Gastric Cancer Risk Estimates in Hereditary Cancer Syndromes: A Systematic Review

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INTRODUCTION

- Approximately 10% of gastric cancers result from monogenic germline predisposition
- The aim of this study was to determine gastric cancer risk in specific hereditary cancer syndromes

METHODS

- A systematic literature review was conducted using the GRADE methodology
- A literature search was conducted in MEDLINE (PubMed), Embase, and Cochrane from June 2016 through November 2021
- Inclusion criteria were articles that detailed gastric cancer risk estimates in patients with Hereditary Diffuse Gastric Cancer (HDGC) (*CDH1* mutation), Lynch Syndrome (LS) (*MLH1*, *MSH2*, *PMS2, MSH6* mutations), FAP, (*APC* mutation) and germline mutations in *BRCA 1, BRCA 2, CTNNA1, MUTYH, SMAD4, BMPR1A, TP53, STK11, ATM, PALB2*, and *PRSS1*
- Two reviewers independently evaluated titles and abstracts for relevance and obtained text of potentially eligible articles, and determined final eligibility after full text review
- Data was reported qualitatively given heterogeneity in available literature that precluded quantitative comparison
- Cancer risks were presented as cumulative risk, relative risk (RR), or a hazard ratio (HR)

Table 1. Gastric Cancer Risk Estimates Across Hereditary Cancer Syndromes

Genetic Mutation/Syndrome	Type of Risk Estimate	Risk Estimate	Number of Studies
HDGC	Cumulative Risk	37.2% – 70.0% (men) 24.7%-63% (women)	4
ATM	RR	3.39 (95% CI, 0.86-13.4)	1
BRCA1/2	RR	2.4-6.9	3
MUTYH	HR	9.3 (95% CI, 6.7-13)	1
LS	Cumulative Risk	14.5-38.7	3
FAP	Cumulative Risk	3.8% (95% CI, 1.2-11.5)	1
LFS	Cumulative Incidence	3.3%	1
PJS	RR	50.2 (95% CI, 22.4-112.5)	1

RR, relative risk, HR, hazard ratio, HDGC, hereditary diffuse gastric cancer, LS, Lynch Syndrome, FAP, familial adenomatous polyposis, LFS, Li-Fraumeni Syndrome, PJS, Peutz-Jeghers Syndrome

*Across all LS mutations, not by individual mutation

RESULTS

- The literature search revealed 2,494 observational studies, of which 27 met inclusion criteria for full-text abstraction
- No articles met inclusion criteria for *PMS2, CTNNA1, SMAD4, BMPR1A, PTEN, TP53, STK11, PRSS1* or *PALB2*
- HDGC cumulative incidence in men by age 70 ranged from 37.2% to 70.0%, while ranges for women were uniformly lower, ranging from 24.7% to 63%
- *ATM* RR 3.39, although not significant
- *BRCA1/2* RR 2.4-6.9
- LS cumulative risk 14.5-38.7
- MUTYH carriers RR 9.3
- LFS cumulative incidence 3.3%
- PJS RR 50.2

CONCLUSIONS

- All studies were deemed low quality
- In HDGC carriers, GC cumulative risk is lower in men than women
- Among individuals with LS, cumulative risk varied widely with a peak lifetime risk estimate of 14.7%-38.7%
- Low quality data reveal increased gastric cancer risk *BRCA 1/2, MUTYH* and *ATM* mutation carriers.
- Prospective large population-based cohort studies are needed in order to accurately determine the gastric cancer risk in hereditary cancer syndromes