

# Melanoma of the Skin in the Danish Cancer Registry and the Danish Melanoma Database

## A Validation Study

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**Background:** The nationwide Danish Cancer Registry and the Danish Melanoma Database both record data on melanoma for purposes of monitoring, quality assurance, and research. However, the data quality of the Cancer Registry and the Melanoma Database has not been formally evaluated.

**Methods:** We estimated the positive predictive value (PPV) of melanoma diagnosis for random samples of 200 patients from the Cancer Registry (n = 200) and the Melanoma Database (n = 200) during 2004–2014, using the Danish Pathology Registry as “gold standard”

reference. We further validated tumor characteristics in the Cancer Registry and the Melanoma Database. Additionally, we estimated the PPV of in situ melanoma diagnoses in the Melanoma Database, and the sensitivity of melanoma diagnoses in 2004–2014.

**Results:** The PPVs of melanoma in the Cancer Registry and the Melanoma Database were 97% (95% CI = 94, 99) and 100%. The sensitivity was 90% in the Cancer Registry and 77% in the Melanoma Database. The PPV of in situ melanomas in the Melanoma Database was 97% and the sensitivity was 56%. In the Melanoma Database, we observed PPVs of ulceration of 75% and Breslow thickness of 96%. The PPV of histologic subtypes varied between 87% and 100% in the Cancer Registry and 93% and 100% in the Melanoma Database. The PPVs for anatomical localization were 83%–95% in the Cancer Registry and 93%–100% in the Melanoma Database.

**Conclusions:** The data quality in both the Cancer Registry and the Melanoma Database is high, supporting their use in epidemiologic studies.

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Description of the process: We estimated the positive predictive value of melanoma diagnosis from the Danish Cancer Registry and Danish Melanoma Database during 2004–2014, using the Danish Pathology Registry as reference. We further validated tumor characteristics in the Danish Cancer Registry and Danish Melanoma Database, including histologic subtype, localization, Breslow thickness, and ulceration. Additionally, we estimated the positive predictive value of in situ melanoma diagnoses in Danish Melanoma Database, and the sensitivity of melanoma diagnoses in 2004–2014 defined as proportions of melanomas in Danish Pathology Registry also recorded in Danish Cancer Registry and Danish Melanoma Database.

Data availability: The data are held in Statistics Denmark and may only be released in aggregated form where individuals remain nonidentifiable, in accordance with Danish law. Access to the abovementioned registries and data linkage requires authorization by the Danish Data Protection Agency (Datatilsynet). The codes used for data retrieval and classification have been provided in the eAppendix.

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Population-based data sources are important for identification of trends in cancer incidence and for establishment and monitoring of preventive and therapeutic strategies.<sup>1,2</sup> In Denmark, detailed nationwide data on melanoma are available in the Danish Cancer Registry and the Danish Melanoma Database.<sup>3–5</sup> Although the data quality of the Cancer Registry is known to be high,<sup>6</sup> several important markers of severity and prognosis of melanoma are not registered. Such information is, however, routinely collected by the Melanoma Database. Further, both in situ melanomas and second primary incident cases of melanomas are recorded in the Melanoma Database, in contrast to the Cancer Registry that only contains records of primary invasive melanoma. The Cancer Registry offers an accurate and almost complete registration of cancer cases in Denmark since 1943.<sup>3</sup> The Melanoma Database was initiated in 1985 and became a clinical quality database in 2011 as part of the Danish Multidisciplinary Cancer Groups.<sup>4</sup> The database holds detailed information on tumor–node–metastasis (TNM) stage as defined by the American Joint Committee on Cancer,<sup>7</sup> and additional information on treatment and other clinical measures.

Knowledge about data quality is a prerequisite for valid use of registry data. However, studies of validity and completeness of melanoma data in the Cancer Registry and the Melanoma Database are sparse.<sup>5,8</sup> Further, although a manifest diagnosis of melanoma is based primarily on histologic verification by a trained pathologist, no previous validation studies have included pathology data in the evaluation.

