Epidemiology and survival outcomes in stages II and III cutaneous melanoma: a systematic review

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Practice points

• There are limited publications on the epidemiology of stages II and III cutaneous melanoma (CM) specifically.
• Incidence rates for stages II and III CM were only reported for US and Swedish populations.
• None of the studies identified in this review reported specific prevalence data for stages II and III CM.
• Survival rates were reported in 33 publications across four continents but heterogeneity in study characteristics makes comparison challenging.
• Five-year disease-specific survival rates ranged from 63–81% in stage II CM, with most studies reporting a rate of over 70%.
• Five-year disease-specific survival rates ranged from 36–63% in stage III CM, with most studies reporting a rate of over 50%.
• We have been unable to gain conclusive knowledge of epidemiology in stages II and III CM.
• Our review highlights that further epidemiological studies focused in stage II and/or III CM are needed to inform and target treatment for better management of the disease.

Aim: Management of cutaneous melanoma (CM) is continually evolving with adjuvant treatment of earlier stage disease. The aim of this review was to identify published epidemiological data for stages II–III CM.

Materials & methods: Systematic searches of Medline and Embase were conducted to identify literature reporting country/region-specific incidence, prevalence, survival or mortality outcomes in stage II and/or III CM. Screening was carried out by two independent reviewers. Results & conclusion: Of 41 publications, 14 described incidence outcomes (incidence rates per stage were only reported for US and Swedish studies), 33 reported survival or mortality outcomes and none reported prevalence data. This review summarizes relevant data from published literature and highlights an overall paucity of epidemiological data in stages II and III CM.

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Cutaneous melanoma (CM), a malignant neoplasm that develops from melanocytes, is the most commonly occurring form of melanoma [1]. Over the last 3 decades, the global incidence of CM has steadily increased and the International Agency for Research on Cancer has predicted that this pattern will continue [2]. In 2018, the estimated age-standardized global incidence rate for CM was 3.1 per 100,000 persons, with nearly 300,000 new cases diagnosed and 60,000 deaths reported for the same year [3]. There has been an emphasis on early detection and the need for better therapeutic strategies at an earlier stage of disease, as advanced disease predicts poorer patient outcomes [4]. Treatment pathways for CM are continuously evolving. For patients with clinical stage II (dermal spread of the tumor) or III melanoma (regional lymph node spread), surgical excision is the standard approach; however, subsequent relapse is experienced by some individuals. Advances in the use of immunomodulating agents
and targeted therapies for treating metastatic disease has led to the assessment and use of such drugs in the adjuvant setting for stage III patients at high risk of recurrence following surgery [5]. The efficacy of such therapies is yet to be established in stage II patients; however, clinical trial data may guide their use in practice [6]. With these factors considered, analysis of the global epidemiology for clinical stages II and III CM populations is necessary to better inform disease burden and treatment protocols.

We conducted a systematic literature review with the objective of gaining insight into global epidemiological data for the stage II and/or III CM population. We analyzed published literature reporting country- or region-specific incidence, prevalence, survival and mortality outcomes. To our knowledge, no published systematic reviews of the global epidemiology and survival/mortality rates of stages II and III CM are available.

Materials & methods

The methodology for conducting this systematic literature review was documented in a review protocol. The process was conducted in line with the Preferred Reporting Items for Systematic Review and Meta-Analyses statement [7].

Search strategy

Systematic searches of Medline and Embase were conducted up to 28 January 2019, to identify studies reporting outcomes for incidence, prevalence, survival and mortality in stage II and/or stage III CM populations. There were no restrictions on language, country, publication type and timeframe to initially keep the scope broad. A range of search terms related to incidence, prevalence, survival and mortality (e.g., death, fatal) and stage II and III disease (e.g., 'stage 3' or 'stage III' or 'stage three' or 'stage 3a' or 'stage IIIa' or 'stage three a' or 'stage 3b' or 'stage IIIb') were used (Supplementary Figure 1). Hand-searching was performed to supplement the electronic searches. This included cross-referencing relevant systematic reviews and reference lists of included peer-reviewed publications and free text keyword searching in internet search engines.

