Cancer Risks among Relatives of *MRE11A*, *NBN* and *RAD50* Mutation Carriers

Nicolette M. Chun[1], Dajun Qian[4], Shuwei Li[4], Virginia Speare[4], Holly LaDuca[4], Hsiao-Mei Lu[4], and Allison W. Kurian[2,3]

[1]Stanford University Medical Center, Stanford, CA; [2]Departments of Medicine and [3]Health Research and Policy, Stanford University School of Medicine, Stanford, CA
[4]Ambry Genetics, Aliso Viejo, CA

Abstract

Background: Next generation sequencing (NGS) technology has greatly expanded options for hereditary cancer risk testing. Timely analysis of families that test positive for mutations in suspected lower risk genes will define their value and assist in formulating reasonable screening recommendations. The MRN complex is composed of three bound proteins (MRE11, RAD50, NBS1), working cooperatively to participate in meiotic recombination, cell cycle checkpoints and telomere maintenance (Williams, 2010). MRN activates the DNA Damage Response (DDR) even in pre-invasive cells. There is evidence that disruption of one member of the complex impacts stability of the other two.

Methods: We have undertaken a pilot study, utilizing retrospective pedigree analysis of N=180 families in which the proband had a mutation in one of the MRN genes (*MRE11A*, *RAD50*, *NBN*) detected through multigene panel testing at Ambry Genetics; looking for evidence of hereditary cancer risk. (Table 1) We include a control cohort of N=180 probands with mutation negative panel testing through Ambry Genetics as well as SEER data.

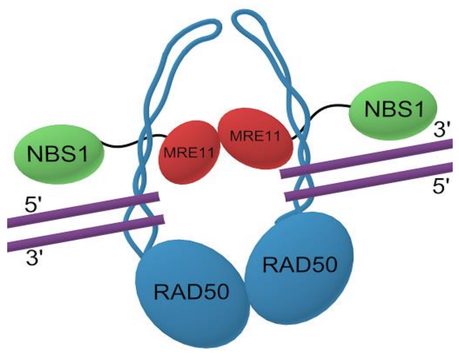
Results: Pedigree analysis of the 180 MRN proband mutation positive families yielded a study cohort of 6277 including 1108 first degree (17.7%), 2768 second degree (44.1%) and 2227 third degree (35.5%) relatives with 174 (2.8%) of unspecified degree of relation. Standardized Incidence Ratios (SIR) relative to population incidence (SEER) were significantly elevated for close and more distant relatives for breast, ovarian and pancreatic cancers across all three mutation types. A cohort of 180 mutation negative probands was then analyzed. SIRs for relatives were elevated for breast, ovarian, pancreatic and gastric cancers in this control cohort.

Conclusion: SIRs were not significantly increased for relatives of MRN carriers vs. MRN-negative probands, but both sets were significant for breast, ovarian, pancreatic, gastric and colon cancers compared to population incidences. We expect this is a reflection of the biased ascertainment in cancer incidence for individuals who proceed with hereditary cancer panel testing. There was a notable trend to higher SIRs for ovarian, gastric and pancreatic in MRN families.

Background & Study Objectives

- Together, the MRN complex proteins (Fig. 1) activate the DNA Damage Response. Their dysfunction is thought to increase cancer risk.
- Here, we aim to quantify cancer risks in MRN mutation carriers (MRN+) by comparing cancer incidences among MRN mutation positive families to SEER data.

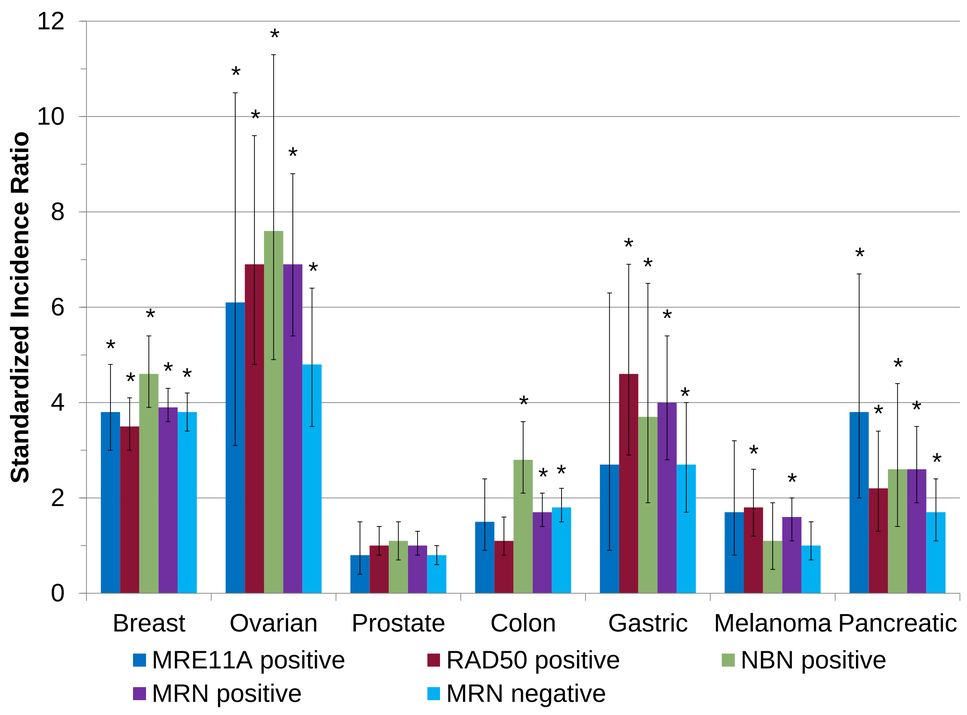
Figure 1. MRN complex



Methods

- MRN+ were identified through hereditary cancer multigene panel testing (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–).

Figure 2. SIRs for selected cancer types in MRN+ and MRN– families



*95% CI does not include 1.0

Table 1. Characteristics of MRN+ probands and their families

Characteristic	Number (%) or mean ± SD (range)
Proband (n=180)	
MRE11A+	28 (15.6)
RAD50+	92 (51.1)
NBN+	60 (33.3)
Age at cancer diagnosis	49.1 ± 11.8 (37.3, 61.0)
Ethnicity	
Caucasian	126 (70.0)
African American/Black	12 (6.7)
Ashkenazi Jewish	6 (3.3)
Asian	5 (2.8)
Hispanic	4 (2.2)
Mixed ethnicity/other	16 (8.9)
Unknown	11 (6.1)
Relatives (n=6277)	
Proband *MRE11A*+	1061 (16.9)
Proband *RAD50*+	3187 (50.8)
Proband *NBN*+	2029 (32.3)
Age at cancer diagnosis	57.9 ± 16.1 (41.8, 74.1)
Relationship to proband	
1st degree	1108 (17.7)
2nd degree	2768 (44.1)
3rd degree & above	2227 (35.5)
Unknown	174 (2.8)

Results

- Among 6277 relatives of 180 MRN+ probands, we observed significant increases over the general population risks of breast, ovarian, colon, gastric, melanoma and pancreatic cancers. (Fig. 2)
- Among 5565 relatives of 180 MRN– probands, we observed significant increases over the general population risks of breast, ovarian, colon, gastric, and pancreatic cancers.
- When comparing SIRs for MRN+ and MRN–, MRN+ showed slightly elevated risks for ovarian, gastric, and pancreatic cancers; however, these differences were not statistically significant.

Take- Home Points

- This is the largest study to date assessing cancer incidence in families with identified MRN mutations.
- 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+.