We conducted a validation study of melanoma diagnoses in the Cancer Registry and the Melanoma Database, estimating positive predictive value (PPV) and completeness, using the Pathology Registry as the gold standard reference. In addition, we examined the validity of key characteristics of melanoma, including topography, morphology, ulceration, and Breslow thickness.

## METHODS

All Danes have a unique civil registration number assigned at birth or immigration,<sup>9</sup> which was used for unambiguous linkage of registries and databases. The study period was from 2004 to 2014, i.e., equivalent to the period after modernization of the Cancer Registry in 2004.<sup>3</sup>

### Data Sources

The Cancer Registry<sup>3</sup> has recorded incident cancer cases since 1943 and offers an accurate and almost complete registration of cancer incidence in Denmark. Cancer diagnoses are coded according to the *International Classification of Disease*, 10th revision, and the *International Classification of Disease for Oncology*, version 3, for topography and morphology codes.

The Melanoma Database<sup>4</sup> was initiated in 1985 to support quality assurance and research of melanoma. Data are reported on standardized forms to the Melanoma Database from pathologists and plastic surgeons undertaking diagnosis and treatment of melanoma patients. Data include histologic tumor characteristics at melanoma diagnosis, e.g., diameter, location, Breslow thickness, and morphologic subtype; and clinical data on treatment, disease progression, and recurrence. Further, both in situ melanomas and second primary incident cases of melanoma (not available in the Cancer Registry) are also recorded.<sup>3</sup> In 2011, the Melanoma Database was included as a clinical quality database within the Danish Multidisciplinary Cancer Groups, administered by the Clinical Quality Program of Danish Regions. The completeness of melanomas in Melanoma Database has increased since its inception and is currently 96% with the Pathology Registry as reference.<sup>10</sup>

The Pathology Registry has nationwide coverage of all histologic examinations performed by hospital pathologists since 2000 and private practicing pathologists since 2005.<sup>11</sup> Histologic diagnoses are recorded using a Danish version of the *Systematized Nomenclature of Medicine* together with full pathology (free text) report.<sup>11</sup> Although some patients with malignant melanoma undergo first biopsy at private pathologists, almost

all Danish melanoma patients are referred to further clinical work-up and surgery in the hospital setting, with appropriate registration (*Systematized Nomenclature of Medicine* codes) of the specific melanoma cases in the Pathology Registry.

### Validity

We estimated the validity of melanoma diagnoses (International Classification of Diseases, 10th revision (ICD-10): C43) on random samples of 200 patients from the Cancer Registry (n = 200) and the Melanoma Database (n = 200). All patients registered in the Cancer Registry or the Melanoma Database with a first-time diagnosis of melanoma during 2004–2014 were eligible for sampling.

The sampling of cases from the Cancer Registry and the Melanoma Database was intended as validation of specific tumor characteristics, notably Breslow thickness and ulceration, described in the complete pathology reports, but not coded in the Pathology Registry, our approximated gold reference. Moreover, we used this validity approach to evaluate whether the coding of melanoma cases in the Pathology Registry was consistent with the description of the melanoma lesions in the complete pathology reports. As this case-by-case evaluation of coding and complete pathology reports was not feasible as an automated approach, we chose to limit this part of our validation study to 200 random records from each of the melanoma data sources (the Cancer Registry and the Melanoma Database).

Using a structured data abstraction form (eAppendix 1; <http://links.lww.com/EDE/B309>), one author (S.A.P.) reviewed pathology reports for all 400 patients. These reports served as gold standard, i.e., a diagnosis of melanoma was considered verified if the diagnosis in the Cancer Registry or the Melanoma Database was compatible with the records in Pathology Registry. To validate the data collection, we evaluated the data abstraction form in 20 patients in a pilot phase by the first author (S.A.P., an MD) and one coauthor (S.K., an experienced dermatopathologist).

