.26); p=0.81). Hazard ratio of CRC for Y179C monoallelic carriers was higher than for G396D monoallelic carriers (4.81 (95%CI, 3.00–7.71) vs 2.42 (95%CI, 1.48–3.98); p=0.05), but there was no difference between biallelic carriers of Y179C and G396D (p=0.84) (Supplementary Table 1).

The standard deviation of the polygenic component was estimated to be 1.11 (0.74–1.49, p<0.001); see the Materials and Methods for a general formula relating this standard deviation to the hazard ratio. At ages less than 50y this formula reduces to Pharoah's formula for early-onset disease[7] and says that monoallelic *MUTYH* mutation carriers with an affected first-degree relative have CRC incidences approximately 4.58 (for males) or 4.97 (for females) times the population incidences. However, Supplementary Figure 2 gives precise hazard ratios for all ages and shows that by age 70y, Pharoah's formula over-estimates relative risks by roughly 30%.

DISCUSSION

Our finding of almost complete penetrance for biallelic *MUTYH* mutation carriers is consistent with previous studies.[8–10] There is some evidence that biallelic mutation carriers move rapidly along a mutator phenotype progression to cancer.[11] These findings support the recommendation that biallelic mutation carriers should consider prophylactic total colectomy with ileorectal anastomosis depending on the individual, age of presentation and number and size of polyps present.[12]

We estimated monoallelic mutation carriers had on average, an approximately 2.5-fold increased risk of CRC compared with the general population, consistent with one previous study.[13] This level of increased risk for monoallelic mutation carriers is similar to that for people with a first-degree relative with CRC, who are recommended 5-yearly colonoscopy starting 10y younger than the youngest case in the family and before age 50y.[13] However, monoallelic mutation carriers who have an affected first-degree relative were at approximately 5-fold increased risk. For these carriers, colonoscopy beginning at age 40y, with follow-up at intervals dependent on the presence or absence of polyps but no less often than every 5 years, may be reasonable.

We observed strong evidence that CRC risks for carriers are highly heterogeneous. The observed heterogeneity in risk could also be caused by environmental factors shared between family members or by differences in risk between mutations. To our knowledge, thus far the only study investigating modifiers of CRC risks for *MUTYH* mutation carriers was on the relationship with hormone replacement therapy, which reported no evidence of interaction between hormone replacement therapy and *MUTYH* mutations.[3]

In this study of 12 variants of *MUTYH* mutations, 93% of the *MUTYH* mutations were Y179C and G396D (Supplementary Table 2); consistent with a previous study of Caucasians.[14] We found CRC risk was higher for monoallelic carriers of Y179C than for

G396D; consistent with previous studies.[3, 15] However, given our approach of genotyping for 12 mutations by MS and WAVE followed by confirmatory Sanger sequencing of *MUTYH* in carriers (Materials and Methods), there is the possibility that we missed other pathogenic mutations in *MUTYH* that were not one of the 12 mutations genotyped. Although we identified additional variants from Sanger sequencing, their pathogenicity was considered inconclusive (unclassified variants) and therefore not included in this analysis. Additional *MUTYH* mutations may reside in different ethnic groups however this cohort was predominantly Caucasian.

We used sophisticated statistical techniques to adjust for ascertainment, to account for residual familial aggregation of disease and therefore avoid bias, and to use data for all family members, whether genotyped or not, and therefore maximized statistical power and avoided survival bias.