Eligibility criteria

Two reviewers independently screened titles and abstracts to determine eligibility for inclusion in this review. Any discrepancies were resolved by discussion, with a third reviewer assessing sources for which a decision could not be reached. Full-text English language publications were retrieved and assessed by the same method. All publications were screened against prespecified criteria, with studies reporting incidence or prevalence in stage II and/or III CM from a regional or national general population, included for review. Publications reporting incidence data that identified patients from a national database or registry were also included. Incidence rates and incident cases (where incidence rates were unavailable) were captured. An incidence rate is defined as the number of new cases divided by the number at risk in a specified population within a given period and is typically reported as cases per 100,000 persons per year [2]. An incident case describes a newly diagnosed individual at particular timepoint [8]. Studies that included patients with mucosal and uveal melanomas, subungual melanoma or melanoma of unknown primary region were excluded. Population sizes associated with survival or mortality outcomes were not considered a limiting factor for study inclusion. In order to summarize the most up-to-date published epidemiological data on CM, publications from the last 10 years only (2009 onward) were included.

Quality assessment

Methodological quality assessment of the included literature was conducted using two separate tools. The Joanna Briggs Institute Critical Appraisal Checklist for Prevalence Studies was used to assess bias in included studies which reported incidence and prevalence [9]. The Risk of Bias Assessment Tool for Non-randomized Studies was adapted to assess included observational studies reporting survival and mortality outcomes [10].

Results

The electronic search strategy identified 2835 publications. Three additional publications were identified from hand-searching. Following the removal of duplicate records, 1942 publications were assessed for eligibility. A total of 91 publications were eligible for inclusion based on title/abstract screening. In total, 41 publications were included either as full-text peer-reviewed publications (n = 35) or as conference abstracts (n = 6). A total of 14 publications reported incidence data and none reported prevalence data. A total of 33 reported survival and mortality rates in the stages II and/or III melanoma populations (Supplementary Figure 2).
Table 1. Publications reporting incidence rates in stage II and/or III cutaneous melanoma.

| Study (year) | Geographical location | Total population size estimate (reported in the publication) | Data source | AJCC staging criteria | Stage of disease | Study timeframe | Timeframe breakdown | Incidence rate (per 100,000 persons/year) | Ref. |
|--------------|-----------------------|-------------------------------------------------------------|-------------|-----------------------|------------------|----------------|-------------------|------------------------------------------|------|
| USA          |                        |                                                             |             |                       |                  |                |                   |                                          |      |
| Fleming (2018)| USA (all 611 counties) | –                                                           | SEER\(^1\) and AHRF | 6th edition         | Stage II        | 2008–2012    | –                 | 2.36 (SD: 2.07)              | [11] |
|              | USA (138 counties with HPSA) | –                                                           |             |                       | Stage III       | –             | –                 | 1.22 (SD: 1.22)              |      |
| Tarhini (2019)| USA                  | –                                                           | SEER\(^1\) | 7th edition           | Stage III       | 2010–2014    | 2010             | 1.21                          | [12] |
|              |                      |                                                             |             |                       |                 |               | 2014             | 1.48                          |      |
|              |                      |                                                             |             |                       |                 |               |                   |                                            |      |
| Europe       |                        |                                                             |             |                       |                  |                |                   |                                          |      |
| Stromberg (2016)| Western Swedish healthcare region, Sweden | 1,490,000 (adult population in 2013) | Population-based national cancer register, linked to additional data from the National Swedish Melanoma Quality Register and Statistics Sweden register | 6th edition | Stage II | 2004–2013 | – | 5.0\(^1\) (95% CI: 4.7–5.3) | [13] |
|              | Southern Swedish healthcare region, Sweden | 1,450,000 (adult population in 2013) |                          | |                  |                 |                   | 3.6\(^1\) (95% CI: 3.4–3.8) |      |

See Supplementary Table 1 for breakdown of incidence rates per year in stage III cutaneous melanoma according to the 7th and 8th AJCC editions.

\(^1\)SEER database represents approximately 30% of the US population [14].

\(^1\)Reported as age-adjusted incidence rate (per 100,000 persons per year).

AHRF: Area Health Resources files; AJCC: American Joint Committee on Cancer; HPSA: Health professional shortage area; NR: Not reported; SD: Standard deviation; SEER: Surveillance, Epidemiology and End Results program.

A total of 20 publications were excluded at full-text due to lack of relevant data; most of these publications reported outcomes combined across multiple disease stages (e.g., including stage I and/or IV) and therefore data specific to stage II and/or III could not be separately extracted. In addition, 20 publications were excluded because they reported data for a melanoma population that was not of interest for this review (e.g., patients with uveal melanoma). Seven publications were excluded for reporting duplicate data and three were not published in the English language (Supplementary Figure 2).

A narrative approach has been taken for this review due to differential reporting of incidence and survival data between studies.

Characteristics of included incidence studies
Outcomes from included incidence studies were captured and reported in two separate data tables: publications reporting incidence rates (Table 1) and publications reporting country- or region-specific incident cases (Table 2).

