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Cancer risks for monoallelic *MUTYH* mutation carriers with a family history of colorectal cancer

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Abstract

Cancer risks for a person who has inherited a *MUTYH* mutation from only one parent (monoallelic mutation carrier) are uncertain. Using the Colon Cancer Family Registry and Newfoundland Familial Colon Cancer Registry, we identified 2,179 first-and second-degree relatives of 144 incident colorectal cancer (CRC) cases who were monoallelic or biallelic mutation carriers ascertained by sampling population complete cancer registries in the United States, Canada and Australia. Using Cox regression weighted to adjust for sampling on family history, we estimated that the country-, age- and sex-specific standardized incidence ratios (SIRs) for monoallelic mutation carriers, compared to the general population, were: 2.04 (95% confidence interval, CI 1.56–2.70; $p < 0.001$) for CRC, 3.24 (95%CI 2.18–4.98; $p < 0.001$) for gastric cancer, 3.09 (95%CI 1.07–12.25; $p = 0.07$) for liver cancer and 2.33 (95%CI 1.18–5.08; $p = 0.02$) for

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endometrial cancer. Age-specific cumulative risks to age 70 years, estimated using the SIRs and US population incidences, were: for CRC, 6% (95%CI 5–8%) for men and 4% (95%CI 3–6%) for women; for gastric cancer, 2% (95%CI 1–3%) for men and 0.7% (95%CI 0.5–1%) for women; for liver cancer, 1% (95%CI 0.3–3%) for men and 0.3% (95%CI 0.1–1%) for women and for endometrial cancer, 4% (95%CI 2–8%). There was no evidence of increased risks for cancers of the brain, pancreas, kidney, lung, breast or prostate. Monoallelic *MUTYH* mutation carriers with a family history of CRC, such as those identified from screening multiple-case CRC families, are at increased risk of colorectal, gastric, endometrial and possibly liver cancers.

Keywords

monoallelic *MUTYH* mutations; colorectal cancer; extracolonic cancer

The *MutY* human homolog gene, hereafter called *MUTYH*, is a base excision repair (BER) gene that plays a major role in detecting and protecting against oxidative DNA damage. It encodes a glycosylase that removes adenines mispaired opposite 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxoG), one of the most stable products of oxidative DNA damage.[1,2] If this function is lost in a cell due to *MUTYH* mutation of both alleles, there are increased G:C→T:A transversions (a guanine-cytosine pair to a thymine-adenine pair)[2] in other genes including tumor suppressors, which could increase cancer risk.[3] Persons carrying germline mutations in both alleles of *MUTYH* (biallelic mutation), whether they are homozygous (mutations on each allele are identical) or compound heterozygous (mutations on each allele are different), have a substantially increased risk of colorectal cancer (CRC),[4–6] with a cumulative risk of 80% at age 70 years.[4] Germline mutations in a single allele of *MUTYH* (monoallelic mutation) are associated with a small increase of 1.15-fold in CRC risk compared to noncarriers,[7] and a twofold increased risk for carriers who have a family history of CRC.[8]

The risk of cancers other than CRC for monoallelic *MUTYH* mutation carriers is less well understood. Several small studies and case-reports have reported extracolonic tumors in either monoallelic or biallelic carriers of *MUTYH* mutations including gastroduodenal polyps and cancer,[9–14] gastric polyp and cancer,[11,14,15] sebaceous adenomas and sebaceous carcinomas[15–19] and brain tumors, especially meningioma.[20] While some studies reported that *MUTYH* mutations could be associated with increased risk of breast cancer[10,15,21] and endometrial cancer[19,22]; others found no association between *MUTYH* mutations and these malignancies.[23,24] Vogt *et al.*[15] has recently shown that biallelic *MUTYH* mutation carriers who have *MUTYH*-associated polyposis (MAP) are at increased risk of duodenal cancer (standardized incidence ratio, SIR 129; 95% confidence interval, CI 15.7–465.9), ovarian cancer (SIR 5.7; 95%CI 1.2–16.7), bladder cancer (SIR 7.2; 95%CI 2.0–18.4) and skin cancers (SIR 2.8; 95%CI 1.5–4.8) compared to the general population. To our knowledge, the risks of extracolonic cancers for monoallelic mutation carriers have not been established. In this study, we estimated the risks of colorectal and extracolonic cancers for monoallelic *MUTYH* mutation carriers who are relatives of CRC cases.

