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The influence of tumor regression, solar elastosis, and patient age on pathologists' interpretation of melanocytic skin lesions

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Abstract

It is not known whether patient age or tumor characteristics such as tumor regression or solar elastosis influence pathologists' interpretation of melanocytic skin lesions. We undertook a study to determine the influence of these factors, and to explore pathologist characteristics associated

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The authors have no duality of interest to declare.

with the direction of diagnosis. To meet our objective, we designed a cross-sectional survey study of pathologists' clinical practices and perceptions. Pathologists were recruited from diverse practices in ten states in the U.S. We enrolled 207 pathologist participants whose practice included the interpretation of melanocytic skin lesions.

Our findings indicated that the majority of pathologists (54.6%) were influenced toward a *less* severe diagnosis when patients were <30 years of age. Most pathologists were influenced toward a *more* severe diagnosis when patients were >70 years of age, or by the presence of tumor regression or solar elastosis (58.6%, 71.0%, 57.0%, respectively). Generally, pathologists with dermatopathology board certification and/or a high caseload of melanocytic skin lesions were more likely to be influenced, while those with more years' experience interpreting MSL were less likely to be influenced. Our findings indicate that the interpretation of melanocytic skin lesions is influenced by patient age, tumor regression, and solar elastosis; such influence is associated with dermatopathology training and higher caseload, consistent with expertise and an appreciation of lesion complexity.

INTRODUCTION

Melanoma staging is determined by histologic characteristics that are known to influence patient outcomes including tumor depth, ulceration, and mitotic rate.(1–3) Of these, tumor depth was the first prognostic factor to be identified(4) and remains the strongest predictor of patient outcomes in the absence of tumor extension or metastases.(1)

While these characteristics form the basis of pathologists' interpretations of melanocytic skin lesions, it remains unclear whether additional characteristics of the lesions or patients also influence interpretations. For example, younger patients, compared to older patients, have lower melanoma incidence rates(5) and higher melanoma survival rates.(6) Consequently, younger patient age might influence pathologists toward a less severe diagnosis, while older patient age may influence toward a more severe diagnosis.

The potential influence of partial tumor regression, uncommon in benign nevi but reported in up to 58% of melanomas,(7) is more difficult to anticipate. To the extent that tumor regression obscures depth of invasion, its presence might influence pathologists toward a more severe diagnosis. On the other hand, melanoma tumor regression may be thought to represent local host immune response,(8) a potentially favorable process. Studies of associations between partial tumor regression and metastasis or survival have produced mixed results, however, with some showing improved outcome(9, 10) and others showing worse outcome.(11–13)

Similarly, it is difficult to predict the potential influence of solar elastosis on the direction of pathologists' diagnosis. More common in older patients,(14) solar elastosis is a microscopic marker of chronic sun exposure,(15) and a diagnostic criterion of certain melanoma subtypes.(16) Thus, its presence might increase suspicion of an atypical melanocytic lesion or melanoma, swaying pathologists toward a more severe diagnosis. On the other hand, several studies suggest improved melanoma outcome for patients affected by solar elastosis,(3, 17, 18) which might influence pathologists toward a less severe diagnosis. Whether

pathologists consider these factors in their diagnostic interpretations is not known. To address this gap in knowledge, we sought to determine whether certain contexts (i.e., patient age, tumor regression, and solar elastosis) influence the severity of pathologists' diagnoses when interpreting melanocytic skin lesions. We also assessed pathologist characteristics in relation to the direction of influence within each context found to be influential.

Although this report does not represent a traditional experimental study, it addresses the important issue of contexts that influence diagnoses that are central to the interpretation of much human experimental data.

