The burden of malignant melanoma — Lessons to be learned from Austria

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Abstract Aim of study: Incidence rates of melanoma, generated by cancer registries (CRs), are susceptible to reporting inconsistencies due to increasing decentralisation of diagnosis. We therefore independently assessed the burden of melanoma in Austria.

Methods: We collected histopathological reports on melanoma of all patients diagnosed in Austria in 2011. Demographic and clinical characteristics, histopathological tumour stages were assessed. Their regional distributions and incidence rates were analysed and compared with data of national and international CRs.

Results: A total of 5246 patients were diagnosed with 1951 in-situ and 3295 invasive melanomas in Austria in 2011 (population 8.4 million). Age, sex and anatomic distribution corresponded to findings in other European countries, however, the incidence of 25/100,000 (world age-standardised rate) for invasive melanomas was two-fold higher than published by the
1. Introduction

The burden of melanoma has been dramatically increasing since the 1950s [1–6]. Worldwide, population-based cancer registries (CRs) generate incidence rates and databases for epidemiological research, cancer prevention, and control [7–10]. Data quality of CRs entirely depends on the completeness of case ascertainment, which is estimated by a variety of standard methods [3,4,7,8,11,12]. However, little is known about the relative merits and weaknesses of such methods, and studies on case completeness (CC) at the level of facilities, where the diagnosis and treatment occurs, are lacking [8,11,13,14].

In Austria, the federal statistics agency “Statistics Austria” runs the national Cancer Registry (CR) and hospital-based facilities are legally obliged to report all newly diagnosed cancer cases (Cancer Statistics Act 1969 and Cancer Statistics Ordinance 1978). Since 1983 the Austrian CR has annually published absolute numbers, incidence rates and trends of malignancies and investigated its CC on national and regional levels with internationally recommended methods [15–18]. In 2007 the International Agency for Research on Cancer (IARC) classified the Austrian data quality as high and in 2012 the Austrian CR estimated an 94% overall CC for 2005 [16,19]. In contrast to hospitals, Austrian clinicians in private practice and non-hospital-based pathology laboratories are not legally obliged to report cancer cases. This might lead to reporting inconsistencies of melanoma cases as those are frequently diagnosed in non-hospital settings [13,14]. Still, Statistics Austria, although suspecting that underreporting influences incidences of various cancer types, assumes that melanoma patients diagnosed in outpatient settings would require subsequent hospital-based treatment leading to their registration [15]. However, this might not apply to thin melanomas.

The Austrian CR published an incidence rate of 12 new melanoma cases/100,000 (world age-standardised rate [WSR]) for 2011, implying a 2.5 fold increase since 1983 similar to increments seen in many Western countries [4,6,15,20,21]. Apart from a true rise in numbers, better documentation by CRs and raised dermatological surveillance may underlie this so called “melanoma epidemic” [17,18,21,22]. On the other hand, the increased detection of early tumours associated with rising skin biopsy and stable disease-specific mortality rates are suggestive of overdiagnosis of melanoma — defined as diagnosing a condition that although fulfilling the pathological criteria for cancer would not go on to cause symptoms and death — and/or false-positive diagnosis — that is overcalling benign lesions as malignant [1,2,22,23]. However, research into these complex and contentious issues on a national level is challenging and evidence remains scarce.

In this population-based study, we obtained complete nationwide numbers of all primary melanomas diagnosed in Austria in 2011. We quantified the exact magnitude of melanoma underreporting to the CR and analysed regional disparities in incidence rates of early and late stage tumours.

2. Methods

2.1. Study population and data collection

The institutional review board of the city of Vienna approved the study, a joint-effort of the Austrian Societies of Dermatology and Pathology. We retrieved all histopathological reports from the year 2011 containing the term “melanoma” in their diagnosis section directly from all hospital- and non-hospital-based pathological and dermatopathological institutes, registered with the Austrian Medical Chamber and the Austrian Economic Chamber, either as hard copies or electronically.

2.2. Inclusion and exclusion criteria

We included only primary melanomas and excluded all patients with residence abroad, reports on metastases,
recurring melanomas, re-excisions, and a history of melanoma before 2011, as stated in referral texts. Furthermore, we excluded reports on biopsies and incomplete excisions from December 2011 without documentation of re-excision, as the Austrian CR might have recorded those in 2012 due to late re-excisions.