A single Swedish study reported age-adjusted incidence rates for the stage II melanoma population [13]. Unadjusted incidence rates for stages II and III melanoma populations were reported in two studies from the USA (Table 1) [11,12].

In the identified publications, data were mostly reported as the number of incident cases within a specific country/region over a specified timeframe (n = 14). Of these publications, five reported the size of the general population from which the incident cases were identified. For the remaining studies, we sourced country-specific population estimates using a recent United Nations report (Table 2) [26]. Three studies reported stage II/III data from the USA [12,24,25] and ten studies reported stage II and/or III in seven European countries covering Denmark [15], England [16], Estonia [18], Germany [23], the Netherlands [17], Sweden [13,19,21,22] and Spain [20].

Incidence rates in stages II & III melanoma
Overall, three studies reported incidence rates in stage II and/or III CM (Table 1). Stromberg et al. compared age-adjusted incidence rates between the Swedish western healthcare and Swedish southern healthcare regions from 2004 to 2013 in the stage II population, reporting a rate of 5.0 (95% CI: 4.7–5.3) and 3.6 (95% CI: 3.4–3.8) per
Table 2. Publications reporting incident cases in stage II and/or III cutaneous melanoma.

| Study (year) | Geographical location | Total population size estimate | Data source | AJCC staging criteria | Stage of disease reported | Study timeframe | Total number of incident cases | Ref. |
|-------------|-----------------------|-------------------------------|-------------|-----------------------|---------------------------|----------------|--------------------------------|------|
| Europe      |                       |                               |             |                       |                           |                |                                 |      |
| Bay (2014)  | Denmark               | 2004: 5,403,000†              | DCR         | –                     | Stage II                  | 2004–2011       | 1393                           | [15] |
|             |                       | 2011: 5,583,000†              | –           |                       | Stage III                 | –              | 850                            |      |
| Herbert     | East Anglia, England  | 2,500,000‡                   | Population-based cancer registry for the Anglia and successor organizations (Public Health England National Cancer Registration and Analysis Service) | 4th edition | Stage II                  | 1996–2015       | 2001–2005 449                   |      |
| (2018)      |                       |                              |             |                       |                            |                | 2006–2010 572                   |      |
|             |                       |                              |             |                       |                            |                | 2011–2015 652                   |      |
| Leeneman    | The Netherlands       | 1989: 14,869,000†             | –           |                       | Stage II                  | 1989–2016       | 11,402                          | [16] |
| (2018)      |                       | 2016: 16,987,330†             | –           |                       | Stage III                 | –              | 8,946                          |      |
| Padrik      | Estonia               | 1,340,000‡ (population in 2011) | ECR         | 7th edition           | Stage II                  | 1995–2012       | 2000–2004 327                   | [17] |
| (2017)      |                       |                               |             |                       |                            |                | 2005–2009 281                   |      |
|             |                       |                               |             |                       |                            |                | 2010–2012 144*                  |      |
| Plym (2014) | Uppsala/O Rebro healthcare region, central Sweden | 2,000,000‡ | Quality Register of Cutaneous Malignant Melanoma (represents 21% of Sweden’s population – 17 national databases) | 6th edition | Stage II                  | 1997–2011       | 1995–1999 254                   | [18] |
| Rios (2013) | Spain                 | 1997: 40,131,560†             | –           |                       | Stage III                 | –              | 2000–2004 327                   |      |
| Rockberg    | Stockholm, Sweden     | 2012: 2,123,337† (Stockholm county population in 2012) | Hospital records and data from five national databases | 7th edition | Stage II                  | 2005–2012       | 2005 78                         | [19] |
| (2016)      |                       |                               |             |                       | Stage III                 | 2006 81         |                                |      |
|             |                       |                               |             |                       |                            | 2007 79         |                                |      |
|             |                       |                               |             |                       |                            | 2008 91         |                                |      |
|             |                       |                               |             |                       |                            | 2009 91         |                                |      |
|             |                       |                               |             |                       |                            | 2010 29         |                                |      |
|             |                       |                               |             |                       |                            | 2011 19         |                                |      |
|             |                       |                               |             |                       |                            | 2012 23         |                                |      |
| Simberg-Danell (2016) | Sweden | 1990: 8,576,000† | SMR (population coverage ~95%) | 6th edition | Stage II                  | 1990–2007       | 1995–1999 254                   | [20] |
| Schoffer (2016) | Germany | 2007: 9,163,000† | Population-based (n = 24) and hospital-based (n = 4) cancer registries | 7th edition | Stage II                  | 2002–2011       | 2002 814                        |      |
|             |                       | 2002: 81,535,000              | UICC†       | Stage II               | 2002–2011       | 2003 642                       |      |
|             |                       |                               |             |                       |                            | 2004 742         |                                |      |
|             |                       |                               |             |                       |                            | 2005 745         |                                |      |
|             |                       |                               |             |                       |                            | 2006 738         |                                |      |
|             |                       |                               |             |                       |                            | 2007 744         |                                |      |
|             |                       |                               |             |                       |                            | 2008 761         |                                |      |
|             |                       |                               |             |                       |                            | 2009 734         |                                |      |
|             |                       |                               |             |                       |                            | 2010 712         |                                |      |
|             |                       |                               |             |                       |                            | 2011 720         |                                |      |
|             |                       |                               |             |                       |                            | 2012 23         |                                |      |