METHODS

Study Design and Sample Selection

We conducted a study of pathologists who interpret melanocytic skin lesions (MSL), including benign nevi, dysplastic nevi, and melanoma. Institutional Review Board approval for all study procedures was obtained from the of the University of Washington, Fred Hutchinson Cancer Research Center, Oregon Health & Sciences University, Rhode Island Hospital, and Dartmouth College. Pathologists were recruited from community practices/laboratories and academic medical centers in 10 states (CA, CT, HI, IA, KY, LA, NJ, NM, UT, and WA). We identified potential participants using Internet searches, professional organizations, and telephone calls to pathology laboratories/practices. Pathologists were invited to participate via email, postal mail, and telephone from July 2013 through August 2014. Eligibility criteria included completion of residency training and/or fellowship training, interpretation of MSL within the previous year, expected continuation of interpreting MSL for the following two years while working in the same state, and verifiable address of practice location.

Survey Content

After consenting to participate, pathologists completed an online survey that elicited general demographic and professional information, including training, practice, and perceptions. A full copy of the survey is available at:http://depts.washington.edu/epidem/faculty/elmore-joann.

Pathologists were asked whether each of certain contexts influenced the direction of their diagnosis of MSL. The potentially influential contexts included patient-level characteristics (patient age <30, patient age >70), tumor-level characteristics (areas of extensive tumor regression, significant solar elastosis).

Primary Outcome

The primary analytic outcome was the direction of diagnostic influence: influence toward a less severe diagnosis, no influence on diagnosis, and influence toward a more severe diagnosis. The vast majority of responses (≥96% within each context) included the no-influence category and only one direction of influence; consequently, the primary outcome was dichotomized as follows: (a) "influence toward a less severe diagnosis" versus "no influence" or (b) "influence toward a more severe diagnosis" versus "no influence,"

depending on pathologists' responses for each context. For example, in the context of tumor regression, 99% of pathologists reported either influence toward a more severe diagnosis or no influence on diagnosis. Thus, in this context, the primary outcome consisted of "influence toward a more severe diagnosis" versus "no influence."

Pathologist Characteristics

We also explored pathologist characteristics in relation to diagnostic influence. Variables of interest included pathologist age, gender, residency training, dermatopathology fellowship training, dermatopathology board certification, MSL caseload (defined as the per month sum of benign MSL cases and melanoma/melanoma in situ cases), percentage of cases rendered as borderline or uncertain diagnoses in their final assessment, whether the pathologist requested second opinions from other pathologists (within our outside their practice) at least once per month, and whether pathologists requested specialized molecular tests, such as FISH or CGH.

Statistical Analysis

Preliminary analyses showed that pathologist age and years of interpreting MSL were highly correlated ($r = 0.85$; $p < 0.0001$), precluding simultaneous inclusion in multivariable models; thus, we chose to evaluate years of interpreting MSL due to its greater relevance. Due to almost perfect concordance between dermatopathology fellowship training and board certification, we chose dermatopathology board certification to represent specialized knowledge in dermatopathology. Dermatopathology board certification was highly correlated with higher MSL caseload ($r = 0.64$; $p < 0.0001$), and both were considered key variables. To incorporate both into our analysis, we created a three-level composite variable representing dermatopathology (DP) expertise: (1) no DP certification and low MSL caseload (<35 MSL/month), (2) no DP certification and high MSL caseload (≧35 MSL/month), and (3) DP certification (regardless of caseload). Two variables, the frequency of using borderline/uncertain diagnosis in final assessments and the frequency of asking for second opinions, were dichotomized as yes/no because the relationship with the outcome was not linear.

Our primary analysis described the percent of pathologists reporting a direction of diagnostic influence within each of the four contexts. Correlation matrices were used to assess relationships between pathologist characteristics. The association between pathologists' characteristics and the direction of diagnosis was displayed in frequency distributions and assessed in logistic regression models. We began by exploring bivariate (unadjusted) models to identify terms for inclusion in multivariable models. Variables associated with the outcome at $p < 0.10$ in bivariate models were assessed in multivariable models. Variables approaching statistical significance ($p < 0.06$) were retained in the final multivariable models to allow covariate adjustment. By convention, alpha was set at <0.05 (two-sided tests) for statistical significance in the multivariable models. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Pathologist Characteristics

Of the 864 potential pathologist participants initially identified, 301 met eligibility criteria and 207 (69%) completed the online survey. The majority (54%) were age ≥50 years (mean age 51 years) and male (59%) (Table 1). A minority (39%) were board certified in DP, with the remainder certified in anatomic pathology, clinical pathology, hematopathology, or cytopathology. The majority (69%) had interpreted MSL for less than 20 years, and for 63% the caseload was ≥ 35 MSL per month. Most pathologists (90%) reported ever using the terms borderline/uncertain in their final pathology report, and most (89%) reported they requested second opinions of other pathologists at least once per month.