In conclusion, using the largest international study to date we have produced unbiased estimates of CRC risks for *MUTYH* mutation carriers which are the most precise and reliable currently available. In addition to the confirmed very high risk of CRC to biallelic *MUTYH* mutation carriers, CRC risk for monoallelic mutation carriers depends on family history and can be sufficiently high to warrant consideration of more intensive CRC screening than for the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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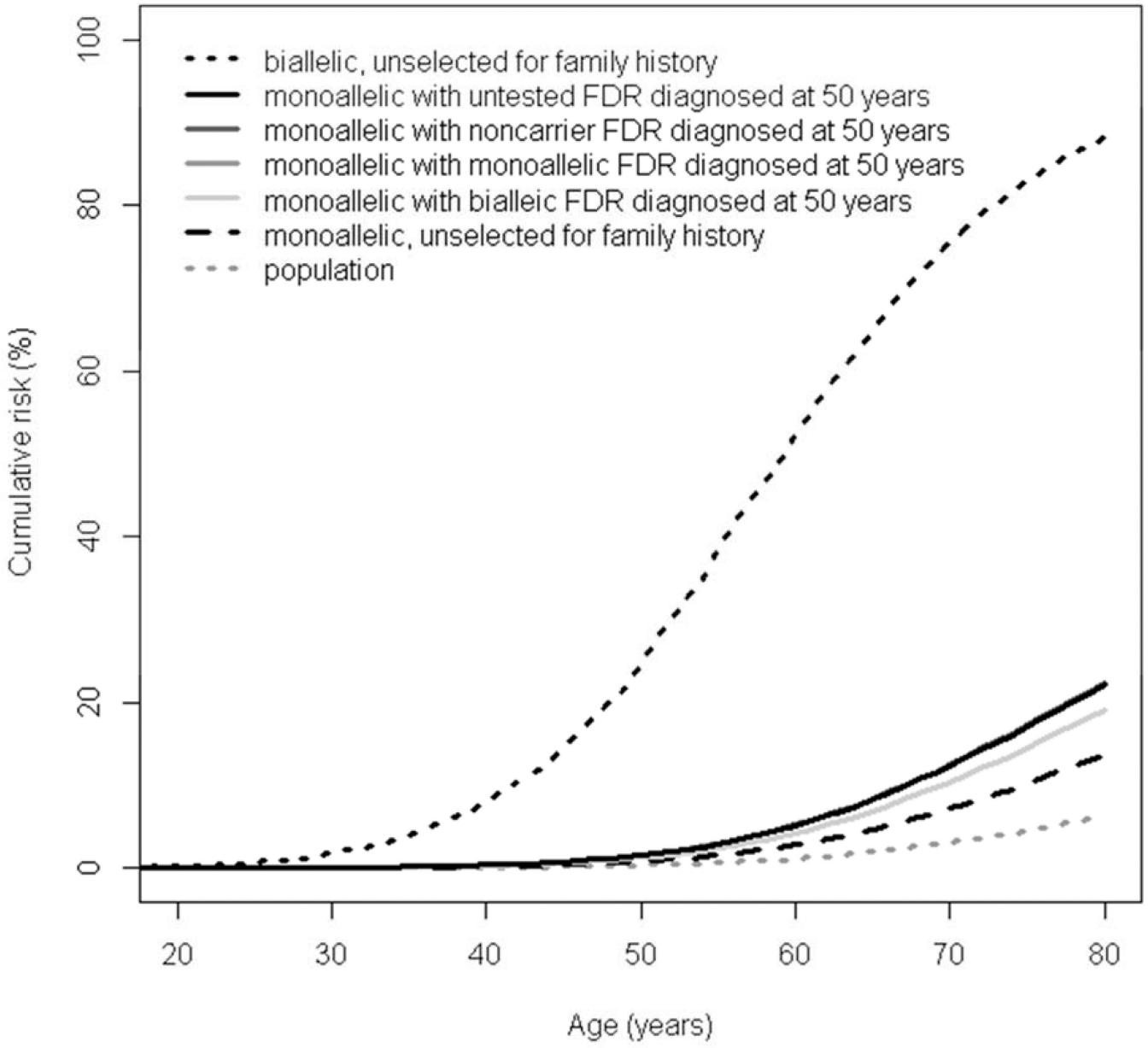

