

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

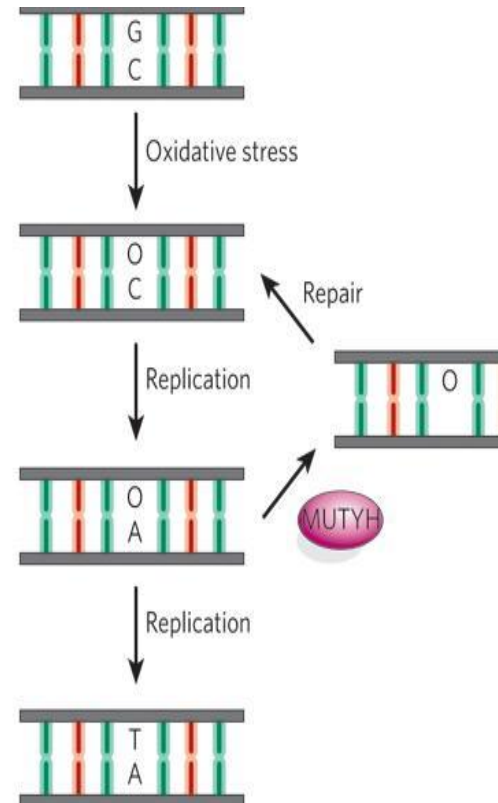
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# What is *MUTYH*?

- The *MutY* human homologue (*MUTYH*, a.k.a *MYH*) is a base excision repair gene.
- Failure to correct mismatches in tumor suppressor genes can lead to cancers
- People with germline defect of *MUTYH* are at increased risk of cancer
- Which cancers?



# Biallelic and monoallelic mutation carriers

Biallelic – mutations inherited from both parents

- Homozygous or compound heterozygous
- ~1 in 3000 of population

Monoallelic – one mutation inherited from one parent

- Heterozygous
- ~1 in 60 of population

# Cancer risks for biallelic carriers

## Colorectal cancer

Cumulative risk to age 70 years of 80%

Jenkins et al. 2006

## Extracolonic cancers

Site	SIR (95% CI)	Risk (%) to age 75 yrs
Duodenum	129 (16–470)	4 (0-9)
Ovary	5.7 (1.2–17)	10 (0-22)
Bladder	7.2 (2.0–18)	6 (0-12)
Skin	2.8 (1.5–5)	17 (4-29)

Vogt et al. 2009

# Cancer risks for monoallelic carriers

## Colorectal cancer

1.15-fold increased risk for carriers

Meta-analyses of Win et al. 2010, Theodoratou et al. 2010

2-fold increased risk for carriers with a family history of CRC

Jones et al. 2009

## Extracolonic cancers

Unknown

A few published clinical studies and case reports of monoallelic carriers with duodenal, skin and endometrial cancers

# Aim of this study

To estimate cancer risks for monoallelic *MUTYH* carriers  
who are relatives of a CRC case

...

because this is the clinical setting in which *MUTYH*  
carriers are likely to be identified

...

and these families might be enriched for other cancer  
predisposing genes

# Population-based families

First- and second-degree relatives of incident CRC cases (probands) recruited from population complete cancer registries

## Colon Cancer Family Registry

Cancer registries in

- USA (Seattle; Minnesota; Los Angeles; Arizona; Colorado; New Hampshire; North Carolina and Hawaii)
- Australia (Victoria)
- Canada (Ontario)

## Newfoundland Familial Colorectal Cancer Registry

Cancer registries in

- Newfoundland and Labrador

# Data Collection and Mutation Testing

- Baseline questionnaire including personal and family history of cancer, screening history and surgery history was obtained from probands and participating relatives
- Reported cancers and ages at diagnosis were confirmed, where possible, using pathology reports, medical records, cancer registry reports and/or death certificates
- Blood samples were requested from participants.
- All available DNA tested for *MUTYH* mutations:

