Cutaneous Melanoma In Situ: Translational Evidence from a Large Population-Based Study

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ABSTRACT

Background. Cutaneous melanoma in situ (CMIS) is a nosologic entity surrounded by health concerns and unsolved debates. We aimed to shed some light on CMIS by means of a large population-based study.

Methods. Patients with histologic diagnosis of CMIS were identified from the Surveillance Epidemiology End Results (SEER) database.

Results. The records of 93,863 cases of CMIS were available for analysis. CMIS incidence has been steadily increasing over the past 3 decades at a rate higher than any other in situ or invasive tumor, including invasive skin melanoma (annual percentage change [APC]: 9.5% versus 3.6%, respectively). Despite its noninvasive nature, CMIS is treated with excision margins wider than 1 cm in more than one third of cases. CMIS is associated with an increased risk of invasive melanoma (standardized incidence ratio [SIR]: 8.08; 95% confi-

dence interval [CI]: 7.66–8.57), with an estimated 3:5 invasive/in situ ratio; surprisingly, it is also associated with a reduced risk of gastrointestinal (SIR: 0.78, CI: 0.72–0.84) and lung (SIR: 0.65, CI: 0.59–0.71) cancers. Relative survival analysis shows that persons with CMIS have a life expectancy equal to that of the general population.

Conclusions. CMIS is increasingly diagnosed and is often overtreated, although it does not affect the life expectancy of its carriers. Patients with CMIS have an increased risk of developing invasive melanoma (which warrants their enrollment in screening programs) but also a reduced risk of some epithelial cancers, which raises the intriguing hypothesis that genetic/environmental risk factors for some tumors may oppose the pathogenesis of others. *The Oncologist* 2011;16:896–903

INTRODUCTION

Cutaneous melanoma is a serious threat for the public health because of its incidence rates—which have risen faster than those for any other malignancy in Caucasian

populations over the last 30 years [1–3]—and because of its intrinsic chemoresistance, which makes this disease one of the few malignancies for which no standard systemic therapy is recommended [4–7]. Therefore, early diagnosis cur-

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rently represents the “best therapy” for this type of skin cancer.

As for epithelial tumors, the invasive form of melanoma must be differentiated from the “in situ” tumor where malignant melanocytes remain confined within the skin epithelium (without trespassing the basal membrane): this nosologic entity is called cutaneous melanoma in situ (CMIS) [8, 9] and corresponds to the first level of Clark’s classification system [10, 11] and to stage 0 of the AJCC TNM system [12].

The scientific importance of CMIS lies in the fact that in situ tumors are generally believed to be precursors of invasive tumors: in particular, it has been postulated that such cancers develop through the sequence dysplasia > in situ tumor > invasive tumor. This theory, first formulated for cervical cancer [13], has been rapidly applied to most epithelial tumors, and more recently a similar hypothesis has been made also for cutaneous melanoma [14–19]. The pathologic definition of in situ tumors is tightly associated with a key clinical feature, which is that these cancer precursors are by definition unable to grow and metastasize and thus their surgical removal is curative in virtually 100% of cases. This fact should confine the practical relevance of CMIS to the issue of early diagnosis and screening programs.

In contrast, despite the above considerations, CMIS is linked to some health concerns and unsolved debates regarding its clinicopathologic diagnosis [19–24], therapeutic/follow-up management [20, 25–29], and prognostic relevance [24, 30–32].

Patients diagnosed with CMIS have a higher risk of developing invasive melanoma [33], which prompts clinicians to enroll patients with CMIS into screening programs [29, 33, 34]. Moreover, CMIS has been associated with the risk of other cancers [31]. The growing incidence of CMIS is making it difficult to understand whether or not invasive skin melanoma incidence is actually stable or increasing [35] and whether or not the prognosis of patients with a melanocytic tumor is changing [36]. Finally, despite its noninvasive nature, international guidelines—which recommend excision margins ranging from 10 to 20 mm for invasive melanoma—suggest excision margins of 5 mm as the standard treatment for CMIS [4–6], although some investigators suggest the use of Mohs’ surgery [37–39] or even topical therapeutics [40–42].