Further, we validated the histologic subtype and anatomic location of melanoma in the Cancer Registry and the Melanoma Database. Based on the International Classification of Disease for Oncology, version 3 codes in the Cancer Registry, which are highly similar to the *Systematized Nomenclature of Medicine* codes in the Pathology Registry (eAppendix 2a; <http://links.lww.com/EDE/B309>), we categorized the melanoma tumors into five histologic subtypes: superficially spreading melanoma, nodular melanoma, lentigo maligna melanoma, acral lentiginous melanoma, and “other” (remaining subtypes). Using the *International Classification of Disease*, 10th revision, codes from the Cancer Registry (eAppendix 2b; <http://links.lww.com/EDE/B309>), the anatomic location of the melanoma was categorized as “head and neck,” “upper limbs,” “torso,” “lower limbs,” or “other” (overlapping or unspecified location). Finally, we compared information on “Breslow thickness” and “ulceration” recorded in the Melanoma Database, but not the Cancer Registry, with

corresponding records in the Pathology Registry. Breslow thickness was regarded as valid in the Melanoma Database if the value was within  $\pm 0.1$  mm of that in the Pathology Registry. Information on ulceration was predominantly described in free text in the pathology records in the Pathology Registry. Information on present ulceration in the Melanoma Database was confirmed if also recorded in the Pathology Registry.

We also estimated the validity of in situ melanoma diagnoses on a random sample of 100 patients from the Melanoma Database. We did not estimate the corresponding validity for the Cancer Registry since reporting of in situ melanoma is not mandatory.

Finally, we estimated the PPV and sensitivity of melanoma overall according to sex, various age categories (<50, 50–59, 60–69, and  $\geq 70$  years), and calendar time of diagnosis (2004–2007, 2008–2010, and 2011–2014).

### Completeness

The completeness of melanoma diagnoses in the Cancer Registry and the Melanoma Database was estimated by comparison to the Pathology Registry. We included all patients with a first-time melanoma diagnosis (Systematized Nomenclature of Medicine [SNOMED] SNOMED codes) in the Pathology Registry during 2004–2014. Exclusion criteria included “potential in situ lesion,” or only a provisional melanoma diagnosis (i.e., not confirmed at the time of diagnosis). We then identified melanoma patients in the Melanoma Database and the Cancer Registry within  $\pm 60$  days of the diagnosis date in the Pathology Registry. We applied the same strategy to examine completeness of in situ melanoma. In supplementary analyses for both invasive and in situ melanomas, we repeated the analyses using intervals of 0,  $\pm 7$ ,  $\pm 14$ ,  $\pm 30$ , or  $\pm 120$  days of the Pathology Registry diagnosis date.

We sent records of all patients recorded with an invasive melanoma diagnosis in the Pathology Registry but not the Cancer Registry (regardless of differences in date of diagnosis in the registries) to the Danish Health Data Authority (administering Cancer Registry). Herein, resources were allocated to identify programming or other systematic errors in data handling that might explain the observed discrepancy. This effort revealed certain minor errors in the automated coding process (introduced in 2004) used to merge data on histologically verified melanoma from the Pathology Registry with the Cancer Registry. These irregularities in the Cancer Registry were corrected, and the missing cases of histologically verified melanomas were added to the Cancer Registry. Using the corrected Cancer Registry dataset for a post hoc sensitivity analysis, we estimated the completeness of melanoma overall in the Cancer Registry. Finally, the overall specificity for each registry was calculated as the number of individuals in Denmark of 18+ years old in 2014 who did not have a melanoma diagnosis according to, respectively, the Cancer Registry or the Melanoma Database (true negatives) divided by all individuals without melanoma (true negatives + false positives); the number of false positives was estimated based on information in the Pathology Registry.

### Statistical Analysis

We computed PPVs of registry diagnoses, histologic subtypes, and tumor sites, as proportions of each parameter confirmed by the Pathology Registry. For example, the PPV of a melanoma diagnosis in the Cancer Registry was computed as the proportion of patients with melanoma in the Cancer Registry who were also recorded with melanoma in the Pathology Registry. We computed sensitivity as the number of patients in the Cancer Registry and the Melanoma Database, divided by the total number of equivalent patients identified in the Pathology Registry.

All analyses were performed using STATA 14.0 (StataCorp, TX). We used Wilson score method to estimate 95% confidence intervals for all proportions. The study was approved by the Danish Data Protection Agency (record no. 15/30927).