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Incident cases in stages II & III melanoma

Incident cases in stage II melanoma

Stage II incident cases were reported in 13 publications. We identified data from three US studies [12,24,25] and ten European studies (Table 2) [13,15-21,23]. The number of incident cases were reported for a range of timeframes covering the period from 1989 to 2016, using data identified from national cancer registries and hospital records. Publications did not consistently report the size of the general population at the time of data collection, limiting interpretation of the number of incident cases. Additionally, the data source used did not always represent the total melanoma population within the region or country. For example, two studies reported a disparate number of incident cases for a US population; Bhatt et al. reported 59,424 stage II cases over a 12-year period from the National Cancer Database database [24] and Evans et al. reported 9985 cases over a 5-year period from the SEER program database. This difference is likely driven by the higher coverage of National Cancer Database (70%) than that of SEER (30%) [14].

A number of retrospective studies analyzed the number of stage II incident cases over a series of discrete time periods (typically every year or every 5 years) [13,16,18,21,23]. Of these, three reported an increase in stage II incident cases over time [15,16,21]. These increases occurred in the southern and western healthcare regions of Sweden (2004–2008, n = 1,117; 2009–2013, n = 1,253) [13], East Anglia in England (1996–2000, n = 349; 2001–2005, n = 449; 2006–2010, n = 572; 2011–2015, n = 652) [16] and in Stockholm (2005–2008, n = 329; 2009–2012, n = 417) [21]. Herbert et al. also conducted an analysis of stage-specific trends in melanoma incident cases in East Anglia (England) from 1996 to 2015 (Table 2). Adjusted incidence rate ratios indicated statistically significant increases for all melanoma stages [16]. In particular, they observed a 3% increase per year (95% CI: 2–4%) for stage II melanoma [16]. One study in Germany reported an overall decline in the number of cases (2002, n = 814; 2011, n = 720); however, the number of cases remained relatively constant from 2003 onward [23].
Incident cases in stage III melanoma

Stage III incident cases were reported in 12 publications. We identified data from three US studies [12,24,25] and nine European studies (Table 2) [13,15–23]. The number of new cases was generally reported for the whole study timeframe, meaning analysis of trends over time was not feasible.

Fluctuations in incident cases over time in stage III CM were reported by four publications covering Estonia, Germany and Sweden [13,18,21,23]. Incident cases in Estonia from 1995 to 2012 were reported by Padrik et al. from the Estonian Cancer Registry. Data over the 18-year period were presented in three 5-year periods (1995–1999; 2000–2004; 2005–2009) and one 3-year period (2010–2012; Table 2). The number of incident cases peaked between 2004 and 2009 (n = 111); however, as the final timeframe was only 3 years (2010–2012; n = 71), it is not possible to determine a trend [18]. Data from the southern and western healthcare regions of Sweden showed a clear increase in the number of stage III cases. Significantly, cases nearly doubled over two specified time periods (2004–2008, n = 173; 2009–2013; n = 330; Table 2). In the Stockholm region, the highest number of incident cases were reported in 2007 (n = 51) before a gradual decline was observed [13]. Data for a German population also showed an overall increase in the number of cases (2002, n = 260; 2011, n = 392; Table 2) [23].

Two publications reported incident cases in stage III CM in the USA from the SEER database between 2010 and 2014 [12,25]. Evans et al. reported 4953 new cases of stage III disease over the 5-year period [25], compared with Tarhini et al. who reported 7669 (Table 2) [12]. Although both studies used the SEER database, each identified a different number of melanoma patients; Evans et al. identified 103,777 patients using CS Schema v0204+ before applying exclusion criteria [25], while Tarhini et al. identified 191,232 patients and did not stipulate the method used [12]. Despite the difference in the number of incident cases reported in studies, a percentage analysis demonstrated that stage III patients comprised around 7% of all melanoma patients in each study [12,25].

