Association of *BRAF* V600E Status of Incident Melanoma and Risk for a Second Primary Malignancy: A Population-Based Study

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PRACTICE **POINTS**

- Dermatologists should be aware of the long-term risk of second primary malignancies after an incident melanoma.
- *BRAF* mutations occur in melanomas and several other cancers. Our study found that melanoma *BRAF* V600E expression is associated with an increased risk for basal cell carcinomas.

Mutations of the *BRAF* oncogene occur in both melanomas and several other cancers. Our objective was to determine if mutant *BRAF* V600E expression in a population-based cohort of patients with melanoma was associated with the development of a second primary malignancy of any type. Using the resources of the Rochester Epidemiology Project, we retrospectively identified 380 patients aged 18 to 60 years who were diagnosed with an incident melanoma from 1970 through 2009. We reviewed individual medical records to identify second primary malignancies. We evaluated mutant *BRAF* V600E expression from available melanoma tissue specimens and assessed its association with the development of a second primary malignancy. *BRAF* V600E expression in melanomas is associated with an increased risk for basal cell carcinoma (BCC).

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The incidence of cutaneous melanoma in the United States has increased in the last 30 years, with the American Cancer Society estimating that 99,780 new melanomas will be diagnosed and 7650 melanoma-related deaths will occur in 2022.[1] Patients with melanoma have an increased risk for developing a second primary melanoma or other malignancy, such as salivary gland, small intestine, breast, prostate, renal, or thyroid cancer, but most commonly nonmelanoma skin cancer.[2,3] The incidence rate of melanoma among residents of Olmsted County, Minnesota, from 1970 through 2009 has already been described for various age groups[4-7]; however, the incidence of a second primary malignancy, including melanoma, within these incident cohorts remains unknown.

Mutations in the *BRAF* oncogene occur in approximately 50% of melanomas.[8,9] They cause downstream activation of the mitogen-activated protein kinase signaling pathway, stimulating growth in melanoma cell lines.[10] *BRAF* mutations also occur in hairy cell leukemia, papillary thyroid cancers, colorectal cancers, liver cancers, gliomas, lung cancers, sarcomas, ovarian cancers, and breast cancers, with incidence rates varying from 2% to 100%.[9,11,12] V600E is the most common somatic *BRAF* mutation (>90%) and is linked to survival in melanoma.[13] Targeted therapies with small-molecule *BRAF* and *MEK* inhibitors have notably improved survival of patients with advanced or metastatic disease,[14] and molecular testing for *BRAF* mutations is routinely recommended for patients with advanced melanoma.

Although the *BRAF* mutation event in melanoma is sporadic and should not necessarily affect the development of an unrelated malignancy, we hypothesized that

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the exposures that may have predisposed a particular individual to a *BRAF*-mutated melanoma also may have a higher chance of predisposing that individual to the development of another primary malignancy. In this population-based study, we aimed to determine whether the specific melanoma feature of mutant *BRAF* V600E expression was associated with the development of a second primary malignancy.

Methods

This study was approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center (both in Rochester, Minnesota). The reporting of this study is compliant with the Strengthening the Reporting of Observational Studies in Epidemiology statement.[15]

Patient Selection and BRAF *Assessment*—The Rochester Epidemiology Project (REP) links comprehensive health care records for virtually all residents of Olmsted County, Minnesota, across different medical providers. The REP provides an index of diagnostic and therapeutic procedures, tracks timelines and outcomes of individuals and their medical conditions, and is ideal for population-based studies. Since its inception in 1966, the REP has provided the resource for more than 2000 peer-reviewed publications.[16,17]

We obtained a list of all residents of Olmsted County aged 18 to 60 years who had a melanoma diagnosed according to the *International Classification of Diseases, Ninth Revision*, from January 1, 1970, through December 30, 2009; these cohorts have been analyzed previously.[4-7] Of the 638 individuals identified, 380 had a melanoma tissue block on file at Mayo Clinic with enough tumor present in available tissue blocks for *BRAF* assessment. All specimens were reviewed by a board-certified dermatopathologist (J.S.L.) to confirm the diagnosis of melanoma. Tissue blocks were recut, and formalin-fixed, paraffin-embedded tissue sections were stained for *BRAF* V600E (Spring Bioscience Corporation). *BRAF*-stained specimens and the associated hematoxylin and eosin–stained slides were reviewed. Melanocyte cytoplasmic staining for *BRAF* was graded as negative if no staining was evident. *BRAF* was graded as positive if focal or partial staining was observed (<50% of tumor or low *BRAF* expression) or if diffuse staining was evident (>50% of tumor or high *BRAF* expression).

