A Word of Caution regarding Risk Factors for Malignant Transformation of Choroidal Nevi

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Dear Editor,

It is with great interest I read the recently published editorial by Singh and Grossniklaus [1] and the research study by Raval et al. [2] regarding the distinction between choroidal nevi and small choroidal melanomas. The authors should be commended for highlighting a central yet often overlooked issue and for investigating the correlation of growth with histopathological findings. The latter is a much-needed effort in a field where patients rarely undergo diagnostic biopsy prior to treatment.

Following pioneering work by Dr. Gass some 50 years ago, as well as later additions by others, Dr. Shields and colleagues coined a widely recognized mnemonic to help us remember risk factors for growth of choroidal nevi into melanoma: “To find small ocular melanoma using helpful hints daily,” (TFSOMUHHD) [3–8]. In 2019, an updated version of the mnemonic was offered: “To find small ocular melanoma doing imaging” (TFSOMDI), representing thickness >2 mm (by ultrasound), subretinal fluid (by OCT), symptoms of vision loss, orange pigment (by autofluorescence), melanoma hollow (by ultrasound), and diameter >5 mm (by photography) [9].

Mnemonics are useful tools for remembering risk factors. By reminding us to evaluate each parameter, they

may increase diagnostic accuracy and reproducibility and help us avoid delays in the treatment of choroidal melanomas. My respected colleagues should be praised for these contributions. Nevertheless, caution is warranted. In addition to what is highlighted by Singh and Grossniklaus [1], 3 more issues may be mentioned.

The first problem is one of the criteria for classification: if risk factors for malignant transformation are similar or identical to the parameters used for diagnosing choroidal melanoma, the two will correlate regardless of the true biology of the lesion. In the 2009 and 2019 publications by Shields et al. [8, 9], malignant transformation was defined as “enlargement in the basal dimension or thickness of at least 0.5 mm” and “enlargement in basal dimension or thickness by at least 0.5 mm (arbitrary) over a short time period,” respectively. In other words, TFSOMUHHD and TFSOMDI have not actually been shown to identify malignancy, but growth by 0.5 mm. Growth is not the only hallmark of cancer, and very small tumors can harbor *BAP1* mutations and seed metastases [10–13]. Further, in a 2019 publication, Dr. Harbour and colleagues [14] found that documented growth of choroidal nevi was not associated with malignant transformation. The latter was defined as having the highly metastatic

Table 1. Risk of malignant transformation of choroidal nevi in relation to each of the 18 assessed risk factors in the ascending order of relative incidence

Factor	Study, <i>n</i>	MT, <i>n</i>	MT feature present, <i>n</i>	No MT feature present, <i>n</i>	Feature present, <i>n</i>	MT feature absent, <i>n</i>	Feature absent, <i>n</i>	Incidence feature present, %	Overall incidence, %	RI	ARI, %	NNMT
Absence of halo ^a	2,514	180	177	2,218	2,395	3	119	7.4	7.2	1.0	0.2	434
Location in choroid, outer versus inner ^b	2,355	90	50	1,142	1,192	40	1,163	4.2	3.8	1.1	0.4	268
Drusen absence ^b	2,355	90	44	933	977	46	1,378	4.5	3.8	1.2	0.7	147
Vascular compression ^b	2,355	90	44	789	833	46	1,522	5.3	3.8	1.4	1.5	68
Location in choroid, full thickness versus inner ^b	2,355	90	27	395	422	63	1,933	6.4	3.8	1.7	2.6	39
Dome shaped versus flat configuration ^b	2,355	90	79	1,132	1,211	11	1,144	6.5	3.8	1.7	2.7	37
Margin <3 mm from optic disc ^a	2,514	180	105	712	817	75	1,697	12.9	7.2	1.8	5.7	18
Diameter >5 mm, by photography ^b	2,355	90	66	778	844	24	1,511	7.8	3.8	2.0	4.0	25
RPE atrophy ^b	2,355	90	23	247	270	67	2,085	8.5	3.8	2.2	4.7	21
RPE hyperplasia ^b	2,355	90	10	91	101	80	2,254	9.9	3.8	2.6	6.1	16
Thickness >2 mm ^a	2,514	180	82	360	442	98	2,072	18.6	7.2	2.6	11.4	9
Ultrasonographic hollowness ^a	2,514	180	103	355	458	77	2,056	22.5	7.2	3.1	15.3	7
Symptoms ^{*a}	2,514	180	69	235	304	111	2,210	22.7	7.2	3.2	15.5	6
Fluid, by slit-lamp microscopy ^{*a}	2,514	180	71	195	266	109	2,248	26.7	7.2	3.7	19.5	5
Orange pigment, by slit-lamp microscopy ^a	2,514	180	58	135	193	122	2,321	30.1	7.2	4.2	22.9	4
Fluid by OCT, <3 mm from nevus ^b	2,355	90	13	60	73	77	2,282	17.8	3.8	4.7	14.0	7
Fluid by OCT, subretinal cap ^b	2,355	90	24	102	126	66	2,229	19.0	3.8	5.0	15.2	7
Orange pigment by AF ^b	2,355	90	16	60	76	74	2,279	21.1	3.8	5.5	17.2	6

