Does pregnancy influence melanoma prognosis?
A meta-analysis
Athanassios Kyrgidis\textsuperscript{a}, Aimilios Lallas\textsuperscript{a}, Elvira Moscarella\textsuperscript{a}, Caterina Longo\textsuperscript{a}, Roberto Alfano\textsuperscript{b} and Giuseppe Argenzano\textsuperscript{c}

The literature has not been able to conclude whether pregnancy influences the prognosis of melanoma. The aim of this study was to explore the prognosis of melanoma diagnosed during pregnancy or post partum [pregnancy-associated melanoma (PAM)] compared with melanoma in female patients who were not pregnant. We systematically searched for studies of female patients with melanoma that reported outcomes related to survival. Fifteen eligible studies were found. Overall, PAM was associated with a 17% higher mortality compared with melanoma diagnosed in female patients who were not pregnant (hazard ratio = 1.17, 95% confidence interval: 1.03–1.33, \(P = 0.02\)). The heterogeneity associated with this test was moderate (\(P = 0.07; \hat{\tau}^2 = 38\%\)). PAM was also associated with a 50% higher recurrence rate compared with melanoma not associated with pregnancy (hazard ratio = 1.50, 95% confidence interval: 1.19–1.90, \(P < 0.001\)). The heterogeneity associated with this test was low (\(P = 0.69; \hat{\tau}^2 = 0\%\)). A limitation of this meta-analysis is the definition of PAM, which is not unanimous among the studies included. Our results indicate that PAM is associated with a worse prognosis than melanoma not related to pregnancy, both in terms of overall survival and disease-free survival. On the basis of our data, we anticipate that the survival difference we report here will be further amplified with the addition of future well-carried out studies. We suggest that detection of PAM requires particular awareness by healthcare professionals. Melanoma Res 27:280–299 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Keywords: disease-free survival, disease-specific survival, melanoma, meta-analysis, overall survival, pregnancy, systematic review

Introduction
Melanoma accounts for 31% of all malignancies diagnosed in pregnant women [1]. To date, reviews have not been able to conclude whether pregnancy influences the prognosis of melanoma [2–5]. Recently, two large epidemiological cohort studies have been published. The first, from UK, reported on a significantly increased risk [6], whereas the second one, from Sweden, could not document such a correlation [7]. The aim of this review was to systematically gather all available evidence and attempt a meta-analysis of the currently existing evidence with respect to the prognosis of melanoma diagnosed during pregnancy or post partum compared with melanoma in female patients who were not pregnant.

Materials and methods
This report was written in accordance to the PRISMA statement and the MOOSE proposal where feasible.

Selection of relevant studies
Eligible studies for the systematic review were clinical trials that compared survival outcome for patients with melanoma versus pregnant patients with melanoma. Observational cohort studies and case–control studies were also eligible. The quality of included observational studies was evaluated using the Newcastle–Ottawa scale (NOS) [8]. GRADE recommendation and summary of findings table is supplied as Supplementary Material [9]. Case series, case reports, reviews, abstracts, letters to the editor, and cross sectional studies were not eligible.

Search strategy
To identify eligible studies, the main search was performed in the electronic databases MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception through June 2016 using a set of relevant search terms: ‘melanoma*’ (MeSH), ‘Malignant Melanoma*’ (MeSH) or ‘Melanoma, Familial’ (MesH) and any one of the terms ‘Pregnancy’ (Mesh), ‘Pregnant women’ (MesH), and ‘Maternal Fetal Relations’ (MesH) in.

Received 10 October 2016 Accepted 28 December 2016

All supplementary digital content is available directly from the corresponding author.
The main search and the screening of titles and abstracts were completed independently by two reviewers (A.K. and A.L.) (Fig. 1). Studies of female patients with melanoma that fulfilled all of the following criteria were included in the analysis: (a) existence of two groups of patients with melanoma, namely pregnancy-related and control or equivalent; (b) any outcome related to survival had to be reported in the study with the intent of comparing the included groups; and (c) the groups compared had to have received similar intended treatment or the study design included matching participants for treatment received and any other clinical variables.

**Data extraction**

Information from each study was extracted independently by two reviewers (A.K. and A.L.), using a standardized data extraction form. General characteristics of the study, and outcomes for both intervention and control groups were recorded, where available, and double-checked. Survival outcomes in the treatment and control groups of individual studies were calculated on an intention-to-treat basis. Where appropriate, an attempt was made to complete the data set through communication with the authors.

The primary outcome was overall survival (OS) of female patients pregnant or not when diagnosed with melanoma. Disease-specific survival (DSS), disease-free survival (DFS), and time to recurrence also served as primary outcomes of pregnancy-associated melanoma (PAM) patients, but did not provide sufficient data to calculate HR [26,27]. In one study, contact with the authors was fruitful and calculation of HR was feasible because of this [25]. The 15 eligible studies included six cohort studies [6,7,18,19,22,23] and nine case–control studies [13–17,20,21,24]. The NOS scoring for each study is presented in Table 1 and 2.