Using resources of the REP, we confirmed patients' residency status in Olmsted County at the time of diagnosis of the incident melanoma. Patients who denied access to their medical records for research purposes were excluded. We used the complete record of each patient to confirm the date of diagnosis of the incident melanoma. Baseline characteristics of patients and their incident melanomas (eg, anatomic site and pathologic stage according to the American Joint Committee on Cancer classification) were obtained. When only the Clark level was included in the dermatopathology report, the corresponding Breslow thickness was extrapolated from the Clark level,[18] and the pathologic stage according to the American Joint Committee on Cancer classification (7th edition) was determined.

For our study, specific diagnostic codes—*International Classification of Diseases, Ninth* and *Tenth Revisions*; Hospital International Classification of Diseases Adaptation[19]; and Berkson[16]—were applied across individual records to identify all second primary malignancies using the resources of the REP. The diagnosis date, morphology, and anatomic location of second primary malignancies were confirmed from examination of the clinical records. For squamous cell carcinomas and basal cell carcinomas (BCCs), of which multiple tumors could potentially occur in a single patient, the dates of the earliest squamous cell carcinomas and BCCs that occurred before and after the incident melanoma were used. For second primary malignancies, the biopsy date was used as the diagnosis date, except for a few patients who presented with such advanced-stage cancer that the diagnosis was ascertained by clinical examination and radiologic imaging alone.

Statistical Analysis—Baseline characteristics were compared by *BRAF* V600E expression using Wilcoxon rank sum and χ^2 tests. The rate of developing a second primary malignancy at 5, 10, 15, and 20 years after the incident malignant melanoma was estimated with the Kaplan-Meier method. The duration of follow-up was calculated from the incident melanoma date to the second primary malignancy date or the last follow-up date. Patients with a history of the malignancy of interest, except skin cancers, before the incident melanoma date were excluded because it was not possible to distinguish between recurrence of a prior malignancy and a second primary malignancy. Associations of *BRAF* V600E expression with the development of a second primary malignancy were evaluated with Cox proportional hazards regression models and summarized with hazard ratios (HRs) and 95% CIs; all associations were adjusted for potential confounders such as age at the incident melanoma, year of the incident melanoma, and sex.

Results

Demographics—Table 1 shows the demographic and melanoma-specific characteristics of the 380 patients evaluated for mutant *BRAF* V600E expression. At last follow-up, 48 patients had died at a median (interquartile range [IQR]) of 6.7 (1.7–14.0) years after the incident melanoma. The median (IQR) duration of follow-up for the 332 living patients was 11.8 (9.1–18.3) years. Three hundred seventy-eight (99%) patients were White. One hundred thirty-three (35%) and 247 (65%) patients were confirmed to have *BRAF* V600E–positive and *BRAF* V600E–negative melanomas, respectively.

Cumulative Incidence of Second Primary Melanoma—Of 133 patients with positive *BRAF* V600E expression, we identified 14 (10.5%), 1 (0.8%), and 1 (0.8%) who had 1, 2, and 4 subsequent melanomas, respectively. Of the 247 patients with negative *BRAF* V600E expression, we identified 15 (6%), 4 (1.6%), 2 (0.8%), and 1 (0.4%) patients who had 1, 2, 3, and 4 subsequent melanomas,

respectively; *BRAF* V600E expression was not associated with the number of subsequent melanomas (P=.37; Wilcoxon rank sum test). The cumulative incidences of developing a second primary melanoma (n=38 among the 380 patients studied) at 5, 10, 15, and 20 years after the incident melanoma were 5.3%, 7.6%, 8.1%, and 14.6%, respectively.

Cumulative Incidence of All Second Primary Malignancies—Of the 380 patients studied, 60 (16%) had at least 1 malignancy diagnosed before the incident melanoma. Of the remaining 320 patients, 104 later had at least 1 malignancy develop, including a second primary melanoma, at a median (IQR) of 8.0 (2.7–16.2) years after the incident melanoma; the 104 patients with at least 1 subsequent malignancy included 40 with *BRAF*-positive and 64 with *BRAF*-negative melanomas. The cumulative incidences of developing at least 1 malignancy of any kind at 5, 10, 15, and 20 years after the incident melanoma were 15.0%, 20.5%, 31.2%, and 47.0%, respectively. Table 2 shows the number of patients with at least 1 second primary malignancy after the incident melanoma stratified by *BRAF* status.