Material and Methods

Subjects

Subjects were the first- and second-degree relatives of incident CRC cases (probands) recruited from population complete cancer registries by the Colon Cancer Family Registry (Colon CFR) and the Newfoundland Familial Colon Cancer Registry. All probands were excluded from the analysis. Study designs and recruitments for the Colon CFR can be found at http://epi.grants.cancer.gov/CFR/ and have been published previously in detail.[25,26]

Briefly, the Colon CFR recruited probands who were diagnosed with CRC between 1997 and 2007 from population complete cancer registries in the United States (Puget Sound, Washington State; the State of Minnesota; Los Angeles, California; Arizona; Colorado; New Hampshire; North Carolina and Hawaii), Australia (Victoria) and Canada (Ontario). The Newfoundland Familial Colorectal Cancer Registry recruited probands who were diagnosed with CRC between 1999 and 2003 in the Canadian provinces of Newfoundland and Labrador as described in detail by Green *et al.*[27] Attempts were made to recruit the first-degree relatives of probands, and some centers also attempted to recruit second-degree relatives. Written informed consent was obtained from all participants and the study protocols were approved by local institutional research ethics review boards.

Data collection

From 1997 to 2002, baseline information on demographics, personal characteristics, personal and family history of cancer, cancer screening and surgery were obtained from probands and all participating relatives at time of recruitment. From 2002 to 2007, participants were followed-up approximately 5 years after baseline to update demographics, personal characteristics and personal and family history of cancer, cancer screening and surgery. The questionnaires are available at the following URL: https://cfrisc.georgetown.edu/isc/dd.questionnaires.do. The present study was based on all available baseline and follow-up data. Reported cancer diagnoses and age at diagnosis were confirmed, where possible using pathology reports, medical records, cancer registry reports and/or death certificates. The location, histology and behavior of cancer diagnoses were coded and stored using International Classification of Diseases for Oncology, third edition (ICD-O-3).[28] Blood samples and permission to access tumor tissue was requested from participants.

MUTYH mutation testing

All participants who provided a DNA sample were tested for mutations in the *MUTYH* gene. As described in detail by Cleary *et al.*,[5] genomic DNA extracted from each participant was sent to a central testing facility (Analytic Genetics Technology Centre, Toronto, Canada). DNA was screened for 12 previously identified variants of *MUTYH* mutations: Y179C, G396D, Y104X, R274Q, E480X, Q391X, c.1147delC, c.933+ 3A>C, c. 1437_1439delGGA, R241W, c.1228_1229insGG, c.1187-2A→G using the MassArray MALDI-TOF Mass Spectrometry (MS) system (Sequenom, San Diego, CA). Screening for R241W, c.1228_1229insGG and c.1187-2A→G was discontinued when testing of 6,000 samples failed to identify any carriers of these three variants. All samples with MS mobility shifts underwent screening of the entire *MUTYH* coding region, promoter and splice sites regions by denaturing high-performance liquid chromatography (Transgenomic Wave 3500HT System; Transgenomic, Omaha, NE), to confirm the mutation and to identify additional mutations. All MS-detected variants and WAVE mobility shifts were submitted for sequencing for mutation confirmation (ABI PRISM 3130XL Genetic Analyser). The names of *MUTYH* variants were provided in our article using the nomenclature according to the Leiden Open Variation Database version 2.[29]

Statistical analysis

For participants who did not provide a DNA sample for *MUTYH* mutation testing, the probabilities of being a mono-allelic mutation carrier and a biallelic mutation carrier were estimated based on their genetic relationship to the probands and to any other genotyped relatives and the assumptions of Mendelian inheritance with a population allele frequency of 0.0085 for all mutations in *MUTYH* combined.[7] The total number of carriers was estimated by summing the number of known carriers and the carrier probabilities of the ungenotyped

relatives. These calculations were performed using R 2.7.2[30] and a modified version of Mendel 3.2.[31]

SIRs for monoallelic mutation carriers were estimated for the following cancers: colorectal (ICD-O-3 C18-20), gastric (ICD-O-3 C16), liver (ICD-O-3 C22), pancreatic (ICD-O-3 C25), brain (ICD-O-3 C71), kidney (ICD-O-3 C64-65) and lung (ICD-O-3 C34) cancer for both sexes; endometrial (ICD-O-3 C54-55) and breast (ICD-O-3 C50) cancer for women and prostate cancer (ICD-O-3 C61) for men.

