diffuse melanoma. Herein we wish to offer a few additional insights into these important findings.

Thickness likely is a measure of tumor size, and it is known that a larger tumor will generate more mutant cells, including those with the capacity to metastasize.[2] The random mutation rate in uveal melanoma cells for any gene appears rather constant, irrespective of tumor size. The larger (thicker) the tumor, the greater the number of mutated cells, including those capable of intravasating into the vasculature, surviving circulation, and seeding successfully in distant organs, hence the higher the likelihood of clinical metastasis. Two mutations are important for the onset of uveal metastasis. Tumors with *BAP1* mutations display early clinical metastases, while those with *SF3B1* mutations metastasize later.[2] The finding that these 2 types of mutations are most commonly associated with the progression of a uveal nevus into a metastatic melanoma implies that each confers unique and possibly different advantages in the different steps of metastasis that need to be further elucidated.[3]

With regard to patient age, Harbour and associates initially hypothesized that older patients may have more *BAP1* mutations, but found it was not the case.[1] They then proposed that a weakening in the immune microenvironment of the eye may change with age and favor tumor growth. We wish to expand this view and hypothesize that systemic age-related immune changes impact local and distant growth of uveal melanoma. Age alters the functionality of the immune system, a process called "immune senescence" that affects T cells and macrophages.[4] Tumor-immune interactions occur both at the primary tumor site and in invaded organs. Metastatic uveal melanoma cells are found in hematopoietic tissue, including bone marrow[5] and possibly spleen. The expansion of the disseminated cancer cells is constrained by an active immune environment in the liver, the most important end-organ site of uveal melanoma metastasis.[3] Thus the dynamic of tumor-immune cell interactions will likely be modified with age, resulting in lessened antitumor response and increased success of metastatic growth.[4]

Additionally, comprehensive genomic studies by TCGA research consortium have revealed hypoxia signaling as a major transcriptional signature in specific subsets of uveal melanoma at high risk for metastasis.[6] The presence of hypoxia and hypoxia inducible factor 1 (HIF1) signaling in uveal melanoma and the therapeutic value of its targeting have also been recently established.[7] As aging results in decreased blood flow to the choroid,[8] this may accelerate the onset of hypoxia in an emerging tumor, and accelerate tumor vascularization/vasculogenic mimicry,[9] well known risk factors of metastasis. This hypothesis will need to be experimentally assessed in animal models reflecting age-related impediments in blood flow.

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Risk of Stroke After Nonarteritic Anterior Ischemic Optic Neuropathy

EDITOR:

WE ARE INTERESTED TO READ THE STUDY LED BY PARK AND associates[1] about the risk of stroke in patients with nonarteritic anterior ischemic optic neuropathy (NAION). According to this retrospective cohort study, 1125 NAION patients were identified from January 1, 2004 to December 31, 2013, based on the Korean National Health Insurance Service (NHIS)–National Sample Cohort (NSC) database. The occurrence of incident NAION was associated

with an increased risk of subsequent stroke in model 1 (crude analysis; hazard ratio [HR] = 1.31; 95% confidence interval [CI], 0.89–1.92), model 2 (adjusted analysis for demographics; HR = 1.19; 95% CI, 0.81–1.75), and model 3 (adjusted analysis for demographics, comorbidity, co-medication, and the Charlson index score; HR = 1.10; 95% CI, 0.75–1.62), respectively. Because neither of these Cox regression models reached statistical significance, the authors concluded that NAION per se is not associated with a subsequent risk of stroke in the general population.

The statistical power of this study may be reduced by combining different types of stroke as a single outcome measurement. In our previous study[2] consisting of 414 NAION patients and 789 controls based on the National Health Insurance Research Database (NHIRD) of Taiwan, including 1 million beneficiaries' random samples, the risk of ischemic stroke among the subjects with NAION was significantly higher than in those without NAION (HR = 2.03; 95% CI, 1.26–3.25). On the contrary, the risk of hemorrhagic stroke among the subjects with NAION was not statistically different from those without NAION (HR = 1.24; 95% CI, 0.43–3.57). Combining ischemic stroke and hemorrhagic stroke, the risk of all strokes among the subjects with NAION was 1.9 times higher than in those without NAION (95% CI: 1.26–2.96). For ischemic stroke, which accounts for 82.9% of all kinds of stroke in our study, we interpreted the relationship between NAION and all kinds of strokes as a diluted effect of ischemic stroke. However, according to the study design by Park and associates, stroke was defined as patient's first hospital admission with any of the following International Classification of Diseases (ICD)-10 codes: I60 (subarachnoid hemorrhage, I61 (intracerebral hemorrhage), I62 (other nontraumatic intracranial hemorrhage), I63 (cerebral infarction), and I64 (stroke, not specified as hemorrhage or infarction).[3] Although the proportion of ischemic stroke admissions increased from 64.7% in 2000 to 76.1% in 2009 in Korea,[4] the risk of stroke in this study was derived from a combined result of both ischemic stroke and hemorrhagic stroke, which shared different pathogenesis. Our observations already showed that the NAION is a risk factor in subsequent ischemic stroke attack, but not for a hemorrhagic stroke.[2] We do suggest that the hemorrhagic stroke should be separated from ischemic stroke in the investigation of risk of stroke in patients with NAION. Without knowing they are using all strokes as an outcome measurement in this NAION study, care must be taken when interpreting the results offered here.

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Reply

EDITOR:

WE THANK DR. TSAI FOR HIS INTEREST IN OUR PAPER.[1] DR. Tsai and associates already published a study which showed that nonarteritic anterior ischemic optic neuropathy (NAION) is a risk factor for subsequent ischemic stroke but not for hemorrhagic stroke.[2] They suggested that we should separate hemorrhagic stroke from ischemic stroke in the investigation of risk of stroke after NAION. We deeply appreciate Dr. Tsai and associates for pointing out that we should take another opportunity to further analyze our data and clarify the risk of ischemic and hemorrhagic stroke separately after NAION. Based on their suggestion, we divided the outcome according to the type of stroke, ischemic and hemorrhagic stroke, which was defined as the time to first hospital admission with diagnostic codes of ischemic stroke (I60–I62) and hemorrhagic stroke (I63) after entering the cohort, respectively. For each of the types of stroke, we performed the same set of analyses using the 3 time-varying covariate Cox regression models, as we did in our previous article.[1] The results of all three models showed that incident NAION was not associated with an increased risk of subsequent ischemic stroke (hazard ratio [HR] = 1.16; 95% confidence interval [CI], 0.52–2.59 in model 1; HR = 1.10; 95% CI, 0.49–2.45 in model 2; and HR = 1.05; 95% CI, 0.47–2.34 in model 3) and hemorrhagic stroke (HR = 1.44; 95% CI, 0.96–2.17 in model 1; HR = 1.30; 95% CI, 0.86–1.95 in model 2; and HR = 1.19; 95% CI, 0.79–1.80 in model 3). In addition, we performed a sensitivity analysis by using propensity score-based matching in the defined cohort in the same way as previously mentioned. We matched 10 controls to each NAION patient, and details regarding the estimation and