Survival outcomes in stages II & III melanoma

A summary of publications reporting survival and mortality rates in stage II and/or III melanoma is presented in Table 3. Variables including cohort size, survival definition, treatment or diagnosis period and interventions given to patients make data interpretation challenging and prohibit direct comparisons. For the purpose of presenting a clear dataset, weighted means have been calculated for publications with complex subgroup data (Table 3). Subgroup breakdown is provided in Supplementary Tables 3–8.

Five-year disease-specific survival rates in stage II melanoma

Disease-specific survival (DSS) is defined as the percentage of people in a study or treatment group who have not died from a specific disease in a defined period of time [55]. The term melanoma-specific survival (MSS) is also supported by this definition and was used in several publications. A total of four studies from the USA or Japan reported either DSS or MSS rates in a stage II melanoma population (Table 3) [25,34,36,51]. A 5-year MSS rate of 81% was observed among a cohort of 738 patients treated between 1993 and 2013 in the USA [34]. Another US study by Evans et al. reported a 5-year DSS rate of 78% for 9985 stage II patients diagnosed between 2010 and 2014 [25]. A Japanese study comparing survival between patients who received adjuvant DAV-IFN-β therapy and those who did not between 1998 and 2009, reported 5-year MSS rates of 88 and 76%, respectively (Table 3) [51]. A propensity score-matched analysis used to adjust for confounding revealed no significant difference between the two study arms [51]. Overall, 5-year DSS and MSS rates in stage II ranged from 63–81% with most studies reporting a rate of over 70% (Table 3).