SIRs for different cancers were calculated by dividing the observed numbers of cancers by the expected numbers for estimated total monoallelic mutation carriers. The observed numbers of cancers were calculated by multiplying the numbers of observed cancers for subjects by their probabilities of being a monoallelic carrier. The expected numbers of cancers were calculated by multiplying the age-, sex- and country-specific incidence for the general population by the corresponding observation time (person-years) in the study cohort. Age- and sex-specific cancer incidences in 1988–1992 for each country (Australia, Canada and the United States) were obtained from Cancer Incidence in Five Continents.[32] The period of 1988–1992 was selected for analysis because it was the closest available dataset to the mean calendar year of cancer diagnoses in the sample.

Observation time for each subject started at birth and ended at the age at first diagnosis of cancer or last known age or age of death, whichever occurred first. For CRC, we censored each subject at the age of polypectomy (except when it occurred within a year of the diagnosis of CRC) and, for endometrial cancer, we censored each woman at the age of hysterectomy (except when it occurred within a year of the diagnosis of endometrial cancer). Where age at diagnosis of cancer was not reported (20% of all cancer cases), we assumed the age of diagnosis to be 1 year prior to the last known age or, if last known age was not available, the median age at diagnosis of specific cancer for the general population obtained from SEER Cancer Statistics Review (1975–2000).[33]

To account for stratified sampling based on family history, we gave each subject a weight equal to the reciprocal of the family sampling fractions used by each study center. Given all subjects in this study were the first- or second-degree relatives of a proband who was diagnosed with CRC from population complete cancer registries, our risk estimates would be applicable to “monoallelic mutation carriers with a family history of CRC” from the general population.

In our study, we excluded subjects from the analyses who had an estimated probability of being a biallelic mutation carrier of 1% or more to avoid the effect of biallelic mutation on the estimation of cancer risks for monoallelic mutation carriers. As a sensitivity analysis, we compared these SIRs with that for subjects who did not have any biallelic mutation carrier probability *i.e.*, zero probability of being a biallelic mutation carrier. Robust estimates of variance were calculated using the *cluster* subcommand, applied to an identifier variable unique to each family. All reported statistical tests were two-sided and $p < 0.05$ was considered statistically significant. All these statistical analyses were done using Stata 10.0.[34]

Estimated cumulative risks (penetrance) of cancers to age 70 years and their 95%CIs for monoallelic mutation carriers for each sex were calculated by summing over sex-specific incidences incidence_i at age i multiplied by the estimated SIR, based on the population incidences of the United States, using the formula:

$$1 - e^{-\sum_{i=0}^{age} SIR \cdot incidence_i}$$

Results

In total 2,396 subjects (first- and second-degree relatives of probands) were identified from 152 families carrying monoallelic or biallelic *MUTYH* mutations. Of these, we excluded 62 subjects with ≥1% probability of being a biallelic mutation carrier and 155 subjects from eight families because these families were known to segregate a mutation in a mismatch repair (MMR) gene. The remaining 2,179 subjects from 144 families were included in the analyses. Definitive mutation status was known for 131 subjects (80 monoallelic mutation carriers and 51 noncarriers). We estimated there were 772 monoallelic mutation carriers among untested subjects, giving a total estimated number of 852 in our sample. Of these, 404 from 67 families were recruited from Canada, 275 from 56 families from the United States and 173 from 21 families from Australia (Table 1). We estimated there were five biallelic mutation carriers among ungenotyped relatives. Of all reported cancers, 30% were confirmed by pathology report, hospital record, death certificate or cancer registry.