TABLE 1. Demographic and Melanoma-Specific Characteristics[a]

Characteristic	Negative *BRAF* expression (n=247)	Positive *BRAF* expression (n=133)	*P* value
Age at diagnosis, y			
Median (IQR)	45 (33–52)	41 (31–49)	.07
Sex, n (%)			
Female	143 (58)	79 (59)	.77
Male	104 (42)	54 (41)	
Anatomic site (N=379), n (%)			
Trunk	105 (43)	59 (44)	.08
Extremities	113 (46)	49 (37)	
Head and neck	28 (11)	25 (19)	
Pathologic stage (N=379), n (%)			
Noninvasive (stage 0)	64 (26)	14 (11)	.002
Invasive (stage I)	164 (67)	107 (80)	
Advanced (stage II, III, or IV)	18 (7)	12 (9)	
Decade of diagnosis (N=380)			
1970-1979	8 (3)	5 (4)	.88
1980-1989	25 (10)	12 (9)	
1990-1999	71 (29)	38 (29)	
2000-2009	143 (58)	78 (59)	

Abbreviation: IQR, interquartile range.

[a]Patients were residents of Olmsted County, Minnesota, and received their first melanoma diagnosis between 1970 and 2009.

TABLE 2. Second Primary Malignancies After the Incident Melanoma by Mutant *BRAF* Expression Status

Second primary malignancy	No. of patients: *BRAF* positive (n=40)	No. of patients: *BRAF* negative (n=64)
Basal cell carcinoma	25	21
Biliary system	0	1
Bladder	1	1
Brain	0	1
Breast	3	7
Cervix	3	3
Colorectal	0	2
Kidney	1	1
Larynx	0	1
Lung	0	1
Myeloma	0	1
Other female genitalia	1	0
Other nonmelanoma skin cancer	0	2
Pancreas	1	0
Prostate	4	4
Squamous cell carcinoma	8	21
Thyroid	1	1

BRAF *V600E Expression and Association With Second Primary Malignancy*—The eTable shows the associations of mutant *BRAF* V600E expression status with the development of a new primary malignancy. Malignancies affecting fewer than 10 patients were excluded from the analysis because there were too few events to support the Cox model. Positive *BRAF* V600E expression was associated with subsequent development of BCCs (HR, 2.32; 95% CI, 1.35-3.99; *P*=.002) and the development of all combined second primary malignancies excluding melanoma (HR, 1.65; 95% CI, 1.06-2.56; *P*=.03). However, *BRAF* V600E status was no longer a significant factor when all second primary malignancies, including second melanomas, were considered (*P*=.06). Table 3 shows the 5-, 10-, 15-, and 20-year cumulative incidences of all second primary malignancies according to mutant *BRAF* status.

Comment

Association of BRAF *V600E Expression With Second Primary Malignancies—BRAF* V600E expression of an incident melanoma was associated with the development of all combined second primary malignancies excluding melanoma; however, this association was not statistically significant when second primary melanomas were included. A possible explanation is that individuals with more than 1 primary melanoma possess additional genetic risk—*CDKN2A* or *CDKN4* gene mutations or *MC1R* variation—that outweighed the effect of *BRAF* expression in the statistical analysis.

The 5- and 10-year cumulative incidences of all second primary malignancies excluding second primary melanoma were similar between *BRAF*-positive and *BRAF*-negative melanoma, but the 15- and 20-year cumulative incidences were greater for the *BRAF*-positive cohort. This could reflect the association of *BRAF* expression with BCCs and the increased likelihood of their occurrence with cumulative sun exposure and advancing age. *BRAF* expression was associated with the development of BCCs, but the reason for this association was unclear. *BRAF*-mutated melanoma occurs more frequently on sun-protected sites,[20] whereas sporadic BCC generally occurs on sun-exposed sites. However, *BRAF*-mutated melanoma is associated with high levels of ambient UV exposure early in life, particularly birth through 20 years of age,[21] and we speculate that such early UV exposure influences the later development of BCCs. The lack of an association between *BRAF* positivity and the development of other specific cancers is possibly because the mutation is somatic and not inherited or germline, as with the *CDKN2A* mutation, and/or because of the small size of our cohorts.

Development of BRAF*-Mutated Cancers*—It currently is not understood why the same somatic mutation can cause different types of cancer. A recent translational research study showed that in mice models, precursor cells of the pancreas and bile duct responded differently when exposed to *PIK3CA* and *KRAS* oncogenes, and tumorigenesis is influenced by specific cooperating genetic events in the tissue microenvironment. Future research investigating these molecular interactions may lead to better understanding of cancer pathogenesis and direct the design of new targeted therapies.[22,23]

Regarding environmental influences on the development of *BRAF*-mutated cancers, we found 1 population-based study that identified an association between high iodine content of drinking water and the prevalence of T1799A *BRAF* papillary thyroid carcinoma in 5 regions in China.[24] Another study identified an increased risk for colorectal cancer and nonmelanoma skin cancer in the first-degree relatives of index patients with *BRAF* V600E colorectal cancer.[25] Two studies by institutions in China and Sweden reported the frequency of *BRAF* mutations in cohorts of patients with melanoma.[26,27]

Additional studies investigating a possible association between *BRAF*-mutated melanoma and other cancers with larger numbers of participants than in our study may become more feasible in the future with increased routine genetic testing of biopsied cancers.