Influence of Context on Direction of Diagnosis

The percent of pathologists reporting an influence of patient and tumor characteristics on the direction of their diagnosis within each context is shown in Figure 1. A majority of pathologists (54.6%) reported that young patient age (<30 years) would influence them toward a less severe diagnosis, and most (58.5%) reported that older patient age (>70 years) would influence them toward a more severe diagnosis. The majority of pathologists also reported they would be influenced toward a more severe diagnosis in the context of extensive tumor regression (71.0%) or by the presence of significant solar elastosis (57.0%). The full distribution of pathologist characteristics associated with direction of influence within each of the four contexts is provided in Appendix A.

Pathologist Characteristics and the Direction of Diagnosis, by Context

Patient Age <30 Years—Within the context of younger patients (age <30 years), only one variable, years of interpreting MSL, was associated with self-reported influence toward a less severe diagnosis in the bivariate analyses, so multivariable analysis was unnecessary. Compared to pathologists with less experience, those with ≥20 years of experience interpreting MSL were less likely (OR: 0.36; 95% CI: 0.20, 0.67; p=0.001) to be influenced toward a less severe diagnosis in the context of younger patient age (Table 2).

Patient Age >70 Years—Unadjusted analysis showed an association between the outcome and using the term borderline in a final diagnosis, but this variable lost significance when adjusted for other pathologist characteristics. Two variables, DP expertise, and years of interpreting MSL, remained associated with the outcome in adjusted analysis, and were included in the final multivariable model (Table 2). Compared to those without DP certification and with low MSL caseload, those with either a high MSL caseload (OR: 2.03; 95% CI: 0.96, 4.29), or DP certification (OR: 2.82; 95% CI: 1.40, 5.69) were at least twice as likely to be influenced toward a more severe diagnosis when patients were older (global p = 0.012). Compared to pathologists with less experience, those with ≥20 years experience interpreting MSL were less likely to be influenced toward a more severe diagnosis (OR: 0.33; 95% CI: 0.17, 0.63; p = <0.001).

Tumor Regression—Unadjusted analysis showed an association between the outcome and years of interpreting MSL, but this variable lost significance after adjustment for other

pathologist characteristics. Four variables remained associated with the outcome in adjusted models, and were retained in the final multivariable model (Table 2): dermatopathology expertise, years interpreting MSL, using the term borderline in a final diagnosis, and seeking second opinions. Compared to those without DP certification and with low MSL caseload, those with either high MSL caseload (OR: 2.87; 95% CI: 1.25, 6.60), or DP certification (OR: 2.91; 95% CI: 1.29, 6.53) (global p = .0.008) were more likely to be influenced toward a more severe diagnosis. Pathologists who ever used the terms borderline/uncertain when interpreting MSL were also more likely to be influenced toward a more severe diagnosis by tumor regression (OR: 4.73; 95% CI: 1.66, 13.53; p = 0.004), as were those who requested second opinions at least once per month (OR: 3.04; 95% CI: 1.12, 8.26; p = 0.029). Although the association was marginally significant, those with ≥20 years of experience interpreting MSL, compared to those with fewer years, were half as likely to be influenced toward a more severe diagnosis (OR: 0.49; 95% CI: 0.24, 1.02; p = 0.057).