Table 2 shows that among monoallelic mutation carriers with less than 1% probability of being a biallelic mutation carrier, there were: 10 CRCs (SIRs 2.04; 95%CI 1.56–2.70; $p < 0.001$), three gastric cancers (SIR 3.24; 95%CI 2.18–4.98; $p < 0.001$), one liver cancer (SIR 3.09; 95%CI 1.07–12.25; $p = 0.07$) and three endometrial cancers (SIR 2.33; 95%CI 1.18–5.08; $p = 0.02$). There was no statistically significant evidence of increased risks for cancers of the brain, pancreas, kidney, lung, breast or prostate.

When we restricted to the subjects with zero probability of being a biallelic mutation carrier, the estimated total number of monoallelic mutation carriers was 142. The SIRs were: 2.31 (95%CI 1.33–4.22) for CRC, 3.54 (95%CI 1.35–12.18) for gastric cancer and 1.64 (95%CI 0.27–25.46) for endometrial cancer.

Table 3 shows the estimated cumulative risks (penetrance) of different cancers for monoallelic mutation carriers. The estimated cumulative risks to age 70 years were: for CRC, 6% (95%CI 5–8%) for men and 4% (95%CI 3–6%) for women; for gastric cancer, 2% (95%CI 1–3%) for men and 0.7% (95%CI 0.5–1%) for women; for liver cancer, 1% (95%CI 0.3–3%) for men and 0.3% (95%CI 0.1–1%) for women and for endometrial cancer, 4% (95%CI 2–8%).

Discussion

We have assembled the largest series of monoallelic *MUTYH* mutation carriers to date and estimated cancer risks using information from the family data, based on the laws of Mendelian inheritance, known mutation carrier status and the family pedigrees. We have shown that monoallelic *MUTYH* mutation carriers with a family history of CRC have increased risks of colorectal, gastric, endometrial and possibly liver cancers. These observed risks were unlikely to be due to biallelic mutations because we estimated that there were only five biallelic mutation carriers in the whole sample. In the analysis of subjects who had zero probability of being a biallelic mutation carrier, the SIRs did not change much from that from analysis of subjects who had less than 1% probability of being a biallelic mutation carrier.

We observed that monoallelic mutation carriers with a family history of CRC had a twofold increased risk of CRC compared to the general population. A kin-cohort study[4] of the

relatives of *MUTYH* mutation carriers reported that monoallelic mutation carriers who had a family history of CRC were at increased risk of CRC with a hazard ratio of 2.9 (95%CI 1.2–7.0; $p = 0.02$). A retrospective cohort analysis[8] of obligate carriers of monoallelic mutations, being the parents of biallelic carriers, also estimated monoallelic mutation carriers had twice the CRC risk of general population (SIR 2.12; 95%CI 1.30–3.28; $p < 0.01$). Therefore, our estimates are consistent with those from the other studies.

The increased CRC risk for monoallelic mutation carriers in the *MUTYH* gene is consistent with dominant or co-dominant effects of mutations in other DNA repair genes. The mechanism of this risk is not clear but may occur through reduced efficiency of the BER system, alterations of protein–protein interactions or through loss of the wild-type allele in a classic tumor suppressor model (Knudson PNAS 1971). This latter hypothesis is supported by the observed loss of heterozygosity of the 1p region in CRC[35–37] and other cancers.[38–41] In addition to the colon, the *MUTYH* gene is expressed in several tissues including brain, stomach, pancreas, lung, kidney, prostate and endometrium (http://www.ncbi.nlm.nih.gov/IEB/Research/Acembly/av.cgi?c=geneid&org=9606&l=4595). Given these observations, combined with the fact that oxidative damage and the generation of 8-oxoG occurs in a multitude of tissues,[42] one would expect that inherited mutations in the *MUTYH* gene may predispose carriers to the development of other malignancies in addition to the recognized increased risk in CRC.

Several studies have reported upper gastrointestinal tumors including duodenal polyps,[9–11,13,15] duodenal cancer,[12,13,15] gastric polyps[11,15] and gastric cancer[14,15] among carriers of monoallelic or biallelic *MUTYH* mutations. In our study, we found a threefold increased risk of gastric cancers for monoallelic mutation carriers with a family history of CRC compared to the general population. Vogt *et al.*[15] estimated the risk of gastric cancer for biallelic mutation carriers to be SIR of 4.2 (95%CI 0.9–12.3). These two estimates are not inconsistent with each other ($p = 0.7$). Vogt *et al.*[15] also reported an increased risk of duodenal cancer for biallelic mutation carriers with MAP. In this study, we found only one small intestinal cancer (ICD-O-3 C17.9) diagnosed at age 52 years in a female subject who had a probability of 0.5 of being a monoallelic mutation carrier. Data on benign gastro-duodenal tumors were not collected by the Colon CFR.