Because the currently available evidence regarding CMIS is based on a scattered small series, which makes it impossible to draw any reliable conclusion, we intended to perform a dedicated large-scale epidemiologic study to shed some light on the clinical relevance of this nosologic entity: to this aim we used the information obtained from the Surveillance & Epidemiology End Results (SEER) da-

tabase, the largest freely available population-based databank on cancer [43].

MATERIALS AND METHODS

Data were obtained from all 17 U.S. cancer registries participating in the SEER program [44] using the Seer*Stat software (version 6.5.2) [45].

We identified patients with histologically confirmed diagnosis of CMIS (1973–2006). For these cases, we searched for the variables of interest listed in Table 1, as well as those necessary for survival analyses.

CMIS incidence and survival rates were compared with those of invasive skin melanoma ($n = 183,175$), which were also retrieved from the SEER database.

Both overall and disease-specific survival rates were considered, survival estimates being calculated according to the actuarial method (time intervals: 12 months).

Relative survival rates for patients with CMIS were also computed using the Seer*Stat software. Relative survival is a net survival measure representing cancer survival in the absence of other causes of death: it is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer-free individuals, the formulation being based on the assumption of independent competing causes of death. The relative survival rate adjusts for the survival rate of the general population (in this case, the United States population) for that race, sex, age, and date at which the age was coded (if this information is missing, that individual is excluded from the analysis).

The risk of developing other tumors was measured using the standardized incidence ratio (SIR), which is the ratio between the observed and the expected cases of a given event (according to the event incidence in the general population).

Ninety-five percent confidence interval (CI) was used as the measure of estimate variation, as appropriate. Probability values (p values) lower than 5% were considered significant.

RESULTS

The search retrieved 93,853 cases of CMIS in 82,127 patients (Table 1), the great majority being white people (93.1%); 7,597 patients (9.3%) had two or more CMIS. The median age was 63 years (interquartile range [IQR]: 50–74), the disease frequency being higher in males (55.7%); interestingly, also invasive melanoma shows a higher incidence in men (55.5%), whereas the median age is lower (57 years).

Considering the whole time span (1973–2006), CMIS incidence increased from less than 1 case to 14 cases per 100,000 per year, with an annual percentage change (APC)

Table 1. Clinical and pathologic characteristics of 93,853 cases of CMIS retrieved from the SEER database (1973–2006)

Gender		
Male	52,225	55.7%
Female	41,628	44.3%
Age (years)		
Mean (SD)	61.2 (16.0)	
Median (IQR)	63.0 (50–74)	
Race		
White	76,460	93.1%
Other/unknown	5,421	6.6%
Black	246	0.3%
Site		
Head and neck	35,251	37.6%
Trunk	23,381	24.9%
Upper limb	21,395	22.8%
Lower limb	13,109	14.0%
Unknown site	717	0.7%
Laterality		
Left side	39,903	42.5%
Right side	36,457	38.8%
Unpaired site/unknown	17,493	18.6%
Number of CMIS		
Single	74,530	90.7%
Multiple	7,597	9.3%
Total patients	82,127	100%
Pathology		
CMIS NOS	52,531	56.0%
LMM	33,034	35.2%
SSM	7,913	8.4%
ALM	375	0.4%
Treatment		
Excision biopsy NOS	6,386	6.8%
LMM	2,015	31.5%
Other	4,371	68.5%
<1-cm excision margin	52,051	55.5%
LMM	25,391	48.7%
Other	26,660	51.3%
>1-cm excision margin	35,416	37.7%
LMM	5,628	15.9%
Other	29,788	84.1%

Abbreviations: ALM, acro-lentiginous; CMIS, cutaneous melanoma in situ; IQR, interquartile range; LMM, Lentigo maligna; NOS, not otherwise specified; SD, standard deviation; SSM, superficial spreading.

equal to 9.5% (CI: 8.6%–10.5%); this increasing trend outperforms that of invasive skin melanoma (APC: 3.6%, CI: 3.4%–3.8%), as shown in Figure 1. Remarkably, this steep rise of CMIS diagnosis outperforms also that of lung cancer in women (APC: 2.6%, CI: 2.1%–3.0%; SEER data from 293,083 patients) and is slightly higher than the increase in breast in situ carcinoma (APC: 7.1%, CI: 6.1%–8.1%; SEER data from 135,015 patients).

