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BRIEF COMMUNICATION

Risk of Non-Melanoma Cancers in First-Degree Relatives of *CDKN2A* Mutation Carriers

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The purpose of this study was to quantify the risk of cancers other than melanoma among family members of *CDKN2A* mutation carriers using data from the Genes, Environment and Melanoma study. Relative risks (RRs) of all non-melanoma cancers among first-degree relatives (FDRs) of melanoma patients with *CDKN2A* mutations (n = 65) and FDRs of melanoma patients without mutations (n = 3537) were calculated as the ratio of estimated event rates (number of cancers/total person-years) in FDRs of carriers vs noncarriers with exact Clopper–Pearson-type tests and 95% confidence intervals (CIs). All statistical tests were two-sided. There were 56 (13.1%) non-melanoma cancers reported among 429 FDRs of mutation carriers and 2199 (9.4%) non-melanoma cancers in 23452 FDRs of noncarriers. The FDRs of carriers had an increased risk of any cancer other than melanoma (56 cancers among 429 FDRs of carrier probands vs 2199 cancers among 23452 FDRs of noncarrier probands; RR = 1.5, 95% CI = 1.2 to 2.0, *P* = .005), gastrointestinal cancer (20 cancers among 429 FDRs of carrier probands vs 506 cancers among 23452 FDRs of noncarrier probands; RR = 2.4, 95% CI = 1.4 to 3.7, *P* = .001), and pancreatic cancer (five cancers among 429 FDRs of carrier probands vs 41 cancers among 23452 FDRs of noncarrier probands; RR = 7.4, 95% CI = 2.3 to 18.7, *P* = .002). Wilms tumor was reported in two FDRs of carrier probands and three FDRs of noncarrier probands (RR = 40.4, 95% CI = 3.4 to 352.7, *P* = .005). The lifetime risk of any cancer other than melanoma among *CDKN2A* mutation carriers was estimated as 59.0% by age 85 years (95% CI = 39.0% to 75.4%) by the kin-cohort method, under the standard assumptions of Mendelian genetics on the genotype distribution of FDRs conditional on proband genotype.

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Germline *CDKN2A* mutations are associated with an increased risk of melanoma (1) and other cancers (2–14), although the risk for cancers other than melanoma are less well quantified. Germline *CDKN2A* is very rare in the population with an estimated prevalence of 0.01% (15). *CDKN2A* mutations have been found in 1.2% of patients with single primary melanoma, in 3.0% of patients with multiple primary melanomas, and in 10%–25% of multiple-case melanoma families (16).

Pancreatic cancer is one of the most commonly reported non-melanoma cancers to be associated with germline *CDKN2A* mutations (4–8,10). Germline *CDKN2A* mutations have also been associated with an increased risk of other gastrointestinal cancers (4,8), even after excluding pancreatic cancer (5). Several reports suggest that *CDKN2A* mutations may also be associated with an increased risk of breast cancer, lung cancer, childhood cancers, and squamous cancers of the head and neck; however, these associations are not well established (2,3,6,9,11–13). The purpose of this study was to estimate the relative risks of non-melanoma cancers in family members of *CDKN2A* mutation carriers. We then estimated the lifetime risk for non-melanoma cancers in *CDKN2A* carriers by the kin-cohort method.

Probands for this study were recruited for the Genes Environment and Melanoma Study, a multicenter, international population-based case–control study. The details of the Genes, Environment and Melanoma study have been previously published (17), and the lifetime risk of melanoma among *CDKN2A* carriers has been reported previously as well (18,19). Probands were incident melanoma patients with either first or subsequent melanoma who were identified in nine geographic regions in Australia, Canada, the United States, and Italy.