Two clinical studies[19,22] reported patients with a diagnosis of endometrial cancer and biallelic *MUTYH* mutations, and suggested biallelic germline mutations may increase susceptibility to endometrial cancer. Vogt *et al.*[15] did not find statistical evidence of an increased incidence of endometrial cancers for biallelic mutation carriers with MAP (SIR 4.6; 95%CI 0.6–16.5). In our study, we found a twofold increased incidence of endometrial cancer for monoallelic mutation carriers with a family history of CRC. These two estimates are not inconsistent with each other ($p = 0.5$).

We observed a marginal evidence of an increased risk of liver cancer for monoallelic mutation carriers with a family history of CRC. We present this result with a great caution; only one liver cancer case was observed, the confidence interval is wide, and it is possible this was a secondary spread given the liver is a common site for metastasis from another primary cancer. We included only liver cancer cases without another reported cancer in this analysis but we acknowledge that there is still a chance of secondary deposit in liver.

In our study, we did not observe statistically significant evidence of an increased risk of breast cancer for female carriers compared to the general population (SIR 1.27; 95%CI 0.84–1.99; $p = 0.28$). This is consistent with the results of Beiner *et al.*[24] who also did not observe an association between breast cancer and monoallelic mutation of either Y179C (OR 1.1; 95%CI 0.29–4.0; $p = 0.9$) or G396D (OR 1.2; 95%CI 0.44–3.3; $p = 0.7$). However,

Wasielewski *et al.*[21] concluded that the frequency of monoallelic mutation carriers was increased in families with excess breast and colorectal cancer cases.

Considering other extracolonic cancer risks for *MUTYH* mutation carriers, we did not observe statistically significant evidence of an increased risk for cancers of the brain, pancreas, kidney, prostate and lung for monoallelic mutation carriers with a family history of CRC. Consistent with our results, Shin *et al.*[43] and Agalliu *et al.*[44] found that *MUTYH* mutations were unlikely to contribute to prostate cancer risk, and Al-Tassan *et al.*[45] and Vogt *et al.*[15] found *MUTYH* mutations were unlikely to contribute to lung cancer risk.

Several studies[15–19] reported cutaneous tumors including various types of benign tumors (pilomatricomas, sebaceous adenomas, epitheliomas, lipoma) and malignant tumors (melanomas, squamous cell carcinomas, basal cell carcinomas, sebaceous carcinomas) among monoallelic and biallelic *MUTYH* mutation carriers. They also suggested this is similar to Muir-Torre syndrome in which sebaceous gland tumors are present in association with visceral malignancies. We do not have enough information to estimate the skin cancer risk for monoallelic mutation carriers in our study.

Our study showed increased risks of colorectal, gastric and endometrial cancers for monoallelic *MUTYH* mutation carriers with a family history of CRC. The magnitudes of these increased risks are far less than these occurring in Lynch Syndrome caused by germline mutations in MMR genes. However, the occurrence of Lynch Syndrome associated tumors in *MUTYH* mutation carriers is consistent with the possible existence of a common pathway between BER and MMR systems in the DNA repair. We note that MMR mutation carrying families were excluded from this study. Some studies[46,47] also described physiological and functional cooperation between these two systems in reducing replicative error of DNA due to oxidative bases particularly for the *MSH2* and *MSH6* genes (MutSα homolog).

This study was based on, to our knowledge, the largest sample of monoallelic *MUTYH* mutation carriers to date used to investigate the risks of colorectal and extracolonic cancers for monoallelic mutation carriers of *MUTYH*. The estimation of carrier probability was based on confirmed carriers tested not only for the two most common (in Caucasian populations) *MUTYH* mutations, namely Y179C and G396D but also for the nine most frequent known mutations. Using carrier probabilities helps to avoid survival bias because deceased cases unable to provide a blood sample for testing are still represented. Our application of weights to each subject depending on the different sampling strategies will minimize any selection bias due to sampling based on family history. We accounted for familial correlation in the risk of cancer using a robust variance correction to derive appropriate measure of estimate imprecision.