To avoid multiple registration of patients with lesions that were diagnosed and scored by more than one pathologist, two members of our study team independently reviewed all histopathological reports with similar patient details (first and last name and date of birth or postcode). If unequivocal, we recorded only those tumours with the more severe scores. Similarly, we reviewed all patients diagnosed in 2011 with multiple synchronous or metachronous melanomas, defined by equivocal different anatomic localisation and/or morphology.

For incidence analysis of primary cutaneous in-situ (D03 – WHO International Classification of Diseases, 2014) and invasive melanomas (C43), we followed the general recommendations of the IARC and counted only one tumour per patient [24]. In case of multiple primary melanomas, only the first melanoma or, if diagnosed simultaneously, the thicker or, in case of equal thickness, the one with more valid information entered incidence analysis.

2.3. Recorded data

We recorded the postcode of patients and/or referring physicians, diagnosing institution, date of sign-out, sex, age, anatomic localisation, melanoma subtype as indicated in the report, Breslow tumour thickness, Clark level, histopathological tumour stage according to the American Joint Committee against Cancer, regression, numbers of mitosis/mm², ulceration, microsatellitosis, and completeness of excision. Austrian census data and CR’s data were retrieved from the homepage of the Statistics Austria [15]. International incidence rates for 2012 were derived from the GLOBOCAN homepage [25]. Considering the coverage area of pathology laboratories we allocated Austrian States to four regions: eastern (Vienna, Burgenland, and Lower Austria), central-northern (Upper Austria and Salzburg), central-southern (Styria and Carinthia), and western Austria (Tyrol and Vorarlberg).

2.4. Statistical analysis

Mean with standard deviation or median with interquartile range was calculated for quantitative variables, whereas qualitative variables were described using absolute and relative frequencies. Chi-square tests were used to compare proportions. We calculated Mantel–Haenszel age-adjusted risk ratios (MH RR) and 95% confidence intervals to compare incidence rates between sexes. A linear regression, with age and sex as independent variables, yielded estimates of the impact of sex on tumour thickness and the average increase in tumour thickness with age. Age-standardised incidence rates were based on the revised European standard population of 2013 and the Segi world standard population.

Fig. 1. The study’s flow chart of histopathological reports with the term “melanoma” in their diagnosis section displaying numbers of lesions excluded from and included in the incidence analysis.
population from 1960. Confidence intervals for the CC of the national CR were calculated under the assumption that our data represented the total number of melanomas diagnosed in Austria.

3. Results

All 53 Austrian hospital- and non-hospital-based pathology and dermatopathology laboratories took part in the study and a complete list is provided at the end of the discussion section of the manuscript. Four laboratories did not diagnose any melanoma in 2011 and from the remaining 49 we gathered 7783 reports (Fig. 1, Table 1). After exclusion of 2537 reports, incidence analyses were based on 5246 patients with 1951 in-situ and 3295 invasive melanomas registered by the Austrian CR for the same year (Fig. 2, Table 2). Histopathologic staging of tumours was provided in 5176 patients, but lacked sufficient data for classification into sub-stages a/b. The vast majority (n = 4415; 84%) were early stage melanomas (Tis and T1) equally occurring in both sexes (MH RR = 1.1 [1.0–1.1]; p = 0.06). In contrast, melanomas with a Breslow thickness of >4 mm (T4) (n = 149; 3%) affected significantly more men (MH RR = 2.3 (1.7–3.2); p < 0.0001). Breslow thickness did not differ in men and women (p = 0.40) and increased significantly with age (p < 0.0001) at an estimated rate of 0.07 mm per year. Melanoma incidence rose considerably with age and all age groups were evenly under-represented in official estimates (Fig. 2). By compilation of virtually 100% of all newly diagnosed melanomas in Austria in 2011 we found that the CR’s CC varied markedly between Austrian States from 14% for Vienna to more than 90% for Tyrol and Carinthia (Table 3) [15].

Comparison of the study’s incidence rates (25/100,000 WSR for men and women) with estimates from GLOBOCAN for selected countries suggested that Austria had the highest melanoma incidence in Europe and the third highest worldwide behind Australia (41 and 30) and New Zealand (39 and 33) (Fig. 3). This contrasting juxtaposition emphasises the impact of different methodological approaches in case retrieval, adopted by us and by various CRs, on the comparability of international data.