MT, malignant transformation; RI, relative incidence; ARI, absolute risk increased in percentage points; NNMT, number of nevi needed for malignant transformation of one, defined as one divided by the absolute risk increased; OCT, optical coherence tomography; AF, autofluorescence. * Any extent of fluid (trace, moderate, and severe) and any symptom (decreased vision, visual field defect, and flashes/floaters). ^a From Shields et al. [8]. ^b From Shields et al. [9].

Fig. 1. Risk ratios for malignant transformation in presence versus absence of 18 risk factors in the ascending order. Random effects Mantel-Haenszel model. CI, confidence interval. ^aFrom Shields et al. [8]. ^bFrom Shields et al. [9].

gene expression class 2. But, far from all choroidal melanomas have gene expression class 2 and metastases do occur from class 1A and 1B tumors [15]. Both the concept of using gene expression class 2 and 0.5 mm growth as definitions of malignant transformation of nevi must therefore be questioned.

The second problem is one of representativity: the risk factors were identified in cohorts with incidences of malignant transformation (or more precisely: 0.5 mm growth) of 7.2 and 2.4%, respectively [8, 9]. This is 12–36 times higher than the calculated 0.2% risk of malignant transformation of choroidal nevi in the general population [16]. Consequently, the included risk factors may not be representative of all nevi.

The third and the last problem is one of the statistical methods. In the 2009 and 2019 publications by Shields et al. [8, 9], the number of nevi with specific risk factors was reported in “growth into melanoma” and “no growth into melanoma” groups. The opposite may however be more relevant to the clinical setting: to report the risk of malignant transformation in the presence of a specific risk factor.

I have therefore proceeded with calculations of the relative incidence, absolute risk increased, and number needed for malignant transformation (NNMT) based on the original data from the two articles [8, 9]. Further, the risk ratio and 95% confidence interval were calculated for each risk factor. Risk ratios were calculated using a random effects Mantel-Haenszel model with the Review Manager by the Cochrane Collaboration (RevMan Version 5.4; The Cochrane Collaboration, Copenhagen, Denmark, 2014). Positive and negative predictive values were not calculated, as it would give a misleading picture. For example, the positive predictive value of absence of halo was 7.4% in one of the cohorts. This may seem to indicate a valid prognostic test until we realize that the overall incidence of malignant transformation in the cohort regardless of risk factors was 7.2% [8]. Other potential risk factors, such as the ones included in the recently proposed MOLES mnemonic, are not included [17]. Not least since the latter is not intended to identify lesions that will undergo malignant transformation or grow in the future.

A total of 18 risk factors were evaluated. Of these, 8 had statistically weak importance for malignant transformation with relative incidences ≤ 2 and absolute risk increased $\leq 10\%$ (Table 1). These 8 risk factors included absence of halo, absence of drusen, and margin < 3 mm from the optic disc, which were included in the older mnemonic, and diameter > 5 mm by photography, which was included in the newer mnemonic. In analysis of relative risk, absence of halo, absence of drusen, and location in the choroid outer versus inner were not statistically significant. Further, the very strongest risk factor was not included in any of the mnemonics: dome shaped versus flat configuration, with a risk ratio of 6.8 (95% CI: 3.6–12.7, Fig. 1).

These findings have several limitations. Foremost, they are based on previously published group level and not individual raw data, preventing multivariate regression analysis. Several factors are likely correlated, including dome shape and thickness. In line with previous publications, the risk factors are presented as dichotomized options, for example, orange pigment or dome shape “yes” or “no,” whereas such distinctions can be less than obvious in clinical reality.

Nevertheless, one can conclude that in addition to the background problems of classifications and representativity that warrant caution when using all the currently available risk factors for malignant transformation of choroidal nevi, some of them have statistically weak importance even within their own original data and logical framework. Increased awareness of these issues and examinations of the true biology of small choroidal melanocytic lesions are key to resolving this matter. The publications by Singh and Grossniklaus [1] and Raval et al. [2] are a good start.

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Statement of Ethics

The research was conducted in accordance with the Declaration of Helsinki. According to the Swedish Ethical Review Act (law section 2003:460), ethical approval and consent to participate was not required as all work presented herein was based on publicly available anonymized group level data that cannot be used to identify any individuals. No personal, sensitive, or pseudonymized information was accessed. No interventions, treatments, meetings, or other contacts with patients or relatives were carried out, and no tissues or other biological samples were used.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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Data Availability Statement

The data used for this work are publicly available in the articles by Shields et al. [8] (Table 3) and Shields et al. [9] (Table 6).

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