Five-year DSS rates in stage III melanoma

Ten studies reported 5-year DSS or MSS rates in a stage III population; four in the USA, four in Europe, one in Asia and one in Australia (Table 3) [25,28,32,37,40,43,44,46,51,53]. Single-center data reported by Bowles et al. showed a 5-year 52% traditional DSS rate in 760 patients treated between 1990 and 2001 in the USA (Table 3) [32]. Notably, stage IIIb and IIIc patients made up 82% of the stage III population. Further, substage analysis showed that stage IIIa patients had a higher 5-year DSS rate of 78% [32]. This study also reported conditional survival estimates, noting that the 5-year conditional DSS for all stage III patients increased from 45% at time of diagnosis, to 89% for survivors at 5 years. The largest increase in conditional DSS from time of treatment to 5-year survival, was in stage IIIc (39–78%) [32]. Martinez et al., examined a substantially larger cohort from SEER (n = 6868) and observed a 5-year MSS rate of 59% for patients diagnosed between 1988 and 2006 (Table 3) [37]. When stratified by time period of diagnosis, the 5-year MSS rate was 51% for those diagnosed between 1988 and 1999 and 62% for those
| Study (year) | Geographical location for target population | Data source | Period of diagnosis or treatment of cohort | Stage of disease | Size of cohort | Definition of survival rate | Time period | Mean survival rate (%) | Recurrence-free DFS (%) | Ref. |
|-------------|---------------------------------------------|-------------|---------------------------------------------|-----------------|---------------|----------------------------|-------------|----------------------|-----------------------|-----|
| USA         |                                             |             |                                             |                 |               |                             |             |                      |                       |     |
| Balch (2010) USA | AJCC melanoma-staging database | – | Stage III | 2313 | OS | 5-year | 63 | – | [28] |
| Balch‡ (2011) USA | AJCC melanoma-staging database | – | Stage III | 634 | – | 5-year | 61 | 10-year | 45 | [29] |
| Balch (2013) USA | AJCC melanoma-staging database | – | Stage III | 2267 | MSS | 5-year | 63 | – | [30] |
| Balch (2014) USA | AJCC melanoma-staging database | – | Stage II | – | – | – | – | – | – | [31] |
| Bowles (2010) USA | University of Texas MD Anderson Cancer Center | 1990–2001 (patients treated) | Stage III | 760 | DSS | 5-year | 52 | 10-year | 43 | [32] |
| Dawes (2016) USA | SEER | 1992–2009 (diagnosis period) | Stage II | 12,635 | OS | 5-year | 61 | 10-year | 45 | [33] |
| Lee (2017) USA | MSKCC database | 1993–2013 (patients treated) | Stage II | 738 | MSS | 5-year | 81 | – | – | [34] |
| Evans (2018) USA | SEER | 2010–2014 (diagnosis period) | Stage II | 9985 | DSS | 5-year | 78 | – | – | [35] |
| Kurtz (2017) USA | James Cancer Registry | 2009–2015 (patients treated) | Stage II | 146 | RFS | 5-year | 87 | – | – | [36] |
| Lowe (2014) USA | REP | 1970–2009 (diagnosis period) | Stage II | 16 | DSS | 5-year | 63 | – | – | [37] |
| Martinez (2011) USA | SEER | 1988–2006 (diagnosis period) | Stage III | 6868 | OS | 5-year | 51 | – | – | [38] |
| Song (2015) USA | SEER | 2004–2009 (diagnosis period) | Stage IIIb/c | 74 | – | 1-year | 67 | 2-year | 43 | [39] |
| Tan (2019) USA | BIDMC Cutaneous Oncology Program | 1995–2011 (patients evaluated) | Stage II | 45 | OS | 5-year | 57 | – | – | [40] |
| Europe       |                                             |             |                                             |                 |               |                             |             |                      |                       |     |
| Bay (2014) Denmark | Danish Cancer Registry | 2004–2008 (diagnosis period) | Stage II | 771 | RS | 5-year | 83 | – | – | [41] |
| Plym (2014) Sweden | Regional Quality Register of Cutaneous Malignant Melanoma Hospital records and data from five national databases | 1997–2011 (diagnosis period) | Stage II | 1555 | RS | 5-year | 72 | – | – | [42] |
| Rockberg (2016) Sweden | – | 2005–2012 (diagnosis period) | Stage II | 746 | OS | 5-year | 62 | 10-year | 45 | [43] |
| Elsaesser (2012) Germany | Department of Dermatology, University Tübingen records NCR | 1996–2009 (diagnosis period) | Stage II | 781 | OS | 5-year | 82 | – | – | [44] |
| Heisen‡ (2014) The Netherlands | The Netherlands Cancer Institute-Antoni van Leeuwenhoek | 2003–2011 (diagnosis period) | Stage II | 414 | – | 1-year | 71 | 2-year | 48 | [45] |
| Madu (2016) The Netherlands | Netherlands Cancer Institute-Antoni van Leeuwenhoek | 2000–2015 (patients treated) | Stage IIb | 173 | MSS | 5-year | 59 | – | – | [46] |
| Niebling (2013) The Netherlands | Hospital medical records, five centers | 2003–2007 (referral period) | Stage IIb/c | 173 | MSS | 5-year | 67 | – | – | [47] |
| Leiter (2012) Germany, Austria and Switzerland | German-based CMMR | 1976–2007 (diagnosis period) | Stage II | 7879 | RFS | 5-year | 86 | 10-year | 73 | [48] |
| |             |             |                             |             |               |                             |             |                      |                       |     |
diagnosed between 2000 and 2006 (Supplementary Table 7) [37]. Based on univariate analysis, the treatment era was considered a statistically significant predictor of MSS ($p < 0.001$) [37].

A multicenter study reported a 5-year MSS rate of 48% in a cohort of stage IIIb and IIIc patients ($n = 173$) treated between 2003 and 2007 in The Netherlands (Table 3) [44]. Similarly, a single-center Dutch study, which assessed a larger patient cohort ($n = 250$) over a longer timeframe (2000–2015) reported a 5-year MSS rate of 59% in stage IIIb patients [43]. In a hospital-based Japanese study by Matsumoto et al., an MSS rate of 65% was demonstrated in stage III patients treated with DAV-IFN-β therapy, compared to a rate of 36% in stage III patients not receiving DAV-IFN-β therapy [51].

Overall, DSS or MSS rates in stage III ranged from 36% to 63%, with most studies reporting a rate of over 50% (Table 3).

**Five-year disease-free survival or recurrence-free survival rates in stage III melanoma**

Disease-free survival or recurrence-free survival (RFS) is the length of time following a primary cancer treatment that a patient survives without any further signs or symptoms of that cancer [55]. Disease-free survival or RFS was reported in eight of the studies which met inclusion criteria for this review (Table 3) [21,32,35,43,45,49,51,53].