### RESULTS

In the study period 2004–2014, 19,474 cases of melanoma were recorded in the Cancer Registry and 16,950 melanoma cases were recorded in the Melanoma Database. The number of melanoma cases recorded in the Cancer Registry increased from 1,138 cases in 2004 to 2,187 in 2014, and, correspondingly, from 836 to 2,563 in the Melanoma Database.

The overall PPVs of melanoma were 97% (95% CI = 94, 99) in the Cancer Registry and 100% (95% CI = 98, 100) in the Melanoma Database (Table 1). The overall sensitivity was 90% (95% CI = 90, 91) in the Cancer Registry and 77% (95% CI = 76, 77) in the Melanoma Database (Table 2). No substantial variations in PPVs or sensitivity were apparent by age or sex, but the sensitivity increased with calendar time in the Melanoma Database (Table 2).

For Breslow thickness and ulceration in the Melanoma Database, we observed agreement of 96% (95% CI = 92, 98) for thickness and of 75% (95% CI = 69, 81) for ulceration. Regarding in situ melanoma diagnoses in the Melanoma Database, the PPV was 97% (95% CI = 92, 99), whereas the sensitivity was 56% (95% CI = 54, 57).

In supplementary analyses, applying different intervals (0,  $\pm 7$ ,  $\pm 14$ ,  $\pm 30$ ,  $\pm 60$ , or  $\pm 120$  days) for the time between date of melanoma diagnosis in the Cancer Registry/Melanoma Database and the corresponding date in the Pathology Registry revealed gradually increasing sensitivities in both the Cancer Registry (17.7%–91.2%) and the Melanoma Database (28.2%–77.2%); however, the main increase occurred during the first 1–2 weeks (eTable 1; <http://links.lww.com/EDE/B309>).

A total of 1,424 patients were registered with invasive melanoma in the Pathology Registry but not in the Cancer Registry. Reasons for this discrepancy were resolved in collaboration with the Danish Health Authorities (eFigure 1; <http://links.lww.com/EDE/B309>). Consequently, 917 incident cases of melanomas were added to the Cancer Registry during 2004–2014, i.e., 744 cases derived from the Pathology Registry that were not captured by the original registration

**TABLE 1.** PPV and 95% CIs of Codes for Melanoma, Including Subtypes and Recorded Anatomical Localization in the Danish Cancer Registry and the Danish Melanoma Database, Using the Danish Pathology Registry as Gold Standard Reference

	Danish Cancer Registry (n = 200)		Danish Melanoma Database (n = 200)	
	Confirmed/Sample	PPV (95% CI)	Confirmed/Sample	PPV (95% CI)
Any melanoma diagnosis	194/200	97% (94, 99)	200/200	100% (98, 100)
Subtype of melanoma				
Superficial spreading melanoma	145/145	99% (95, 100)	155/161	96% (92, 98)
Nodular melanoma	13/15	87% (62, 96)	25/27	93% (77, 98)
Lentigo maligna melanoma	6/6	100% (61, 100)	2/2	100% (34, 100)
Acral lentiginous melanoma	-	-	2/2	100% (34, 100)
Other/unspecified	28/34	82% (67, 92)	3/8	38% (14, 69)
Anatomical localization				
Head and neck	20/22	91% (72, 98)	24/25	96% (81, 99)
Upper limbs	20/24	83% (64, 93)	24/24	100% (86, 100)
Torso	76/81	94% (86, 97)	89/95	94% (87, 97)
Lower limbs	62/64	95% (86, 98)	42/45	93% (82, 98)
Missing	0/9	-	0/11	-

CI indicates confidence interval.