Austrian pathology laboratories generated the incidence rates of the regions in which they were situated by diagnosing the vast majority of patients, who were living in this region (Fig. 4). Austrian regional incidences of melanoma increased gradually from east to west, which was solely attributable to different incidence rates of Tis and T1 tumours. In contrast, incidences of T2 to T4 tumours were evenly distributed throughout Austria (Table 4, Fig. 5). Even after exclusion of in-situ lesions we noted significantly higher proportions of early invasive T1 melanomas in western and southern-central Austria (443; 80% and 627; 77%, respectively) compared to eastern Austria (825; 70%) (p < 0.0001). Apart from regional factors, varying pathologists’ thresholds for diagnosing thin melanomas might additionally underlie higher melanoma incidences in western Austria. To elucidate this question we excluded patients from western Austria and with them possible confounding factors like higher UV radiation from further analysis [21,26]. This revealed that the proportion of thin melanomas in the population, living in the rest of Austria (n = 4090), was significantly depending on the diagnosing laboratory. Those patients whose tumours were diagnosed by pathology laboratories located in western Austria (n = 76) comprised a significantly
higher percentage of in-situ lesions (57%), as compared to those, whose tumours were diagnosed by laboratories situated in the rest of Austria \( (n = 4014; 34\%) \) \( (p < 0.0001) \). We found no correlation between incidence rates of Tis, Tis/T1 or Tis-T4 melanomas and the density of dermatologists in private practice in Austrian States (Fig. 6).

4. Discussion

The precise estimation of the genuine melanoma incidence is indispensable for epidemiological research and for calculating health care budgets, particularly with the emergence of costly therapeutic options for progressive disease like immunomodulatory drugs. We demonstrate that in Austria the burden of melanoma is grossly underestimated as official incidence rates lacked 64\% \( (n = 1235) \) in-situ and 54\% \( (n = 1761) \) invasive melanomas in 2011. One reason for underreporting melanoma to CRs is the increasing shift of diagnosis and treatment to non-hospital-based facilities, which applied to 53\% of patients in our study \[3,13,14\]. It is most likely that the Austrian CR missed a substantial number of these lesions because cancer reporting is not legally mandatory for non-hospital-based facilities and the CR depends ‘passively’ on case notifications \[15\]. However, four regional registries in western Austria adopted more “active”

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<td>incidence rates of in-situ and invasive malignant melanoma in Austria in 2011</td>
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ESR = European age-standardised incidence rate; WSR = world age-standardised incidence rate. Total rates (crude, ESR, and WSR) for in-situ and invasive melanomas are bold. Incidence rates were rounded to whole numbers.
methods of case retrieval and provided their data to the national CR. This influenced Austrian data in two ways: (1) western Austrian States displayed higher official melanoma rates than their eastern counterparts, which lack own regional CRs and (2) as shown by comparison with our study’s results, CC of official data is significantly higher for western than for eastern Austrian States [15,27].

The alarming number of newly diagnosed, yet unrecognised, melanomas in Austria may imply serious consequences. On the one hand it suggests that underreporting affects national and international melanoma incidence rates, time trends and their comparability far more than previously estimated, as: (1) Statistics Austria like many other well-established CRs follows standards of the IARC [15,19,24,28]; (2) population-based melanoma incidence rates of countries like France and Germany match Austrian official figures [5,25]; (3) “active” data retrieval in our study yielded 50% higher melanoma rates for Austria than GLOBOCAN projected for the United States, thus indicating the potential scale of melanoma underreporting [3,13,14,25]; (4) melanoma incidences vary grossly among United States from 12/100,000 (WSR) in Texas to 34/100,000 in Utah [13,20,21,25].

On the other hand reporting inconsistencies of large proportions of thin melanomas with an excellent prognosis may also impact the comparability of international melanoma-specific survival data and account for the relatively low, recently published, Austrian survival rates [10,29].