Solar Elastosis—Two variables: years interpreting MSL, and ordering FISH/CGH or other molecular tests, were associated with the outcome in the unadjusted analysis, but were not statistically significant after adjustment for other pathologist characteristics. Three variables remained associated after adjustment, and were included in the final multivariable model: DP expertise, using borderline/uncertain diagnosis, and requesting second opinions (Table 2). Compared to non-DP certified, low-MSL volume pathologists, those with either high MSL volume (OR: 2.06; 95% CI: 0.98, 4.35), or DP certification (OR: 4.07; 95% CI: 1.98, 8.38) were more likely to be influenced toward a more severe diagnosis (global p = <0.001). Pathologists who ever used the terms borderline/uncertain when interpreting MSL were also more likely to be influenced toward a more severe diagnosis (OR: 2.94; 95% CI: 1.03, 8.37; p = 0.044), as were those who requested second opinions at least once per month (OR: 5.45; 95% CI: 1.92, 15.43; p = 0.001).

DISCUSSION

We identified four influential contexts that impact the severity of diagnosis: younger patient age, older patient age, tumor regression, and solar elastosis. Only one context, younger patient age, influenced pathologists toward a less severe diagnosis. The three remaining contexts influenced pathologists toward a more severe diagnosis.

Our results concerning patient age are compatible with studies showing a more favorable prognosis in younger patients than in older patients.(6) In addition, melanoma is less common in younger than in older individuals(5); thus, the prior probability of disease and the predictive value of a diagnosis of melanoma are greater in older populations.

A majority of pathologists in our study reported they were influenced toward a more severe diagnosis by melanoma with extensive tumor regression. Such influence may reflect longstanding concerns that tumors with regression have invaded beyond their measurable depth.(19) Consistent with this concern, some studies have shown a worse outcome for patients with regressed tumors (reviewed in Piepkorn & Barnhill, 2014).(20) Other studies, however, have indicated that tumor regression predicts better outcome, while still others have shown no association (reviewed in Piepkorn & Barnhill, 2014).(20) A recent meta-

analysis of 14 studies,(10) published after our study was underway, noted a strong, inverse association between tumor regression and lymph node metastasis, implying more favorable survival, but heterogeneity was substantial among the analyzed studies.(10) It should also be noted that nearly half of melanomas disseminate without first invading the regional lymph nodes.(21, 22) Thus, the prognostic role of tumor regression, which has implications for diagnostic interpretation, and possibly for staging, remains unclear.

The majority of pathologists in our study were also swayed toward a more severe diagnosis by the presence of significant solar elastosis, a biological marker of chronic sun exposure.(15) This finding seems inconsistent with the relatively slow radial growth rate of lentigo maligna melanoma, the histologic subtype for which solar elastosis is a diagnostic criterion,(16) and with past studies showing a favorable influence of solar elastosis on prognosis.(3, 17, 18) However, solar elastosis is an indicator of long term sun exposure, which is a known risk factor for lentigo maligna melanoma,(23) and is infrequently found with benign nevi, so its presence in a melanocytic skin lesion may increase suspicion of malignancy.

We also explored pathologist characteristics associated with influence on the direction of diagnosis. Pathologists with more years of MSL interpretation, who also were necessarily older, were less likely to be influenced toward a less severe diagnosis in the context of younger patient age. They were also less likely to be influenced toward a more severe diagnosis in the context of older patient age and tumor regression. While speculative, these findings may reflect complacency or over-confidence in those with long-term experience interpreting MSL.

Our findings were similar for pathologists who had high MSL caseloads, but lacked DP certification, and for those with DP board certification. Both groups were more likely to be influenced toward a more severe diagnosis in the contexts of older age, tumor regression, and solar elastosis. Those who designated tumors as borderline/uncertain in their final reports, and who requested a second opinion at least monthly were also more likely to be influenced toward a more severe diagnosis in contexts of tumor regression or solar elastosis. These pathologist characteristics are consistent with a higher level of sophistication and appreciation of lesion complexity, although requesting second opinions may also reflect laboratory policies.