Study Limitations—Limitations of this retrospective epidemiologic study include the possibility of ascertainment bias during data collection. We did not account for known risk factors for cancer (eg, excessive sun

TABLE 3. Cumulative Incidence of Second Primary Malignancies[a]

Rate	*BRAF* positive, %	*BRAF* negative, %	Hazard ratio (95% CI)	*P* value
All cancers			1.47 (0.98-2.19)	.06[b]
5 y	14.5	15.2		
10 y	20.3	20.7		
15 y	39.0	27.1		
20 y	60.0	40.5		
All cancers excluding second primary melanomas			1.65 (1.06-2.56)	.03[b]
5 y	11.0	12.1		
10 y	16.8	16.2		
15 y	35.9	21.7		
20 y	55.0	32.7		

[a]Melanomas were assayed for mutant *BRAF* V600E expression by immunohistochemistry.

[b]Cox proportional hazards regression model.

exposure, smoking). The Olmsted County population is mostly White, and residents have relatively easy access to health care; these factors should be considered when generalizing the results to other populations. Basal cell carcinomas are common skin cancers, and there may be other risk factors influencing the development of BCCs in our cohort. *BRAF* mutation analysis was available in only a small number of patients (n=380; aged 18–60 years), which would have reduced our capacity to identify statistically significant associations. A positive *BRAF* result did not differentiate between high and low expression levels, but expression levels may affect patient outcomes. One study showed that high *BRAF* expression correlated with significantly poorer overall (*P*=.009) and disease-specific 5-year survival (*P*=.007) for 232 patients with primary melanoma.[28]

The main clinical implications from this study are that we do not have enough evidence to recommend *BRAF* testing for all incident melanomas, and *BRAF*-mutated melanomas cannot be associated with increased risk for developing other forms of cancer, with the possible exception of BCCs. Future research should assess *BRAF* mutation status of any second primary malignancies that arise after an incident *BRAF*-positive melanoma.

Conclusion

Physicians should be aware of the risk for a second primary malignancy after an incident melanoma, and we emphasize the importance of long-term cancer surveillance. The association between *BRAF* expression in incident melanomas and a higher rate of BCC development may provide indirect evidence that high levels of UV light exposure in early life can increase the risk for BCCs later. Although *BRAF* mutations occur in several nonmelanoma cancers, further studies are needed to determine whether *BRAF* tissue expression in melanoma affects the development of other cancers.

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APPENDIX

eTABLE. Associations of Melanoma *BRAF* V600E Expression With Second Primary Malignancies

New primary malignancy	Incident melanoma *BRAF* expression[a]	Hazard ratio (95% CI)[b,c]	*P* value
Women			
Breast (n=219)	Negative	1.0 (reference)	
	Positive	1.05 (0.31-3.48)	.94
Cervix (n=207)	Negative	NE	NE
	Positive		
Men			
Prostate (n=156)	Negative	1.0 (reference)	
	Positive	2.01 (0.57-7.05)	.28
All patients			
Basal cell carcinoma (n=353)	Negative	1.0 (reference)	
	Positive	2.32 (1.35-3.99)	.002
Squamous cell carcinoma (n=374)	Negative	1.0 (reference)	
	Positive	0.73 (0.36-1.49)	.39
Second primary melanoma (n=380)	Negative	1.0 (reference)	
	Positive	1.54 (0.81-2.93)	.19
Bladder or urinary tract (n=379)	Negative	NE	NE
	Positive		
Lung (n=380)	Negative	NE	NE
	Positive		
Colorectal (n=379)	Negative	NE	NE
	Positive		
Any gastrointestinal (n=379)	Negative	NE	NE
	Positive		
Any hematologic (n=376)	Negative	NE	NE
	Positive		

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eTABLE. (continued)

New primary malignancy	Incident melanoma *BRAF* expression[a]	Hazard ratio (95% CI)[b,c]	*P* value
Any of the aforementioned malignancies (n=320)	Negative	1.0 (reference)	
	Positive	1.47 (0.98-2.19)	.06
Any of the aforementioned malignancies excluding second melanoma (n=320)	Negative	1.0 (reference)	
	Positive	1.65 (1.06-2.56)	.03

Abbreviation: NE, not evaluated.

[a]Patient numbers indicate those without a history of the specific malignancy. *BRAF* expression refers to expression of the somatic V600E mutation.

[b]Associations were adjusted for age at melanoma diagnosis, year of incident melanoma, and sex. For single-sex analyses, associations were adjusted for age and year of incident melanoma.

[c]Relationships marked NE were not evaluated because <10 patients in the subset had the new primary malignancy of interest (too few to support the Cox proportional hazards regression model).