With regard to CMIS location, “head and neck” was the body site with the highest incidence (37.6%), followed by the extremities (36.8%), with a modest prevalence of left-sided lesions (52.2% of lateralized lesions). Noticeably, also invasive melanoma shows a slightly higher incidence in the left side of the body (51.9% of lateralized lesions), whereas the trunk is the most frequently affected site (34.7%). At pathology evaluation, CMIS not otherwise specified (NOS) was the most common diagnosis (56.0%). Lentigo maligna CMIS ($n = 33,034$; 35.2%) occurred in older patients (median age: 70 years) and was mainly (but not exclusively) localized in the head and neck region (66.2%).

Treatment consisted of surgical removal of the lesion with an excision margin <1 cm in most cases (55.5%); however, 37.7% of cases were treated with wider excision (margin >1 cm), with no significant change of this percentage over the past 2 decades (Figure 2). Different extent of surgical excision margins (i.e., <1 cm versus >1 cm) did not appear to affect melanoma-specific survival (log-rank test p value = 0.52).

CMIS associated with a significantly increased risk of cancer in general and invasive melanoma in particular (standardized incidence ratio [SIR]: 8.08, 95% CI = 7.66–8.57), the mean onset time (mean age at event – mean age at exposure) being 13.8 years. Unexpectedly, CMIS was also associated with a reduced risk of malignancies arising from the respiratory (SIR: 0.65, 95% CI = 0.59–0.71) and digestive (SIR: 0.78, 95% CI = 0.72–0.84) system (Table 2), a feature shared by invasive melanoma (SIR: 0.77 [95% CI = 0.73–0.82] and 0.89 [95% CI = 0.85–0.93], respectively).

After a mean follow-up of 68.2 months, 12,649 patients (15.4%) have died, 532 (0.6%) of melanoma: overall (upper panel) and melanoma-specific (lower panel) survival rates of patients with CMIS and with invasive melanoma are shown in Figure 3. Importantly, life expectancy of patients diagnosed with CMIS does not differ from that of the general population, which is clearly not the case for patients with invasive melanoma (relative survival rates for both populations as well as their combination are shown in Figure 4). Considering the 5-year survival rates, the prognosis of patients diagnosed with cutaneous melanoma (inva-

Figure 1. Incidence of cutaneous melanoma (invasive melanoma, CMIS, and globally considered) over the past 3 decades (1973–2006) according to the Surveillance Epidemiology End Results (SEER) data.

Abbreviation: CMIS, cutaneous melanoma in situ.

Figure 2. Treatment of cutaneous melanoma in situ over time (1973–2006) according to the Surveillance Epidemiology End Results (SEER) data.

Abbreviation: NOS, not otherwise specified.

sive + CMIS) has been improving over the past 3 decades (the melanoma-specific survival rate increased from 85.0% to 93.9%); though slightly reduced, this favorable trend is maintained also after removing the potentially “diluting” effect of CMIS (Figure 5).

DISCUSSION

Using the largest series ever reported on, we have described some key epidemiologic features of cutaneous melanoma in situ (CMIS) that could shed some light on the clinical relevance of this nosologic entity. While presenting the results, we are aware of the fact that although the SEER database provides investigators with a unique opportunity of generating and testing medical hypotheses on an unprecedented large series of patients, under-reporting is a potential limit of this databank, especially when it comes to conditions like CMIS that are routinely and increasingly treated in the outpatient setting.

Although most investigators agree that the incidence of skin melanoma is rising worldwide [1–3], some have questioned this statement, sustaining either that benign lesions

are erroneously included in the calculations [46] or that the increased incidence regards mainly invasive [47] or in situ lesions [48], or even that the incidence is declining [49]. As shown in Figure 1, according to the SEER data, the incidence of CMIS is remarkably increasing over the past 3 decades, which might be related to an actual “epidemic” of CMIS (as postulated for invasive melanoma [36]) but also to the increased attention paid by physicians and the general population to the early diagnosis of skin melanoma (so called “skin awareness”) [50–52]. As reported in the Results section, this rise of incidence is steeper than that of any other invasive and in situ malignancy. Importantly, the increase in CMIS incidence does not account for the whole increment in skin melanoma (in situ + invasive) incidence, as invasive melanoma rates are also growing, although at a slower pace (Figure 1).