**Results**

The results of the search strategy are presented in Fig. 1. As shown in Table 1 and 2, 17 relevant studies were finally included in the qualitative synthesis. Calculation of HRs was possible for 15 studies, which were eligible for the quantitative syntheses. Two studies reported on survival outcomes of pregnancy-associated melanoma (PAM) patients, but did not provide sufficient data to calculate HR [26,27]. In one study, contact with the authors was fruitful and calculation of HR was feasible because of this [25]. The 15 eligible studies included six cohort studies [6,7,18,19,22,23] and nine case–control studies [13–17,20,21,24]. The NOS scoring for each study is presented in Table 1 and 2. Of the 15 eligible studies, 13 reported on OS [6,13–21,23–25] and two studies reported on DSS [7,22]. Among the 15 studies included, four reported on both OS and DFS [13,16,17,24]. These studies were included in both quantitative syntheses for OS and DFS. Thus, the quantitative approach included 13 studies in the meta-analysis for OS, two in the meta-analysis for DSS, and four studies in the meta-analysis for DFS.

Among the nine case–control studies [13–17,20,21,24], two did not include matching of cases to controls [13,17], two included age-matching [20,24], and four [15,16,21,25] included stage and/or Breslow thickness. The 0.05 level of significance was considered to be important. Meta-analysis was carried out using Review Manager 5 software [Review Manager (RevMan), Oxford, UK: The Cochrane Collaboration, 2011].

For survival outcomes, we used the natural logarithm of the hazard ratio (HR) and the corresponding 95% confidence intervals (CIs) as data points for the meta-analysis. For studies not reporting HRs, we estimated HRs and the associated statistics according to the information presented in the study report [10]. For studies reporting univariate survival analysis, we extrapolated HR and 95% CI from survival curves adopting the hierarchical series of steps proposed by Parmar et al. [11]. Both fixed-effect and random-effect models were used. Funnel plots and Egger’s test for small-study effects were used to determine the likelihood of publication bias [12]. Heterogeneity was examined with the $I^2$-statistic. We prespecified a sensitivity analysis of studies controlling for stage and/or Breslow thickness. The 0.05 level of significance was considered to be important. Meta-analysis was carried out using Review Manager 5 software [Review Manager (RevMan), Oxford, UK: The Cochrane Collaboration, 2011].
Table 1  Summary of the 17 studies included in the systematic review

