CDKN2A

The *CDKN2A* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The *CDKN2A* gene codes for two different proteins called p16(INK4a) and p14(ARF). The p16(INK4a) protein interacts with other proteins to help regulate how the cell copies itself. The p14(ARF) protein interacts with other proteins to help regulate cell division and death. Mutations in *CDKN2A* can affect one or both of the proteins.

Like most genes, each person has two copies of the *CDKN2A* gene: one inherited from each parent. A mutation in a single *CDKN2A* gene inherited from either parent is known to increase risks of melanoma, including multiple melanomas diagnosed at younger ages, and pancreatic cancer.

Mutations in the *CDKN2A* gene are thought to account for 20-40% of hereditary melanoma.[1] Individuals with a *CDKN2A* mutation have an increased risk of developing dysplastic nevi (atypical moles) which must be monitored because they can change into melanoma.

Certain factors can greatly increase risk of melanoma, including an individual's geographic region, ethnicity and sun exposure. For example, melanoma is 20 times more common in Caucasians than it is in African Americans.[2] The risk of pancreatic cancer also varies depending on whether a person has a history of smoking cigarettes.[3]

In general, the risks of melanoma and pancreatic cancer are lower for mutations in the CDKN2A gene that affect the p14(ARF) protein compared to mutations that affect the p16(INK4a) protein, but the age of onset of those cancers may be younger.[1,4,5]

How common are mutations in the *CDKN2A* gene?

Mutations in the *CDKN2A* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *CDKN2A* mutations are ongoing.

[1] Goldstein AM, Chan M, Harland M, et al. High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. Cancer Res. 2006;66(20):9818-28.
[2] What are the risk factors for melanoma skin cancer? American Cancer Society Website. http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-risk-factors Updated February 01, 2016.
[3] McWilliams RR, Wieben ED, Rabe KG, et al. Prevalence of CDKN2A mutations in pancreatic cancer patients: implications for genetic counseling. Eur J Hum Genet. 2011;19(4):472-8.
[4] Begg CB, Orlow I, Hummer AJ, et al. Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. J Natl Cancer Inst. 2005;97(20):1507-15.
[5] Bishop DT, Demenais F, Goldstein AM, et al. Geographical variation in the penetrance of CDKN2A mutations for melanoma. J Natl Cancer Inst. 2002;94(12):894-903.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *CDKN2A* gene, her chances of developing melanoma and pancreatic cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

Cancer by age 80	Average US woman[6]	With *CDKN2A* mutation
Melanoma	1.3%	28-67%[1,4,5]
Pancreatic	<1%	58%[1,7]

Elevated: Risk is increased, but further research may clarify the exact risk figure.

Men

If a man has a mutation in the *CDKN2A* gene, his chances of developing melanoma and pancreatic cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

Cancer by age 80	Average US man[6]	With *CDKN2A* mutation
Melanoma	1.9%	28-67%[1,4,5]
Pancreatic	1.1%	58%[1,7]

Elevated: Risk is increased, but further research may clarify the exact risk figure.

Screening guidelines

Below is a summary of screening guidelines from the American Cancer Society (ACS). Because there are no published screening guidelines specific to individuals with *CDKN2A* mutations, these guidelines are for individuals who have the same risk of melanoma as the average US individual. Your healthcare provider may use these ACS Guidelines to help create a customized screening plan for you. They might also make additional recommendations to reduce the risk of melanoma.

[6] Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2010-2012. DevCan software (http://surveillance.cancer.gov/devcan) V 6.7.0, Accessed June 2015.
[7] McWilliams RR, Wieben ED, Rabe KG, et al. Prevalence of CDKN2A mutations in pancreatic cancer patients: implications for genetic counseling. Eur J Hum Genet. 2011;19(4):472-8.

Women and Men

Melanoma[8]

- Your healthcare provider may discuss skin exams and eye exams for melanoma screening.
- To reduce the chance of developing melanoma, the American Cancer Society recommends limiting exposure to UV light by avoiding excess sun exposure, wearing a hat, sunglasses and long protective clothing, applying sunscreen with SPF of 30 or higher and avoiding tanning beds and sun lamps.
- Any new, unusual, or changing moles should be reported to your provider or dermatologist.

Pancreatic cancer[9]

- Currently, there are no pancreatic cancer screening guidelines from the ACS or National Comprehensive Cancer Network (NCCN) specific to *CDKN2A* mutation carriers. Your provider may discuss screening or referral to a specialist.

Useful resources

American Melanoma Foundation

An organization supporting melanoma research, and providing advocacy and public awareness of melanoma.

www.melanomafoundation.org

National Pancreas Foundation

An organization committed to funding pancreatic cancer research, and providing support and education about pancreatic cancer.

www.pancreasfoundation.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions.

www.kintalk.org

Last updated May 15, 2017

[8] Skin Cancer Prevention and Early Detection. The American Cancer Society. Available at www.cancer.org. Updated 3/20/2015. Accessed April 2015.

[9] International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut.* March 2013; 62(3):339-47.