Updated December 2019 (NCCN v1.2020)

CHEK2 Mutations

CHEK2 risk data are predominately based on frameshift pathogenic/likely pathogenic mutations, the most well-studied of these being the c.1100del Northern European founder mutation. Current NCCN guidelines (v1.2020) note that the risks for most missense mutations are unclear, but some missense mutations appear to be associated with lower cancer risks compared to frameshift mutations.[1] Management should be based on best estimate of cancer risks for the specific mutation, per NCCN.

Cancer Risks and General Management Recommendations

Cancer Type	*CHEK2* Mutation Carrier Cancer Risks	General Population Lifetime Cancer Risks	Surveillance/Management Recommendations[1,2]
Female Breast[3-7]	Primary: 23-48% Second Primary: Up to 29% (within 10 years of initial diagnosis)	12.4%	*Surveillance* • Age 40 years: Annual mammogram with consideration of tomosynthesis; consider breast MRI with contrast ○ Age to initiate breast surveillance may be modified based on family history (typically 5-10 years earlier than the youngest breast cancer diagnosis in the family, but no later than age 40) *Surgery* • Insufficient evidence to support risk-reducing mastectomy based on *CHEK2* mutation status alone; management should be based on personal risk factors and family history
Male Breast[8]	0.4%-1.0%	0.1%	*Management* • No consensus management guidelines • Discuss family history and breast cancer surveillance options (i.e., clinical breast exam) with a physician to determine an appropriate surveillance regimen
Colorectal Cancer (CRC)[9]	Increased (lifetime risk unknown)	4.2%	*Surveillance* • Age 40 years: Colonoscopies every 5 years (or more frequently based on findings) ○ Age to initiate colon surveillance may be modified based on family history (beginning at age 40 or 10 years prior to the earliest age of CRC diagnosis in a first-degree relative (i.e., parent, sibling, child), whichever comes first) • For individuals with a personal history of CRC: Consult with physician to determine appropriate colon cancer risk management options
Prostate[10]	Up to 27% based on family history of prostate cancer	11.2%	*Surveillance* • No consensus management guidelines • Discuss family history and prostate cancer surveillance options (i.e., PSA, digital rectal exam)

			with a physician to determine an appropriate surveillance regimen

Other Cancer Risks: Kidney and thyroid cancers have also been observed more frequently in individuals with a *CHEK2* mutation, but true lifetime risk figures are unknown. Currently, there are no management guidelines for these other cancer risks. Individuals with a *CHEK2* mutation are encouraged to discuss these cancer risks, along with family history and personal risk factors, to establish an appropriate surveillance regimen.

Implications for Family Members/ Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *CHEK2* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References

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