The parallel increase of both invasive and in situ melanoma supports the hypothesis that the former tumor passes through the phase of CMIS before becoming capable of infiltrating surrounding tissues and metastasizing. The small but consistent prevalence of left-sided lesions and male gender in both invasive and in situ melanoma might be seen as additional epidemiologic evidence of the relationship between the two diseases. On the other hand, the higher rate of CMIS in the head and neck region supports the hypothesis that lentigo maligna CMIS (the most frequent type of CMIS in this body area) has a lower tendency to progress to invasive melanoma.

Considering the last decade, the ratio between invasive and in situ melanoma is about 1.5:1 (Figure 1); assuming that each invasive melanoma passes through the phase of CMIS (although no direct proof of this hypothesis exists), this ratio might imply that approximately 3 out of 5 cases of CMIS might progress to invasive melanoma. Lending support to this hypothesis, the risk of developing invasive melanoma is approximately eight times higher in people diagnosed with CMIS as compared with the general population (Table 2). The increased risk of invasive melanoma in patients with a previous diagnosis of CMIS was already known, although in smaller series its extent was probably overestimated: for instance, in a series of 3,766 Swedish patients diagnosed with CMIS from 1958 to 1992, Wassberg and colleagues reported a SIR of 22.2 [31], which is almost three times higher than that observed in the SEER series. Moreover, the same investigators described a higher risk of cancer in general (SIR: 2.2, 95% CI: 2.0–2.4) and some tumors in particular, such as breast cancer (in females), gastrointestinal cancers, and hematologic malignancies [31]. In this regard, the SEER data allowed us to confirm the higher risk of some hematologic tumors (Table 2), whereas no increased risk of breast carcinoma could be found (SIR: 1.01, 95% CI: 0.91–1.11). Surprisingly, we found that the

Table 2. Risk of invasive tumors in patients with CMIS

Tumor type	Observed	Expected	SIR	95% CI	Excess risk	Mean age at event
All sites	5,181	4,255	1.22	1.18–1.25	33.1	71.7
All solid tumors	4,660	3,789	1.23	1.19–1.27	31.1	71.5
Melanoma of the skin	1,236	153	8.08	7.66–8.57	38.7	68.6
Prostate	1,115	905	1.23	1.16–1.31	7.5	73.1
Lip	22	13	1.69	1.06–2.56	0.3	77.4
All hematological	396	350	1.13	1.02–1.25	1.7	73.5
Non-Hodgkin lymphoma	200	170	1.18	1.02–1.35	1.1	72.9
Lymphocytic leukemia	91	57	1.60	1.28–1.95	1.2	72.9
Chronic lymphocytic leukemia	78	50	1.56	1.23–1.94	1.0	73.3
Digestive system	659	844	0.78	0.72–0.84	–6.6	74.9
Colon, rectum and anus	402	520	0.77	0.70–0.85	–4.2	75.4
Liver, gallbladder, biliary ducts	47	68	0.69	0.51–0.92	–0.8	75.8
Pancreas	81	108	0.75	0.59–0.93	–1.0	74.3
Respiratory system	442	685	0.65	0.59–0.71	–8.7	74.5
Larynx	15	38	0.39	0.22–0.65	–0.8	77.2
Lung and bronchus	423	640	0.66	0.60–0.73	–7.8	74.4

Standardized incidence ratios were calculated based on 37,745 persons (person-years: 279,451; mean person-years at risk: 7.4; mean age at exposure: 58.9). Excess risk is per 10,000.

Abbreviations: CI, confidence interval; CMIS, cutaneous melanoma in situ; SIR, standardized incidence ratio.

risk of gastrointestinal tumors is even diminished in patients with CMIS (along with the risk of lung cancer; see Table 2), which highlights the importance of having at disposal large databases to draw reliable conclusions, especially when the event rates are relatively low.

Despite the fact that CMIS is associated with a significantly increased risk of invasive tumors, it is interesting to note that the life expectancy overlaps with that of the general population (5-year relative survival rate = 100%; Figure 4). This might be linked (at least in part) by two factors: first, the melanoma-specific mortality rates are quite low (0.3% at 5 years), which suggests that invasive melanomas arising in people with CMIS are mainly represented by thin lesions with a high curability rate; this phenomenon might in turn be related to the enrollment of these patients into screening programs. Second—as mentioned above—persons with CMIS are at lower risk of cancers that are considered “big killers,” such as lung and colorectal carcinomas, an observation never reported before.

