Abstract Preview

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Cancer risks are elevated among relatives of *MRE11A, RAD50* and *NBN* mutation carriers but similar to mutation-negative families in a laboratory-based cohort

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BACKGROUND: Genes for which cancer risks are not well characterized are included on clinical next-generation sequencing-based multi-gene panel tests (MGPT), including *MRE11A*, *RAD50*, and *NBN* (MRN). The protein products of these genes form the MRN complex and play an integral role in meiotic recombination and telomere maintenance. We aimed to further characterize cancer risks of MRN mutation carriers (MRN+) through family history analysis.

METHODS: MRN+ were identified through hereditary cancer MGPT at a commercial laboratory. Complete family cancer histories were obtained from ordering clinicians as approved in an IRB reviewed protocol (n=180). Standardized Incidence Ratios (SIRs) relative to population incidences of breast, ovarian and other cancers were calculated for relatives of MRN+. A comparison cohort consisted of 180 families with a proband negative for MRN mutations (MRN–).

RESULTS: Among 6277 relatives of MRN+, SIRs were greater than two times the population risk for breast, ovarian, pancreatic, gastric cancer and melanoma when MRN complex genes were combined (Table 1). However, similar risks were also observed for relatives of MRN– compared to the general population (Table 1). SIRs for ovarian, gastric and pancreatic cancers trended higher for relatives of MRN+ compared to MRN–, but were not statistically significant.

CONCLUSIONS: Relatives of MRN+ have substantially elevated cancer risks compared to the general population; however, these risks are similarly increased among relatives of MRN–, likely reflecting an ascertainment bias in this laboratory cohort. As such, we are unable to determine whether the increased risks in relatives of MRN+ are attributable to the MRN mutation or other factors increasing familial risk. Future studies should investigate cancer risks among relatives of unselected MRN+.

Table 1. SIRs in relatives by mutation carrier status of index proband*

	MRE11A+	RAD50+	NBN+	MRN+	MRN-
Cancer	SIR (95% CI)	SIR (95% CI)	SIR (95% CI)	SIR (95% CI)	SIR (95% CI)
Breast	**3.8 (3.0-4.8)**	**3.5 (3.0-4.1)**	**4.6 (3.9-5.4)**	**3.9 (3.6-4.3)**	**3.8 (3.4-4.2)**
Ovarian	**6.1 (3.1-10.5)**	**6.9 (4.8-9.6)**	**7.6 (4.9-11.3)**	**6.9 (5.4-8.8)**	**4.8 (3.5-6.4)**
Colon	1.5 (0.9-2.4)	1.1 (0.8-1.6)	**2.8 (2.1-3.6)**	**1.7 (1.4-2.1)**	**1.8 (1.5-2.2)**
Gastric	2.7 (0.9-6.3)	**4.6 (2.9-6.9)**	**3.7 (1.9-6.5)**	**4.0 (2.8-5.4)**	**2.7 (1.7-4.0)**
Melanoma	1.7 (0.8-3.2)	**1.8 (1.2-2.6)**	1.1 (0.5-1.9)	**1.6 (1.1-2.0)**	1.0 (0.7-1.5)
Pancreatic	**3.8 (2.0-6.7)**	**2.2 (1.3-3.4)**	**2.6 (1.4-4.4)**	**2.6 (1.9-3.5)**	**1.7 (1.1-2.4)**

* CI: confidence interval; bold type: CI does not include 1

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