We sought to estimate the relative risks (RRs) for developing various cancers in family members of probands with known *CDKN2A* mutations by comparing the cancer incidence in first-degree relatives (FDRs) of carriers with cancer incidence in FDRs of noncarriers. Relative risks were calculated as the ratio of estimated event rates (number of cancers/total person-years) in FDRs of carriers vs noncarriers. Exact Clopper–Pearson-type 95% confidence intervals (CIs) for the relative risks and the corresponding Clopper–Pearson-type exact binomial test for ratios of two proportions with corresponding two-sided *P* values were also calculated. We then used the kin-cohort design (20–23) to estimate cancer risks in *CDKN2A* carriers. The kin-cohort method uses the disease status data in relatives and genotype data on the proband. The method permits estimation of the risk in carriers as a function of risks in relatives of carriers and relatives of noncarriers and makes standard Mendelian genetics assumptions on the genotype distribution of unobserved genotypes in FDRs conditional on the observed genotype status of the proband. Population-based sampling of probands provides an important advantage over prior study designs because it minimizes ascertainment bias.

CONTEXT AND CAVEATS

Prior knowledge

Germline *CDKN2A* mutations are associated with an increased risk of melanoma. The relationship between *CDKN2A* mutations and the risk for non-melanoma cancers has not been well studied, in part, because these mutations are rare in the general population.

Study design

Data from family members of *CDKN2A* mutation carriers were used to calculate the relative and lifetime risks of non-melanoma cancers.

Contribution

First-degree relatives of *CDKN2A* mutation carriers had an increased risk for all non-melanoma cancers, gastrointestinal cancer, and colorectal cancer. These individuals also had an increased lifetime risk of developing any cancer, excluding melanoma, compared with first-degree relatives of noncarriers.

Implication

The increased risk of developing non-melanoma cancers among family members of *CDKN2A* mutation carriers may influence cancer screening and prevention for these individuals.

Limitation

The small number of cancers observed among the study participants should be considered when interpreting the findings.

From the Editors

To characterize the risk estimates, we compared the reported history of cancer among the set of 429 FDRs identified by the 65 probands who were determined to be carriers with the reported history among 23 452 FDRs identified by 3537 probands who were not carriers. Total person-years in FDRs of carriers were 20 298 years and 123 073 years for FDRs of noncarriers. There were 56 (13.1%) non-melanoma cancers reported among 429 FDRs of mutation carriers and 2199 (9.4%) non-melanoma cancers in 23 452 FDRs of non-carriers. Overall rate ratios for cancer incidence in FDRs of carriers was compared with FDRs of noncarriers and corresponding exact Clopper–Pearson-type tests and confidence intervals were calculated (http://cran.r-project.org/web/packages/ratio.test/). We used the marginal likelihood approach proposed by Chatterjee and Wacholder (23) to estimate the penetrance of different cancers in *CDKN2A* carriers, accompanied by a bootstrap confidence interval (we used R-package kin-cohort, http://cran.r-project.org/web/packages/kin.cohort/). All statistical tests were two-sided. A P value of less than .05 was considered statistically significant.

Table 1 shows a summary of cancers in FDRs by carrier and noncarrier status. The results indicate that FDRs of carriers of *CDKN2A* mutation were at an increased risk for all non-melanoma cancers (56 cancers among 429 FDRs of carrier probands vs 2199 cancers among 23 452 FDRs of non-carrier probands, RR = 1.5, 95% CI = 1.2 to 2.0), gastrointestinal cancer (20 cancers among 429 FDRs of carrier probands vs 506 cancers among 23 452 FDRs of noncarrier probands, RR = 2.4, 95% CI = 1.4 to 3.7), and colorectal cancer (10 cancers among 429 FDRs of carrier probands vs 328 cancers among 23 452 FDR of noncarrier probands, RR = 1.9, 95% CI = 0.9 to 3.4). However, only the relative risks for all non-melanoma and gastrointestinal cancers are statistically significant (P = .003 and P < .001, respectively). A sevenfold increased risk of pancreatic cancer in FDRs that was also statistically significant was also observed (five cancers among 429 FDRs of carrier probands vs 41 cancers among 23 452 FDR of noncarrier probands, RR = 7.4, 95% CI = 2.3 to 18.7, P = .002). A statistically significant increased risk for Wilms tumor in FDRs of carriers was observed (P = .005), although only two Wilms tumors were reported in FDRs of *CKDN2A* carrier probands and three in FDRs of noncarrier probands (RR = 40.4, 95% CI = 3.4 to 352.7). Because the numbers are very small, these results should be interpreted with caution.