Y179C	G396D	Y104X
R274Q	E480X	Q391X
c.1147delC	c.933+3A>C	c.1437_1439delGGA

# Mutation carrier probability

For participants who did not provide a DNA sample, we estimated their probability of being monoallelic and biallelic carrier, based on:

- genetic relationship to other genotyped relatives
  - Mendelian inheritance
  - population allele frequency of 0.85%
- The total number of carriers was estimated by summing the number of known carriers of the genotyped relatives and the carrier probabilities of ungenotyped relatives
  - Calculations performed using a modified version of MENDEL 3.2

# Statistical Analysis (1)

- Standardised Incidence Ratio (SIR) for each cancer were calculated from Observed/Expected number of cancers
- Expected number of cancers based on age-, sex- and country-specific incidence (Cancer Incidence in Five Continents)
- Censored observation time at the
  - age of polypectomy,
  - age of hysterectomy
- To account for familial correlation, we used robust estimates of variance
- Cumulative cancer risks (penetrance) to age 70 yrs calculated based on US population incidences

# Results (1)

- Identified 152 mutation carrying families
- Excluded
  - 8 families – mutation in a mismatch repair gene
  - 144 probands
  - 62 relatives with  $\geq 1\%$  chance of being biallelic (confirmed biallelic carriers = 4)

## Monoallelic carriers

Country	Number of families	Number of relatives	Estimated number of monoallelic <i>MUTYH</i> mutation carriers
Canada	67	946	404
USA	56	778	275
Australia	21	455	173
Total	144	2,179	852

# Results (2)

Cancer-specific standardised incidence ratios (SIRs) for monoallelic *MUTYH* mutation carriers

	Median age of diagnosis, year (min–max)	Observed number	Expected number	SIR (95%CI)	<i>P</i>
Both sexes					
<b>Colorectal cancer</b>	<b>67 (24–89)</b>	<b>10</b>	<b>4.93</b>	<b>2.04 (1.56–2.70)</b>	<b>&lt;0.001</b>
<b>Gastric cancer</b>	<b>71 (48–85)</b>	<b>3</b>	<b>0.85</b>	<b>3.24 (2.18–4.98)</b>	<b>&lt;0.001</b>
<b>Liver cancer</b>	<b>62 (30–83)</b>	<b>1</b>	<b>0.24</b>	<b>3.09 (1.07–12.25)</b>	<b>0.07</b>
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					
<b>Endometrial cancer</b>	<b>60 (19–85)</b>	<b>3</b>	<b>1.09</b>	<b>2.33 (1.18–5.08)</b>	<b>0.02</b>
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

# Results (3)

Cumulative cancer risks to age 70 yrs (%) for monoallelic *MUTYH* mutation carriers

	Carriers of monoallelic <i>MUTYH</i> mutations	USA general population (Reference)
CRC		
male	6% (5–8%)	3%
female	4% (3–6%)	2%
Gastric cancer		
male	2% (1–3%)	0.6%
female	1% (0.5–1%)	0.2%
Liver		
male	1% (0.3–3%)	0.2%
female	0.3% (0.1–1%)	0.1%
Endometrial cancer	4% (2–8%)	2%

# Strengths

- Largest sample of monoallelic carriers to date
- Genetic testing was conducted for the nine most common mutations
- Used all genotyped and non-genotyped individuals
- Estimates are relevant to typical carriers identified in a clinical setting through genetic screening of multiple-case CRC families

# Limitations

- Needed to use carrier probabilities for a large proportion of relatives
- Large proportion of cancers in relatives could not be verified
- Estimates were imprecise due to small numbers of cases

# Summary

- Monoallelic *MUTYH* mutation carriers who are relatives of CRC cases are at:
  - ~2-times population risk of CRC & endometrial cancer
  - ~3-times population risk of gastric & liver cancers
- These risk estimates are relevant to carriers identified by family cancer clinics
- Our data might support expanding the testing to relatives of CRC cases found to have a monoallelic *MUTYH* mutation
  - unaffected monoallelic carriers can be identified who might benefit from surveillance for CRC and some other cancers

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