In a study of stage III patients treated between 2009 and 2015 in the USA, Kurtz et al. reported a 5-year RFS rate of 77% (Table 3) [35]. There was a statistically significant difference in 5-year RFS between disease stages. Notably, 5-year RFS rate in the stage IIc population was lower than that reported in the stage IIIa population; however, disease recurrence was experienced at an earlier timepoint for stage IIIa patients [35]. Comparatively, a 5-year RFS rate of just 17% was observed in a cohort of 239 patients in Sweden diagnosed between 2005 and 2012, despite a 5-year overall survival rate of 57% for the same patient group (Table 3) [21]. Data from Germany showed a 5-year RFS rate of 57% in a larger cohort of 1669 patients diagnosed between 1976 and 2007 [45]. The study also reported that as time progresses post-diagnosis, the risk of developing recurrence significantly decreases ($p < 0.05$) [45].

**Quality assessment of epidemiology studies**

Supplementary Figure 3 presents results from the Joanna Briggs Institute assessment. Strengths of the studies included their retrospective design, adequate sample size and the description of participant characteristics. Major limitations for many studies were the lack of clear population denominators, as this precluded calculation of incidence rates and cumulative incidence, in addition to lack of statistical analysis per melanoma stage. All studies employed a retrospective study design. Ten studies described valid methods to identify the condition, including the use of International Classification of Disease coding [11,12,16,18,19,21–25].

Domains from the Risk of Bias Assessment Tool for Non-randomized Studies were tailored to allow for consistent assessment across studies and results are presented in Supplementary Figure 4. A key strength of all the studies was appropriate selection and high inclusion of study participants in survival analyses. The major limitation was the lack of clear reporting on interventions given to patients, either in the form of surgical or adjuvant intervention [15,18,19,21,23,25,28–31,33,34,36–38,40–42,44,45,48–50,52–54].

**Discussion**

This review indicates a paucity of published incidence and prevalence data specific to stage II and III CM populations. Most of the included studies reporting incidence data are in US or Swedish population. Only three published studies provided incidence rates; Stromberg et al. presented an age-standardized incidence rate and the remaining two identified patients from the same data source (US SEER) [11–13]. There is a clear need for more epidemiological studies in this patient population. Despite the breadth of information that can be obtained from publicly available databases such as Globocan and IHME, these sources lack the granularity to obtain direct incidence/prevalence estimates by clinical stage.

Notably, our review yielded no published literature reporting incidence and prevalence of the stage II and III populations from Asian countries. This may in part be due to the rarity of the condition in this area of the world [56]. However, the review did capture mortality and survival data from four publications from China and Japan [49–52].

The apparent rise in incidence rates and incident cases of stages II and III CM reported by publications captured in this review could be suggestive of an overall increase in incidence in this patient population on a larger scale [12,13,16,18,21].

Most incidence data captured in this review were reported as incident cases. Unrepresentative population coverage of national databases combined with limited reporting of general population details in the included publications.
restricts interpretation of trends in incidence. Crude incidence rates could be determined from incident cases using population sizes extracted from the UN database but would have to be interpreted with caution [26]. Further, change in general population size over time is a significant consideration for included studies, which reported general population estimates for a timepoint toward the end of their study period, as a crude incidence rate calculated from the reported data would likely underestimate incidence at the beginning of the study period [13,18,21]. Comparing adjusted incidence rates is preferred, to account for differences such as age and time of diagnosis within a population [57].

Incident cases reported in East Anglia (UK), Estonia, Germany and in different healthcare regions of Sweden could be used to estimate the change in the number of newly diagnosed cases over time and, in some cases, to identify specific timepoints of peak incidence. However, changes in general populations over time were not described for the included studies that reported absolute incident cases. Moreover, clinical stage was reported as unknown for some patients, meaning absolute numbers are difficult to compare within melanoma stage [15,18,22,24]. Consequently, we cannot accurately conclude any trends in incidence based on the results from this review.

Other literature suggests a higher rate of earlier stage diagnosis, which may be due to improved diagnosis, screening programs and public health awareness. In a study which assessed the correlation between the rate of skin biopsies and incidence of melanoma in the USA between 1986 and 2001, a mean biopsy rate increase of 2.5-fold among patients aged ≥65 was observed. During this period, incidence of melanoma increased from 45/100,000 persons to 108/100,000 persons, with 1000 additional biopsies, equating to an extra 6.9 melanoma diagnoses [58]. Notably, data reported by Padrik et al. showed a peak in the number of incident cases of stage II CM (n = 327) compared with the lowest number of incident cases of stage III (n = 58) during the same period in Estonia [18]. Moreover, data published by Fleming et al. showed a higher density of primary care providers was correlated with a higher number of stage II incident cases, suggesting patient access as well as public health awareness campaigns play a role in influencing higher incidence in earlier stage disease [11].