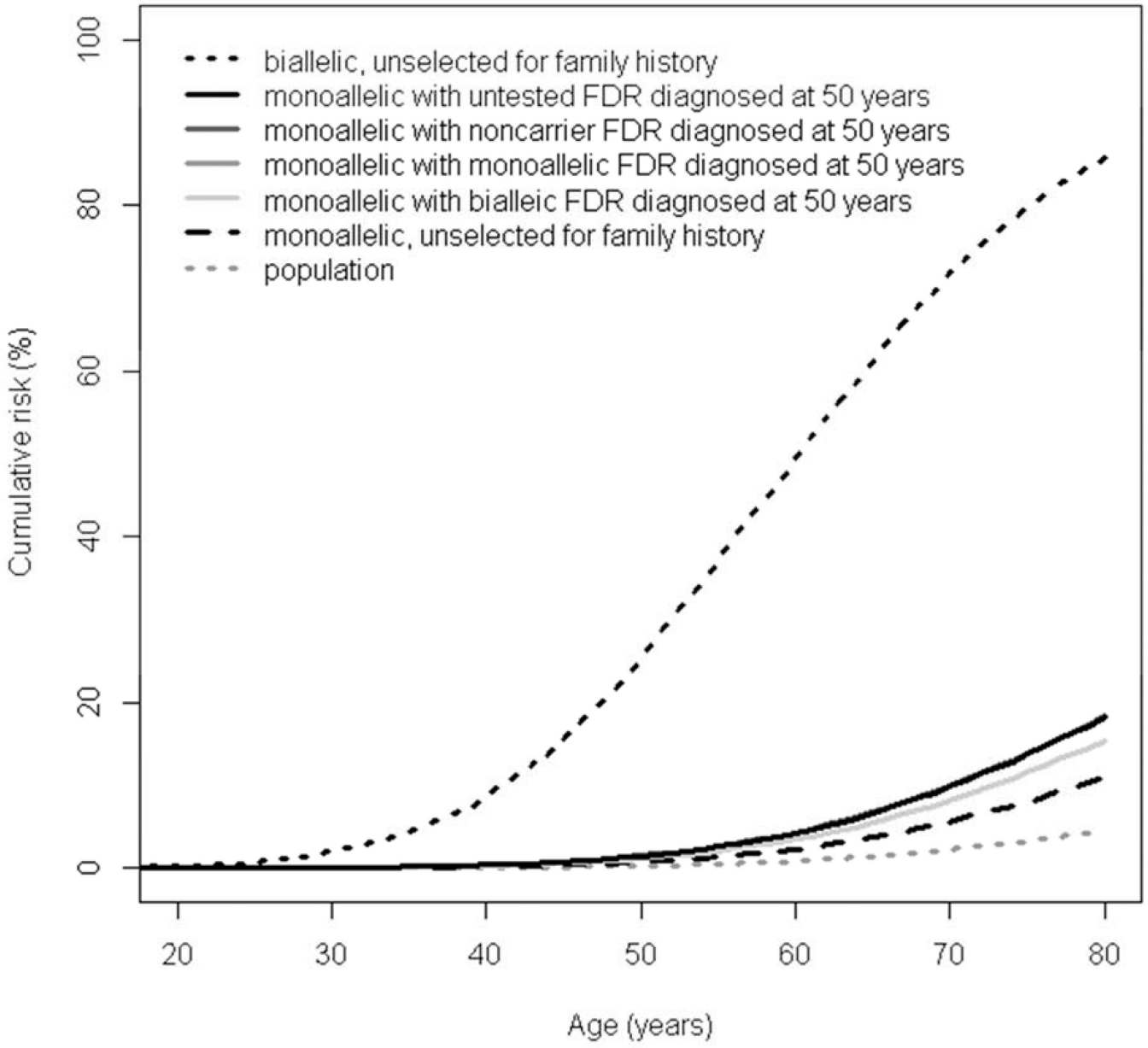

Figure 1.

Cumulative risk of colorectal cancer for (A) male and (B) female *MUTYH* mutation carriers. Note that the risks for a monoallelic carrier with an affected firstdegree relative (FDR) who is either untested, a noncarrier or a monoallelic carrier are virtually identical (see Table 1) so the unbroken, darker grey lines cannot be distinguished in the figure.

Table 1

Cumulative risks (95% confidence intervals) of colorectal cancer for biallelic and monoallelic *MUTYH* mutation carriers

Age (years)	General population	Biallelic mutation carriers irrespective of family history	Monoallelic mutation carriers				
			irrespective of family history	with untested FDR diagnosed at 50 years	with non-carrier FDR diagnosed at 50 years	with monoallelic FDR diagnosed at 50 years	with bialleic FDR diagnosed at 50 years
Male							
30	0.01	1.8 (0.4–6.8)	0 (0–0.1)	0.1 (0.1–0.1)	0.1 (0–0.1)	0.1 (0–0.1)	0.1 (0–0.1)
40	0.07	8.1 (2.1–25.2)	0.2 (0.1–0.3)	0.4 (0.3–0.6)	0.4 (0.2–0.7)	0.4 (0.2–0.6)	0.3 (0.2–0.5)
50	0.3	24.8 (7.7–57.1)	0.8 (0.5–1.3)	1.6 (1.0–2.5)	1.6 (1.0–2.5)	1.6 (1.0–2.5)	1.3 (0.8–1.9)
60	1.1	52.3 (21.8–85.4)	2.8 (1.8–4.5)	5.2 (3.4–7.8)	5.2 (3.4–7.9)	5.2 (3.4–7.7)	4.2 (2.8–6.3)
70	2.9	75.4 (41.2–96.6)	7.2 (4.6–11.3)	12.4 (8.6–17.5)	12.5 (8.6–17.7)	12.4 (8.6–17.4)	10.4 (7.0–15.0)
80	6.2	88.2 (58.4–99.3)	13.6 (8.8–21.1)	22.2 (16–29.8)	22.3 (16.1–30)	22.2 (16.1–29.9)	19.1 (13.2–26.6)
Female							
30	0.01	2 (0.7–5.5)	0 (0–0.1)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.1 (0–0.1)
40	0.06	8.7 (3.1–20.7)	0.2 (0.1–0.3)	0.4 (0.2–0.6)	0.4 (0.2–0.7)	0.4 (0.2–0.6)	0.3 (0.2–0.5)
50	0.3	25.4 (10.8–49.1)	0.8 (0.5–1.2)	1.5 (0.9–2.3)	1.5 (0.9–2.4)	1.5 (0.9–2.4)	1.2 (0.8–1.8)
60	0.8	49.4 (25.3–76.3)	2.3 (1.5–3.7)	4.3 (2.8–6.4)	4.3 (2.8–6.6)	4.3 (2.8–6.5)	3.5 (2.2–5.2)
70	2.1	71.7 (44.5–92.1)	5.6 (3.6–8.8)	9.9 (6.7–14.2)	10 (6.7–14.4)	9.9 (6.7–14.2)	8.2 (5.4–12.0)
80	4.4	85.7 (61.8–97.8)	10.9 (7–16.8)	18.2 (12.8–24.9)	18.3 (12.9–25.2)	18.2 (12.8–25.0)	15.4 (10.4–21.9)

FDR, first-degree relative; CRC, colorectal cancer.