**TABLE 2.** PPV and Sensitivity Reported in Frequency and Proportion with 95% CIs of Codes for Melanoma Stratified by Year, Age, and Sex in the Danish Cancer Registry and the Danish Melanoma Database, Using the Danish Pathology Registry as Gold Standard Reference

	Danish Cancer Registry		Danish Melanoma Database	
	PPV (95% CI)	Sensitivity (95% CI)	PPV (95% CI)	Sensitivity (95% CI)
Overall	194/200 (97; 94, 99)	17,193/19,013 (90; 90, 91)	200/200 (100; 98, 100)	14,594/19,013 (77; 76, 77)
2004–2007	51/53 (96; 87, 99)	4,744/5,454 (87; 86, 88)	42/42 (100; 92, 100)	3,540/5,454 (65; 64, 66)
2008–2010	59/61 (97; 89, 99)	4,746/5,251 (90; 90, 91)	58/58 (100; 94, 100)	3,592/5,251 (74; 73, 75)
2011–2014	84/86 (98; 92, 99)	7,703/8,308 (93; 92, 93)	100/100 (100; 96, 100)	7,462/8,308 (90; 92, 93)
Age (years)				
<50	68/69 (99; 92, 100)	5,537/6,164 (90; 89, 91)	72/72 (100; 95, 100)	4,759/6,164 (77; 76, 78)
50–59	26/27 (96; 82, 99)	2,865/3,150 (91; 90, 92)	30/30 (100; 89, 100)	2,407/3,150 (76; 75, 78)
60–69	46/48 (96; 86, 99)	4,746/5,251 (92; 91, 93)	45/45 (100; 92, 100)	3,387/4,342 (78; 77, 79)
≥70	54/56 (96; 88, 99)	4,807/5,357 (90; 89, 91)	100/100 (100; 93, 100)	4,041/5,357 (75; 74, 77)
Sex				
Men	92/96 (96; 90, 98)	7,866/8,642 (91; 90, 92)	91/91 (100; 96, 100)	6,675/8,642 (77; 76, 78)
Women	102/104 (98; 93, 100)	9,327/10,371 (90; 89, 91)	109/109 (100; 97, 100)	7,919/10,371 (76; 76, 77)

CI indicates confidence interval.

procedure in the Cancer Registry and 173 cases that were correctly recorded in the Cancer Registry as part of standard procedures updating historical information. These revisions yielded an increase in the overall sensitivity of the Cancer Registry from 93% (95% CI = 92, 93) to 97% (95% CI = 97, 98) in analyses based on updated Cancer Registry data. The overall specificity in 2014 was 99.978% (95% CI = 99.977, 99.979) in the Cancer Registry and 99.965% (95% CI = 99.964, 99.967) in the Melanoma Database.

It should be noted, though, that these sensitivity and specificity estimates were based on all data available, i.e., we

disregarded potential differences in dates of diagnosis between the Cancer Registry and the Pathology Registry.

## DISCUSSION

In this validation study of registration of skin melanoma in the Cancer Registry and the Melanoma Database, we found a high validity of melanoma diagnoses in both data sources. The completeness of the Cancer Registry was also high and increased further after addition of data from the Danish Health Data Authority obtained by cross-linking the Cancer Registry with data from the Pathology Registry. The completeness



**TABLE 3.** Agreement with 95% CIs of Ulceration and Breslow Thickness as Recorded in the Danish Melanoma Database, Using the Danish Pathology Registry as Gold Standard Reference

Ulceration	
Confirmed/Sampled	Agreement (95% CI)
150 <sup>a</sup> /200	75% (69, 81)
Ulceration value	No. with ulceration value (n = 150)
Present	13
Absent	137
Ulceration value in the 44 cases coded in Danish Melanoma Database but not described in the pathology register	No. with ulceration value (n = 44)
Present	1
Absent <sup>b</sup> (possible confirmed)	43
(Confirmed + possible confirmed)/sampled	Agreement (95% CI)
193/200	97% (93, 99)
Breslow Thickness <sup>c</sup>	
Confirmed/Sampled	Agreement (95% CI)
191/200 <sup>d</sup>	96% (92, 98)

<sup>a</sup>Ulceration value in one case could not be confirmed. Five cases had missing information on ulceration in both registries. Forty-four cases were coded in the Danish Melanoma Database but not described in the pathology registry.

<sup>b</sup>In 43 cases, the ulceration value could be categorized as possible confirmed. Possible confirmed refers to the melanomas coded with no ulceration in the Danish Melanoma Database, and with no description of the ulceration in the pathology register.