CMIS association with higher incidence of invasive melanoma could well be due to the similar genetic background and/or environmental risk factors characterizing the two nosologic entities; in contrast, it appears much more difficult to explain the finding that people with CMIS carry a lower risk of epithelial tumors generally featuring worse prognosis (in terms of mortality rates intended as ratio of disease-specific deaths to incidence) as compared with in-

vasive melanoma. Considering that invasive melanoma shares this epidemiologic feature with CMIS, an intriguing hypothesis might be that the genetic background and/or the environmental risk factors underlying skin melanoma development can oppose the carcinogenesis of some epithelial tumors. Besides representing a scientific challenge, such findings could represent a hint (or a warning) while analyzing and/or comparing molecular profiles of different tumors, as they are (at least in past) conflicting with the theory of common cancer pathways [53–55].

The extent of CMIS-free margins obtained with surgical excision does not appear to have a significant impact on melanoma-specific survival, as suggested by the similar rates of melanoma-related deaths in patients with <1 cm as compared with those with >1 cm excision margins. As a corollary, CMIS is likely best managed simply with a pathologically margin-free excision: wider margin excisions—which continue to represent a significant proportion of the surgical treatments (more than one third; see Figure 2) over the past 2 decades—should be discouraged.

Finally, the SEER data allowed us to verify whether the prognosis of invasive melanoma has been changing over the past 30 years independently of the impact of the increasing CMIS incidence. Interestingly, as shown in Figure 5, the prognosis of patients diagnosed with cutaneous melanoma (invasive + CMIS) has been improving over the past 3 decades (the melanoma-specific survival rate increased

Figure 3. Overall (upper panel) and melanoma-specific (lower panel) survival rates at 1, 2, 3, 4, and 5 years for patients with CMIS, invasive melanoma, and globally considered (Surveillance Epidemiology End Results [SEER] data 1973–2006).

Abbreviation: CMIS, cutaneous melanoma in situ.

Figure 4. Relative survival rates at 1, 2, 3, 4, and 5 years for patients with CMIS, invasive melanoma, and globally considered (Surveillance Epidemiology End Results [SEER] data 1973–2006).

Abbreviation: CMIS, cutaneous melanoma in situ.

from 85.0% to 93.9%); although slightly reduced, this favorable trend—which has been questioned by some investigators [56]—is maintained also after removing the potentially “diluting” effect of CMIS advocated by some authors [57, 58]. Our data do not allow discernment on whether this positive finding is due to earlier diagnosis

Figure 5. Trends of melanoma-specific 5-year survival rates for patients with cutaneous melanoma in situ (CMIS), invasive melanoma and globally considered over the past 3 decades (Surveillance Epidemiology End Results [SEER] data 1973–2006).

Abbreviation: CMIS, cutaneous melanoma in situ.

(which is notoriously accompanied by lower risk of melanoma-related death) or ameliorated therapeutic strategies (e.g., adjuvant interferon-alpha, sentinel node biopsy), which is a matter of continuous debate [57–61]; however, within the frame of this debate, it appears important to have clarified—by means of such a large series—the separate impact of invasive and in situ melanoma in the epidemiology of the deadliest skin disease.

Taken together, the above analysis of the SEER data can be regarded both as the basis of a practical guideline for the management of CMIS and as a source of some hints regarding melanoma epidemiology and cancer predisposition. In particular, we conclude that CMIS is a condition more and more frequently diagnosed with no significant impact on life expectancy: accordingly, its relevance is mainly linked to the clinical [22, 62] and pathologic [21, 63, 64] difficulty in making a differential diagnosis with invasive melanoma. Although their enrollment in screening programs for the early detection of skin melanoma is warranted because of the risk of developing invasive melanoma, patients diagnosed with CMIS should be reassured on the benign nature of their condition that is associated with a normal life expectancy. Finally, the fact that CMIS increasing incidence does not nullify the positive trend regarding the prognosis of invasive melanoma and the fact that an in situ tumor is associated with a lower risk of some invasive cancers deserves further attention and investigation.

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AUTHOR CONTRIBUTIONS

Conception/Design: Simone Mocellin, Donato Nitti

Provision of study material or patients: Simone Mocellin, Donato Nitti

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