Our study relies on self-reported data describing the influence of direction of diagnosis, but there is no reason to assume pathologists would incorrectly report their usual practice. We also did not compare the diagnostic accuracy of pathologists with more years of MSL interpretation to that of pathologists with specialized DP expertise. However, a recent analysis, based on the same group of pathologists, showed a significantly lower percentage of malpractice suits among those with DP fellowship training or board certification,(24) suggesting greater accuracy among those with specialized training. Our sample of pathologists, although arising from diverse settings and geographic areas, may not generalize to the population of US pathologists. However, we found no differences between pathologists who agreed to enroll in our study and those who did not. We also cannot be certain that the direction of influence reported by pathologists reflects their actual practice. Strengths of our study include the diversity of the study sample, which represents

pathologists in ten states, a 69% response rate among eligible participants, exceeding the national standard for physician surveys,(25) the detailed information gathered on the survey, and the quality of the analysis.

Our findings underscore complexity inherent in the subjective process of histological diagnosis of melanocytic skin lesions, revealing possible explanations for diagnostic discordance rates for melanoma and illustrating the potential for misclassification errors, with potentially substantial public health impacts, when identifying patient populations diagnosed with this maligancy. Future research may be helpful to assess the potential role of additional pathologist characteristics and other factors not evaluated here, as well as to determine whether the factors identified in this study may result in biases associated with the interpretation of more recent, “objective” diagnostic technology, including immunohistochemical markers, fluorescence in situ hybridization, comparative genomic hybridization, and gene expression profiling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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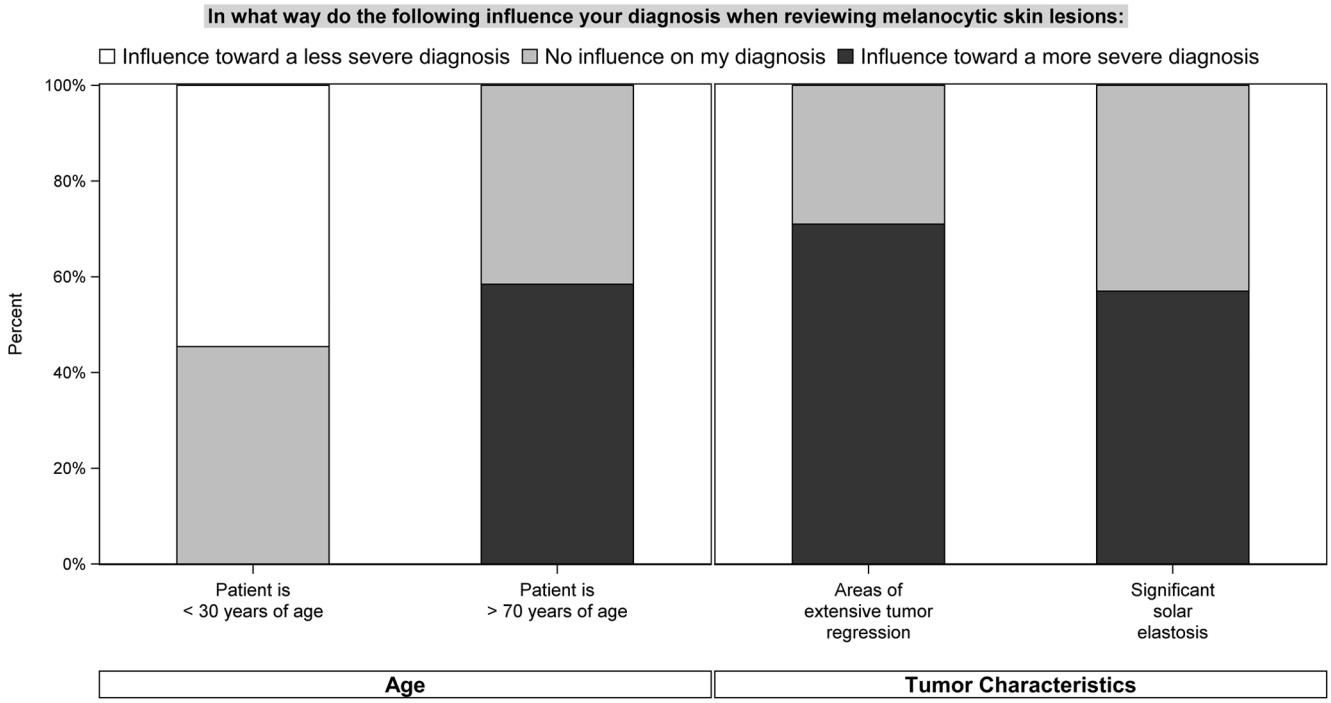