<sup>c</sup>Breslow thickness in the Danish Melanoma Database was considered confirmed if within  $\pm 0.1$  mm of the value reported in the pathologist-free text in the pathology registry.

<sup>d</sup>In eight of the cases, there was no description of the Breslow thickness in the pathology registry. One case could not be confirmed because of disagreement of the value of the Breslow thickness between the two registries.

CI indicates confidence interval.

of melanoma diagnoses in the Melanoma Database increased markedly since initiation of the database. Further, validity measures of other tumor characteristics, including subtypes, localization, Breslow thickness, and ulceration, were generally high.

Our study had several strengths. We used the Pathology Registry as gold standard reference for validation of diagnoses, localization, and tumor characteristics. The Pathology Registry data also allowed ascertainment of completeness, i.e., by cross-linking the Pathology Registry with the Cancer Registry and the Melanoma Database. We believe that use of the Pathology Registry is a unique strength of our study in an international context because this registry holds detailed information on histologic examinations performed in Denmark.

Our study also had some limitations. We aimed primarily at addressing the validity of melanoma diagnoses overall in the two data sources. The statistical precision was therefore limited in some strata, and particularly for the rarer types of melanoma. Our choice of the Pathology Registry as gold standard reference introduced some limitations. The

information in the Pathology Registry is lacking for certain variables, e.g., ulceration. For ulceration, the Melanoma Database may even provide better data, as pathologists reporting to the Melanoma Database are actively instructed to record whether ulceration was present, as opposed to the Pathology Registry, where reporting of ulceration is left to the discretion of the individual pathologist and is often only reported if present. Also for site of melanoma, the Melanoma Database data may be of superior quality, as the specific site(s) of the melanoma lesion(s) is reported by the plastic surgeon performing the surgical intervention to the Melanoma Database, whereas information in the Pathology Registry is relying solely on the pathologist's reporting and knowledge. We used the Pathology Registry as an approximated gold standard for assessing the sensitivity of melanoma in the Cancer Registry and the Melanoma Database. Our manual review of pathology reports of melanoma preparations in the Pathology Registry revealed that some cases of in situ (<2.0%) or noncutaneous (<0.50%) melanoma were erroneously recorded as invasive cutaneous melanoma in the Pathology Registry. Although the use of the Pathology Registry as gold standard reference thus entails some limitations, we believe that the Pathology Registry provides an excellent reference, particularly considering the scale and detail of the information available in this nationwide data source.<sup>11</sup>

The completeness of the Cancer Registry was already high before the modernization in 2004.<sup>3,6,8</sup> Based on the present study, correction of the automated algorithm for registration at the Cancer Registry further improved the sensitivity of the Cancer Registry melanoma diagnosis. In a broader context, we believe that our study highlights a general demand for validation of cancer registration as part of substantial changes in the registration procedures, including automated algorithms and cross-linkage of registries, and that such validation should be conducted at the level of site-specific cancer, to achieve the highest degree of completeness and validity.

Our results offer guidance on future use of the Cancer Registry and the Melanoma Database for research purposes. The consistently high PPV during 2004–2014 indicates that both registries are excellent resources for identification of patients with melanoma for analytical studies (e.g., risk or prognosis studies) in the entire study period. However, our results also reveal that descriptive studies of nationwide incidence rates of melanoma based solely on the Cancer Registry or, notably, the Melanoma Database would need to incorporate changes in sensitivity of diagnosis over time. An important strength of both the Cancer Registry and the Melanoma Database is the possibility of linkage to other Danish data sources with information on, e.g., use of prescription drugs, vital statistics, and comorbidities.

In conclusion, we showed that the validity of overall and type-specific melanoma diagnoses was high in both the Cancer Registry and the Melanoma Database. The Cancer Registry is an attractive resource for studies of incidence and trends of

melanoma in Denmark owing to its high completeness ensured via the traditional and mandatory reporting of cancer diagnoses. The Melanoma Database will increasingly also be able to fulfill this role, provided the current high completeness of this register is maintained. An important feature of using both the Cancer Registry and the Melanoma Database is achievement of more comprehensive information on key tumor characteristics than available solely in the Cancer Registry.

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