Age-specific cumulative risks from the kin-cohort analyses in *CDKN2A* carriers are presented in Figure 1. The risk difference in carriers and noncarriers is more pronounced in late age, greater than age 75 years for most cancer types investigated. The lifetime risk of any cancer other than

Table 1. Number of different cancers among first-degree relatives (FDRs) of *CDKN2A* carriers (n = 65) and non-carriers (n = 3537) in the Genes, Environment and Melanoma Study*

Site	No. of cancers	RR (95% CI)†	P‡
All non-melanoma cancer			
FDRs of carriers	56	1.5 (1.2 to 2.0)	.003
FDRs of noncarriers	2199		
All gastrointestinal cancer			
FDRs of carriers	20	2.4 (1.4 to 3.7)	<.001
FDRs of noncarriers	506		
Colorectal cancer			
FDRs of carriers	10	1.9 (0.9 to 3.4)	.10
FDRs of noncarriers	328		
Other sites§			
Pancreas			
FDRs of carriers	5	7.4 (2.3 to 18.7)	.002
FDRs of noncarriers	41		
Breast			
FDRs of carriers	4	0.7 (0.2 to 1.8)	.69
FDRs of noncarriers	339		
Brain			
FDRs of carriers	2	1.9 (0.2 to 7.1)	.58
FDRs of noncarriers	64		
Lung			
FDRs of carriers	7	1.4 (0.6 to 3.0)	.44
FDRs of noncarriers	293		
Wilms tumor			
FDRs of carriers	2	40.4 (3.4 to 352.7)	.005
FDRs of noncarriers	3		

* A total of 3602 probands were included in the study. There were 429 FDRs of carriers and 23 452 FDRs of noncarriers included in the analysis. CI = confidence interval; RR = relative risk.

† RRs were the ratio of estimated event rates (number of cancers/total person-years) in FDRs of carriers vs noncarriers. Exact Clopper–Pearson-type 95% CIs for the RRs were also calculated.

‡ Two-sided P values were calculated by the Clopper–Pearson-type exact tests for ratios of binomial proportions.

§ Not all sites are reported in the table.