Analysis of the regional distribution of Austrian incidence rates in our study revealed 33 invasive melanomas/100,000 (European age-standardised rate [ESR])...
in eastern Austria, which was comparable to 31/100,000 (ESR) in the Cantons of Zurich and Zug/Switzerland in 2011 documented by their regional CR (personal communication). Remarkably, incidences gradually increased westwards and western Austria showed by far the highest numbers with 53/100,000 (ESR). Possible explanations are a higher UV exposure in western mountainous areas, differing recreational activities or earlier detection by patients and doctors due to a higher population’s awareness of skin self-examination [21,26]. However, we demonstrate that (1) these regional disparities were exclusively attributable to differences in numbers of early (Tis/T1) melanomas and that (2) pathology laboratories in western Austria accounted for the incidence rates of western Austria. They diagnosed higher proportions of thin melanomas compared to laboratories in the rest of Austria, which was still significant after exclusion of regional confounding factors indicating overdiagnosis and/or false-positive diagnosis of thin melanomas. Indeed experts regard the lack of firm pathologic criteria for the diagnosis of early melanomas as one of the greatest challenges in dermatopathology [2,22]. It is therefore conceivable that a significant variability in pathologists’ thresholds for the interpretation of the biologic behaviour of thin melanocytic lesions contributed to the observed regional trends [2,22].

Certain findings of our study warrant a more critical evaluation. First, we lacked access to data prior to 2011; therefore, we cannot completely rule out that patients with a history of melanoma before 2011 were included in the incidence analysis. Based on data, which specified a 1% per year risk of Californian melanoma patients to develop secondary primary melanomas and on official Austrian incidence rates from 2001 to 2010, we calculated that this might apply to a maximum of 150 patients in our cohort [30]. However, exclusion of those would only marginally change our incidence of invasive melanoma from 39 to 37/100,000 (crude rate) and underreported cases would still be significant. Additionally, these differences are probably much lower, due to our efforts to exclude such patients in the first place. Secondly, we could not analyse the influence of skin

| Table 4 |
|------------------|-----------------|-----------------|-----------------|-----------------|
|                 | Eastern ESR     | Central-southern ESR | Central-northern ESR | Western ESR |
| In-situ melanomas | 15              | 18              | 29              | 52             | 53             | 36             |
| Invasive melanomas  | 33              | 19              | 45              | 26             | 40             | 26             | 53             | 36             |

European (ESR) and world age-standardised rates (WSR)/100,000. Incidence rates were rounded to whole numbers.

Fig. 5. Distribution of melanomas (crude incidence rates) according to their tumour stage (Tis-T4) for eastern, central-north, central-south, and western Austria as well as for whole Austria.

Fig. 6. Correlation of the incidence rates of melanomas with the density of dermatologists in private practice within the nine Austrian States.
biopsy rates on national and regional melanoma incidences [1]. Indeed, the high numbers of Austrian dermatologists in private practice, accounting for 53% of all melanoma specimens in 2011, may lead to more frequent skin biopsies and higher incidence rates. Yet, we could not find any association between the density of dermatologists and the melanoma incidence rates in Austrian states. Thirdly, the study was not designed to investigate overdiagnosis, which is particularly challenging in the context of thin melanomas, which have, once excised an excellent prognosis. However, the even regional distribution of melanoma-specific mortality rates ranging from 2.0 to 2.4 throughout Austria further supports our hypothesis that melanoma overdiagnosis adds to the disease burden [15,23]. Finally, our results may not be generalised to countries beyond central Europe due to potential differences of population behaviour, genetic and demographic make-up, environmental factors, specific legal frameworks as well as pathologists’ and dermatopathologists’ training programmes.

In conclusion, we revealed an alarming, yet unrecognised, number of melanomas in Austria in 2011. Similarities in incidence rates suggest this might also affect other Western countries with well-established CRs. The consequences are underestimation of the true melanoma burden with its socio-economic implications and reduced international comparability of incidence and survival data [5,21,29]. Our results highlight the need to adjust the Austrian legal framework for reporting cancer cases to the CR and may help to foster its data quality as it has been shown that CRs perform better in terms of CC when their data is used in etiological or clinical research [10]. Moreover, we show, that CC is significantly enhanced by “active” retrieval of a single case-finding source such as histopathological reports from hospital- and non-hospital-based facilities [7]. Finally, significant regional trends in numbers of thin melanomas may at least in part indicate overdiagnosis and/or false-positive diagnosis and emphasises the impact of pathologists’ thresholds for the diagnosis of early melanomas on overall incidence rates.

**Conflict of interest statement**

The authors state no conflict of interest.

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