The study has some limitations. The presence of unverified cancers, unaccounted for time and geographic variation, and the use of carrier probabilities rather than actual tests for mutation status, might increase the imprecision of SIR estimates more than is given by the current confidence intervals, whose width reflects the small numbers of cancer cases.

We have shown that carriers of a monoallelic mutation in *MUTYH*, who are relatives of CRC cases also found to carry a *MUTYH* mutation, are at approximately twice the population risk cancer of CRC and endometrial cancer and three times the population risk of gastric and liver cancer. Commonly, *MUTYH* genetic testing is conducted only for the relatives of biallelic mutation carriers to try to identify other biallelic mutation carriers given their high risk of colorectal polyps and cancer. Our data support expanding *MUTYH* genetic testing to relatives of CRC cases found to have a monoallelic mutation in *MUTYH* so that

unaffected monoallelic mutation carriers can be identified, as these carriers could benefit from surveillance to reduce their increased risk of some cancers.

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Abbreviations

BER	base excision repair
CI	confidence interval
Colon CFR	Colon Cancer Family Registry
CRC	colorectal cancer
MAP	*MUTYH* associated polyposis
MUTYH	the *MutY* human homologue
SIR	standardized incidence ratio

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Table 1

Number of families, relatives and monoallelic *MUTYH* mutation carriers in the study

Country	Number of families	Number of relatives[1]	Estimated number of monoallelic *MUTYH* mutation carriers[2]
Canada	67	946	404
USA	56	778	275
Australia	21	455	173
Total	144	2,179	852

[1] Total number of first- and second-degree relatives (probands were excluded).

[2] Total number of monoallelic *MUTYH* mutation carriers in each family was estimated by summing the number of known carriers and the carrier probabilities of the ungenotyped relatives.

Table 2

Standardized incidence ratios (SIRs) for carriers of monoallelic *MUTYH* mutations compared to the general population for cancers by sex

	Median age of diagnosis, year (min–max)	Observed number[1]	Expected number	SIR (95%CI)[2]	*p*
Both sexes					
Colorectal cancer	67 (24–89)	10	4.93	2.04 (1.56–2.70)	<0.001
Gastric cancer	71 (48–85)	3	0.85	3.24 (2.18–4.98)	<0.001
Liver cancer	62 (30–83)	1	0.24	3.09 (1.07–12.25)	0.07
Pancreatic cancer	65 (52–83)	1	0.90	0.91 (0.34–3.25)	0.87
Brain cancer	54 (35–84)	1	0.74	1.66 (0.66–5.45)	0.35
Renal cancer	65 (46–76)	1	0.82	0.91 (0.36–2.97)	0.86
Lung cancer	70 (26–82)	4	5.57	0.71 (0.44–1.21)	0.18
Female					
Endometrial cancer	60 (19–85)	3	1.09	2.33 (1.18–5.08)	0.02
Breast cancer	62 (35–83)	7	5.63	1.27 (0.84–1.99)	0.28
Male					
Prostate cancer	69 (39–87)	3	4.17	0.69 (0.46–1.06)	0.08

[1]Observed number of cancers for monoallelic mutation carriers were calculated by multiplying the numbers of cancers by the probabilities of being a monoallelic carrier. Numbers were rounded to no decimal place.

[2]Confidence interval based on with robust variance correction for familial correlation in risk

Table 3

Cumulative risks of colorectal, gastric, liver and endometrial cancer to age 70 years for carriers of monoallelic *MUTYH* mutations

	Cumulative Risk % (95%CI)
CRC	
Male	6.39 (4.92–8.36)
Female	4.42 (3.40–5.81)
Gastric cancer	
Male	1.81 (1.22–2.77)
Female	0.69 (0.47–1.06)
Liver cancer	
Male	0.75 (0.26–2.96)
Female	0.27 (0.09–1.08)
Endometrial cancer	3.94 (2.01–8.38)