Stromberg et al. reported disparate age-adjusted incidence rates for stage II disease between the southern and western healthcare regions of Sweden [13]. This could be explained by several factors, including risk behavior and UV-exposure. These factors were also discussed by Padrik et al., who referred to Estonia’s increased accessibility and affordability of holidaying in sunny locations and use of tanning beds following an open market transition [18].

Changes to diagnosis or staging criteria over time may influence ‘true’ incidence of cancer stage. As demonstrated from results captured in the review by Tarhini et al., differences in incidence rates are observed based on the AJCC staging criteria used. Overall, an increase in incidence was shown regardless of staging criteria (7th edition vs 8th edition AJCC); however, a significant number of patients were reclassified in a higher stage III subgroup under 8th edition criteria [12]. These results could suggest movement toward a lower threshold for higher grade diagnoses over time. Notably, when assessing the different AJCC staging criteria used across longer timeframes over all studies, it becomes increasingly challenging to decipher trends.

Five-year DSS or MSS rates for stage II CM ranged from 63 to 81% and from 36 to 63% for the stage III. The ranges could be explained by variation in treatments given to patients. Chi et al. reported that surgical intervention and the use of adjuvant therapies were significant prognostic factors for patients with stages I–III melanoma [49]. Other reported factors known to influence survival rates include treatment era, adverse population characteristics and age [37,43,46].

Survival rates were generally reported from large registry data and single-center databases. It is likely that the same patient population was captured in different studies in this review, due to geographical and time period crossover. Additionally, when comparing across studies, different study populations had varying levels of substage breakdown reported, with some publications not reporting these data subsets at all.

Regarding patient survival as an outcome, conditional survival estimates may be an effective approach to account for changes in patient risk profiles over time, in order to more accurately predict longer-term survival. Bowles et al. reported an increase of 44% in 5-year DSS from time of diagnosis to 5 years post-diagnosis when applying this method [32].

Ultimately, for studies reporting survival and mortality, heterogeneity in the clinical characteristics and in the reporting of interventions patients received significantly limited comparison of outcomes, making it difficult to draw meaningful conclusions from the existing literature.
**Conclusion**

Overall, the aim of this review was to gain further insight into the epidemiology of stages II and III CM, as these outcomes inform clinical burden of the disease in this patient population. We have been unable to gain conclusive knowledge in this area or identify meaningful trends due to reporting limitations (specifically the reporting of incidence data). Further, this review highlights a gap in published research on the epidemiology of stages II–III CM. Ultimately, the findings presented here provide a platform for the planning of relevant studies that will generate detailed evidence to inform the treatment and management of stages II and III CM.

**Future perspective**

We predict that melanoma research will continue to evolve rapidly to keep pace with advancements in treatment of the disease. Currently, published epidemiological studies in stages II and III CM are lacking and much of the available data cannot be used to determine trends. Efforts to support the development of high coverage cancer registries are paramount to developing the evidence base for interventions with potential for better disease management. Comprehensive records including patient stage at diagnosis are required. The healthcare sector has a responsibility to collect data that will accurately inform national and regional population-based registries and the implementation of mandatory reporting would encourage quality coverage.

**Supplementary data**

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/mmt-2019-0022

**Author contributions**

R Miller, I Shui, A Brandtmüller, E Scherrer and K Cadwell were involved in the conception, design and planning of the study; R Miller was responsible for acquisition of the data; R Miller and S Walker were responsible for data analysis; I Shui and K Cadwell also carried out data interpretation. R Miller drafted the manuscript and all authors were involved in critical review and manuscript revisions. The final manuscript was approved by all authors.

**Financial & competing interests disclosure**

I Shui and E Scherrer are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. A Brandtmüller is an employee of MSD: Pharma Hungary Ltd. R Miller, S Walker and K Cadwell are employees of PHMRLtd and were contracted by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA to perform this systematic review. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Authors identify patients from a population-based national cancer register linked to additional data from the national Swedish Melanoma register. It is the only included study which reports age-standardized rates and it also investigated the difference in the incidence between healthcare regions, within discrete time periods and for the overall study timeframe.

Authors compare the effect of American Joint Committee on Cancer staging criteria (7th and 8th editions) on the incidence rate of stage III cutaneous melanoma. Of the three studies which reported incidence rates, Tarhini et al. were the only authors to report an incidence rate for each year within the study timeframe for stage III disease.

Authors identify patients from a population-based non-randomized cohort study linked to additional data from the national Swedish Melanoma register. It is the only included study which reports age-standardized rates and it also investigated the difference in the incidence between healthcare regions, within discrete time periods and for the overall study timeframe.

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