Genetic counseling complexities of *CHEK2* positivity: Medical management implications for patients and families

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Background

- The expanded use of multi-gene panel (MGP) testing for inherited cancer risk, inclusive of moderate penetrance genes, has resulted in medical management complexities
- Heterozygous *CHEK2* mutations confer >20% lifetime breast cancer (BC) risk, the threshold at which annual breast MRIs are a consideration per national guidelines[1,2,3]
- Estimated colorectal cancer (CRC) risk is two-fold among carriers, similar to the risk level for individuals with a first-degree relative (FDR) with CRC[4]
- *CHEK2*-associated cancer risks may vary based on certain factors:
  1. Family history of BC (higher BC risks with positive BC family history)[1]
  2. Mutation type (truncating mutations with higher BC risks and lower CRC risk and vice versa for missense mutations)[1,2,4]
  3. Other cancers present in the family[5]

Objectives

- Among a group of *CHEK2* mutation positive probands:
  - ➢ Determine CRC surveillance beyond a positive CRC family history
- Among FDRs and SDRs of *CHEK2* mutation positive probands unaffected with cancer:
  - ➢ Calculate lifetime BC risk
  - ➢ Assess the proportion in whom breast surveillance recommendations would be impacted by *CHEK2* mutation positivity beyond that of family history alone

Methods

- Clinical, demographic and family history data was collected from a registry-based and clinical cohort of 33 probands with pathogenic or likely pathogenic *CHEK2* mutations
- Lifetime BC risks were calculated for each unaffected female FDR and SDR less than age 80 using BOADICEA and summary statistics were generated for level of BC risk
- Similarly, family history of CRC among FDRs and SDRs was abstracted for probands

Results

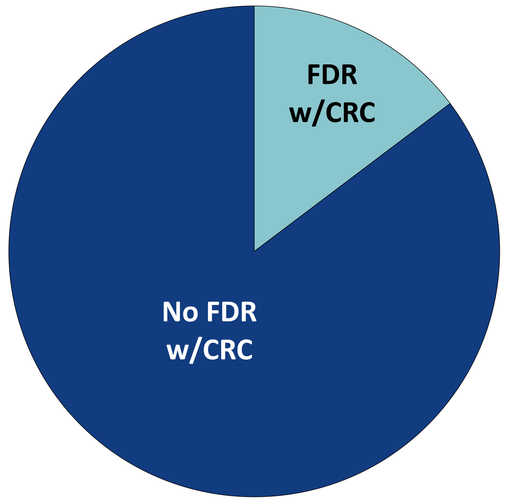
Proband Characteristics (n=33)

	n (%)
Gender	
Female	31 (93.9)
Male	2 (6.1)
Personal History of Cancer	
Yes	27 (81.8)
Breast	19 (70.4)
Ovarian	2 (7.4)
Other	9 (33.3)
No	
Family History of Cancer (among FDRs or SDRs)	
Yes	
Breast	24 (72.7)
Colon	12 (36.3)
Other*	22 (66.7)
No	0 (0)
***CHEK2* Mutation Type**	
Truncating	18 (54.5)
Missense	12 (36.4)
Other	3 (9.1)

**Most common 'other' cancer types: uterine, prostate, melanoma, pancreatic, ovarian, stomach*

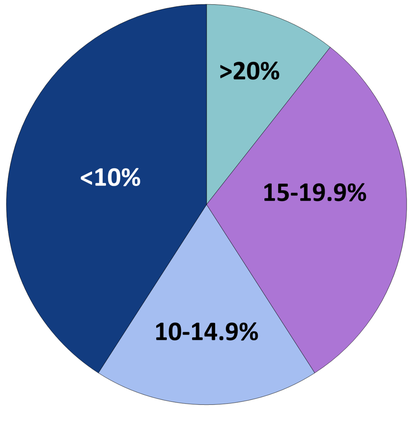
Family History of Colon Cancer in a FDR among *CHEK2* Positive Probands

84.8% (n=28) of probands did not have a first-degree relative diagnosed with colon cancer



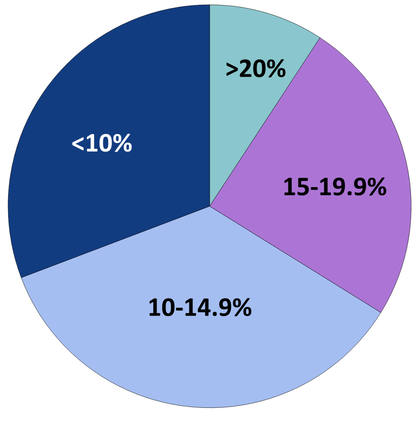
FDR Lifetime Breast Cancer Risk Estimates (n= 62)

88.7% (n=55) of FDRs had a lifetime breast cancer risk estimate <20% based on family history alone



SDR Lifetime Breast Cancer Risk Estimates (n= 63)

90.5% (n=57) of SDRs had a lifetime breast cancer risk estimate <20% based on family history alone



Lifetime BC Risk for FDRs and SDRs based on *CHEK2* Mutation Type Identified in the Family

	Mutation Type	N	Mean Lifetime BC Risk (%)
FDRs	Truncating	30	12.4
	Missense	26	13.1
SDRs	Truncating	23	14.1
	Missense	33	10.7

**Excludes information for three families with "other" mutation types*

Discussion

- Lifetime risk of BC was <20% in ~90% of FDRs and SDRs
  - ➢Thus, *CHEK2* positivity would impact BC surveillance recommendations beyond that based on a family history of BC alone
- Most (~85%) of probands did not have a FDR with CRC
  - ➢Thus, *CHEK2* mutation positivity may impact CRC surveillance beyond that recommended based on family history CRC alone
- Lifetime BC or CRC risk did not differ based on the presence of a truncating vs. missense *CHEK2* mutation in a family
  - ➢However, our sample size was very limited
- Limitations:
  - ➢Potential for underestimation of BC risks in some relatives based on their current age
  - ➢Lack of inclusion of personal risk factors in BODICEA may have impacted BC risk estimates

Conclusions

- Findings suggest that *CHEK2* mutation positivity informs BC risk management among the majority of FDRs and SDRs and CRC risk management for most probands beyond that based on family history alone

References

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