Figure 1.

MPATH - Patient and Tumor Characteristics and the Direction of a Diagnosis (n=207)

Table 1

Characteristics of participating pathologists (n=207)

Pathologist characteristic	number (%)
Age (yrs.)	
< 40	36 (17.4)
40–49	59 (28.5)
50–59	71 (34.3)
≥ 60	41 (19.8)
Mean age (SD)	51 (10.2)
Sex	
Male	123 (59.4)
Female	84 (40.6)
Board certification	
Dermatopathology (DP) ***	81 (39.1)
Other	126 (60.9)
Melanocytic skin lesion caseload per month **	
Low	76 (36.7)
High	131 (63.3)
Composite variable: DP certified and melanocytic skin lesion caseload **	
Not DP certified, low caseload	72 (34.8)
Not DP certified, high caseload	54 (26.1)
DP certified	81 (39.1)
Years interpreting melanocytic skin lesions	
<20	143 (69.1)
≥20	64 (30.9)
Ever interpret melanocytic skin lesions as borderline or uncertain	
No	21 (10.1)
Yes	186 (89.8)
Asks for second opinion at least once per month	
No	22 (10.6)
Yes	185 (89.4)
Requests FISH/CGH or other molecular analysis	
No	128 (61.8)
Yes	79 (38.2)

* sum of number of melanomas + benign melanocytic skin lesions interpreted per month

** average number of melanocytic skin lesions interpreted/month: low caseload <35/month; high caseload ≥35/month.

*** pathologists in this category have single or multiple certifications/fellowship training including dermatopathology

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for the association between pathologist characteristics and direction of diagnosis, by patient age and tumor characteristics* (n=207)

Context	**Patient age < 30**	**Patient age > 70**	**Tumor regression**	**Solar elastosis**
Direction of influence on diagnosis	**Less Severe (vs. No Influence)**	**More Severe (vs. No Influence)**	**More Severe (vs. No Influence)**	**More Severe (vs. No Influence)**
Pathologist characteristic	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**
DP certification and melanocytic skin lesion caseload**	n/a			
Not DP certified, low caseload	- -	- ref -	- ref -	- ref -
Not DP certified, high caseload		2.03 (0.96,4.29)	**2.87 (1.25,6.60)**	2.06 (0.98,4.35)
DP certified		**2.82 (1.40,5.69)**	**2.91 (1.29,6.53)**	**4.07 (1.98,8.38)**
Years interpreting melanocytic skin lesions				
< 20	- ref -	- ref -	- ref -	
≥ 20	**0.36 (0.20,0.67)**	**0.33 (0.17,0.63)**	0.49 (0.24,1.02)	n/a
Interprets melanocytic skin lesions as borderline or uncertain	n/a	n/a		
No			- ref -	- ref -
Yes			**4.73 (1.66 -13.53)**	**2.94 (1.03,8.37)**
Asks for second opinions	n/a			
No		- n/a-	- ref -	- ref -
Yes	.		**3.04 (1.12,8.26)**	**5.45 (1.92,15.43)**

*OR adjusted for variables with results shown in the same column. Variables denoted by n/a (not applicable), were not included in the adjusted model. Variables associated with the outcome at $p < 0.05$ are shown in bold.

**Average number of melanocytic skin lesions interpreted/month: low caseload <35/month; high caseload ≥35/month