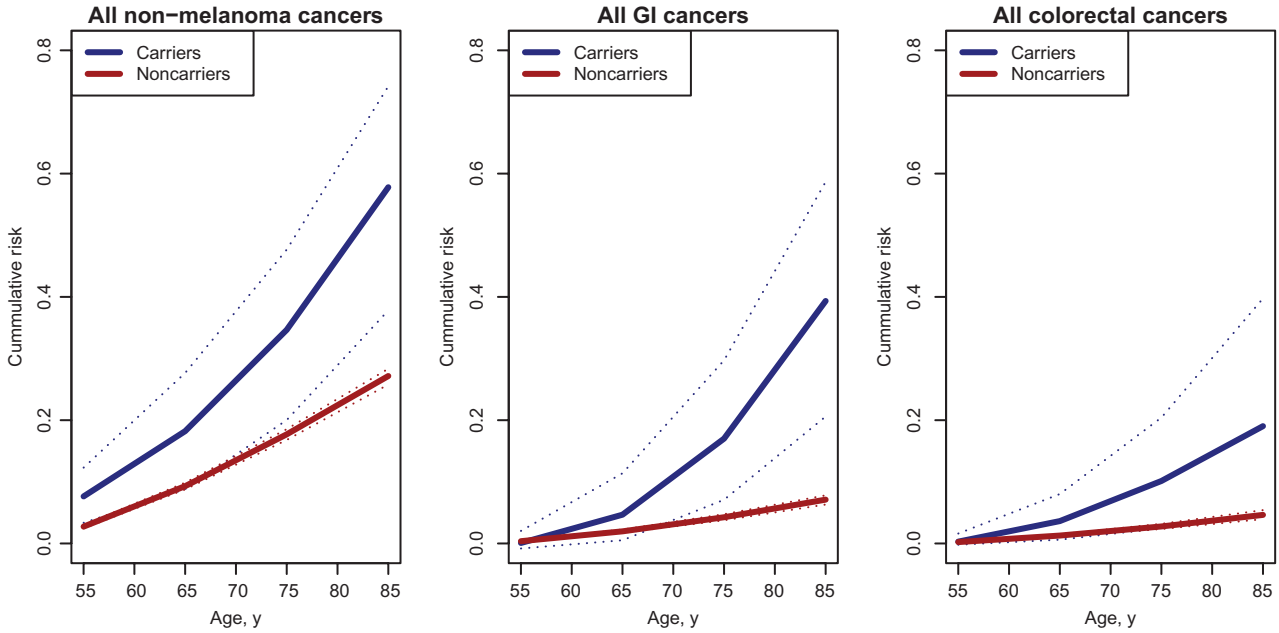

Figure 1. Age-specific cumulative risks for all non-melanoma cancers, all gastrointestinal (GI) cancers, and colorectal cancer in *CDKN2A* mutation carriers as obtained by a kin-cohort analysis. The **dashed line** represents the 95% bootstrap confidence interval.

melanoma among *CDKN2A* mutation carriers was estimated as 59.0% (95% CI = 39.0% to 75.4%) by age 85 years. Additional descriptive statistics stratified by site, analyses including extended relatives, and numerical results from the kin-cohort method corresponding to Figure 1 are given in Supplementary Tables 1–3 (available online).

Our study supports the findings of previous studies that have shown an increased risk for cancers other than melanoma in *CDKN2A* carriers and offer more precise less biased estimates of risk. Previous reports have noted an increased risk for gastrointestinal cancers, particularly pancreatic cancer (8). Our study observed comparable increased risks for these cancers with the advantage of population-based sampling. Contrary to two published reports of an increased risk of breast cancer among *CDKN2A* mutation carriers, we observed that no increased risk though the sample sizes are limited (7,9). An unexpected finding from our study was an increased risk for Wilms tumor. This particular finding has not been previously reported and may warrant further investigation, especially in light of two recent studies that reported an increased risk for development of childhood cancers (11,13).

One recent study examined the risk of cancer for sites other than melanoma in *p16-Leiden* mutation carriers and found statistically significantly increased risks of digestive, eye/brain, female genital, lip/mouth/pharynx, pancreatic, respiratory, and non-melanoma skin cancers in known carriers (24). This study reported relative risks of 4.2 (95% CI = 2.9 to 5.9) for cancers other than melanoma and 3.7 (95% CI = 1.4 to 8.1) for digestive system cancers for mutation carriers, results comparable to those we obtained by the kin-cohort method. Another recent kin-cohort study (25) reported penetrance of pancreatic cancer in *CDKN2A* carriers by age 80 years to be 57.6% (95% CI = 7.8% to 85.6%) with a relative risk estimate substantially higher compared with that reported in our study.

The principal limitation of the Genes, Environment and Melanoma study data is that probands' reports of cancer history in relatives are prone to error without additional validation (26,27). This error, however, is likely to be non-differential because the probands all had melanoma and did not know their genotype at the time at which they were asked about their family history of cancer and is thus likely to lead to bias toward the null in the risk estimates. The comparatively small numbers of cancers in *CDNK2A* mutation carriers' families also limit our findings.

Any analysis of the impact of a single gene relies on the assumption that if other unknown genes influence risk, then their effects are equivalent the two groups being compared (eg, carriers vs noncarriers of the gene under investigation). The influence of other risk genes can result in extrafamilial variation, and the marginal likelihood method we used accounts for such residual familial correlation after controlling for *CDKN2A* status.

Our study provides further evidence that *CDKN2A* mutations are associated with increased risk for several cancers other than melanoma. These results have implications for family members of *CDKN2A* mutation carriers, even in the absence of genetic testing, as they may influence decisions and behaviors regarding screening and preventative measures to be undertaken or encouraged by physicians.

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