<table>
<thead>
<tr>
<th>References</th>
<th>Place</th>
<th>Design</th>
<th>Outcome</th>
<th>Total number of patients in the study</th>
<th>Number of PAM cases</th>
<th>Number of MM controls</th>
<th>Stage</th>
<th>Matching (case–control or adjustment (cohort)a)</th>
<th>Breslow thickness PAM (mm)</th>
<th>Breslow thickness MM (mm)</th>
<th>Mean age PAM (years)</th>
<th>Mean age MM (years)</th>
<th>Mean follow-up timeb</th>
<th>NOS scoringb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reintgen et al. [13]</td>
<td>Duke University Comprehensive Cancer Center, Durham, North Carolina</td>
<td>Case–control</td>
<td>OS, DSS</td>
<td>1026 During pregnancy</td>
<td>58</td>
<td>585</td>
<td>1</td>
<td>None</td>
<td>1.9</td>
<td>1.51</td>
<td>29.2</td>
<td>33.1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>McManamny et al. [14]</td>
<td>Frenchay Hospital, Bristol</td>
<td>Case–control</td>
<td>OS</td>
<td>264 During pregnancy</td>
<td>23</td>
<td>241</td>
<td>1</td>
<td>None, post-hoc not significant for thickness</td>
<td>1.62 (survived)</td>
<td>1.72 (survived)</td>
<td>28.7</td>
<td>32.3</td>
<td>2 months–20 years</td>
<td>6</td>
</tr>
<tr>
<td>Wong et al. [15]</td>
<td>John Wayne Cancer Clinic, UCLA</td>
<td>Case–control</td>
<td>OS</td>
<td>685 During pregnancy</td>
<td>66</td>
<td>619</td>
<td>1</td>
<td>Computer aided: age, tumor depth, anatomic, histopathologic Age, stage, anatomic, histology, tumor depth, Clark level, ulceration</td>
<td>2.17</td>
<td>1.52</td>
<td>28.9</td>
<td>29.6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Slingluff et al. [16]</td>
<td>Duke University Comprehensive Cancer Center, Durham, North Carolina</td>
<td>Case–control</td>
<td>OS, DSS</td>
<td>186 During pregnancy</td>
<td>100</td>
<td>86</td>
<td>1, 2, 3</td>
<td>Age, stage, anatomic, histology, tumor depth, Clark level, ulceration</td>
<td>2.38</td>
<td>1.71</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MacKie et al. [17]</td>
<td>University of Glasgow, Istituto Tumori di Milano, Tulane University</td>
<td>Case–control</td>
<td>OS, DSS</td>
<td>388 During Pregnancy but vs. 1) before, 2) after, 3) between</td>
<td>92</td>
<td>296</td>
<td>1</td>
<td>–</td>
<td>1.28</td>
<td>1.07</td>
<td>29.3</td>
<td>35</td>
<td>11.6 years (median)</td>
<td>6</td>
</tr>
<tr>
<td>Lens et al. [18]</td>
<td>Swedish National Cancer and Mortality Registry</td>
<td>Cohort</td>
<td>OS</td>
<td>5535 During pregnancy</td>
<td>185</td>
<td>5348</td>
<td>–</td>
<td>Breslow thickness, Clark's level, and tumor site Age</td>
<td>0.855</td>
<td>0.81</td>
<td>–</td>
<td>–</td>
<td>10 years (maximum)</td>
<td>6</td>
</tr>
<tr>
<td>O'Meara et al. [19]</td>
<td>California Office of State-wide Health Planning and Development, SEER</td>
<td>Cohort</td>
<td>OS</td>
<td>2863 During pregnancy or within the first year post partum</td>
<td>412</td>
<td>2451</td>
<td>All</td>
<td>–</td>
<td>4.28</td>
<td>1.69</td>
<td>34±3.7</td>
<td>34±7.7</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>Miller et al. [20]</td>
<td>Tel-Aviv Sourasky Medical Center</td>
<td>Case–control</td>
<td>OS</td>
<td>76 During pregnancy or up to 6 months after pregnancy</td>
<td>11</td>
<td>65</td>
<td>–</td>
<td>Age</td>
<td>4.28</td>
<td>1.69</td>
<td>34±3.7</td>
<td>34±7.7</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>Moller et al. [6]</td>
<td>Cancer registration data set for the UK population</td>
<td>Cohort</td>
<td>OS</td>
<td>16529 Pregnancy 0–1 years before cancer diagnosis (moving window)</td>
<td>306</td>
<td>16222</td>
<td>AI</td>
<td>Cox regression for TNM available</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11 years (maximum)</td>
<td>6</td>
</tr>
<tr>
<td>References</td>
<td>Place</td>
<td>Design</td>
<td>Outcome</td>
<td>Total number of patients in the study</td>
<td>Melanoma diagnosis in relation to pregnancy (PAM definition in each study)</td>
<td>Number of PAM cases</td>
<td>Number of MM controls</td>
<td>Stage</td>
<td>Matching (case-control or adjustment cohort)</td>
<td>Breslow thickness PAM (mm)</td>
<td>Breslow thickness MM (mm)</td>
<td>Mean age PAM (years)</td>
<td>Mean age MM (years)</td>
<td>Mean follow-up time</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>--------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>-----------------------</td>
<td>-------</td>
<td>---------------------------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Zhou et al. [21]</td>
<td>University of Texas MD Anderson Cancer Center</td>
<td>Case-control</td>
<td>OS</td>
<td>41</td>
<td>During pregnancy or up to 6 months after pregnancy diagnosed within 9 months before or within 2 years after a delivery</td>
<td>18</td>
<td>18</td>
<td>1, 3, 4</td>
<td>Stage, age, Breslow depth, ulceration, mitotic site</td>
<td>1.63</td>
<td>2</td>
<td>30</td>
<td>31</td>
<td>Median: 376 months (range: 3.8–96.5 months)</td>
</tr>
<tr>
<td>Johansson et al. [7]</td>
<td>National Swedish Cancer Registry</td>
<td>Cohort</td>
<td>DSS</td>
<td>6857</td>
<td>During pregnancy</td>
<td>1019</td>
<td>5838</td>
<td>IA, IB, II, III–IV</td>
<td>Cox regression for age available</td>
<td>–</td>
<td>–</td>
<td>31</td>
<td>34.7</td>
<td>10 years (maximum)</td>
</tr>
<tr>
<td>Stensheim et al. [22]</td>
<td>Cancer Registry of Norway</td>
<td>Cohort</td>
<td>DSS</td>
<td>4620</td>
<td>During pregnancy</td>
<td>160</td>
<td>4460</td>
<td>All</td>
<td>Cox regression for age and TNM available</td>
<td>–</td>
<td>–</td>
<td>NR, no difference between 2.28</td>
<td>NR, no difference between 1.22</td>
<td>31.8</td>
</tr>
<tr>
<td>Travers et al. [23]</td>
<td>Massachusetts General Hospital Pigmented Lesion Clinic</td>
<td>Cohort</td>
<td>OS</td>
<td>465</td>
<td>During pregnancy or within the first year post partum</td>
<td>45</td>
<td>420</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>1.7</td>
<td>30</td>
<td>36</td>
<td>Median: 109 months</td>
</tr>
<tr>
<td>Dayanani et al. [24]</td>
<td>University Medical Center Groningen</td>
<td>Case-control</td>
<td>OS, DSS</td>
<td>2567</td>
<td>During pregnancy</td>
<td>46</td>
<td>368</td>
<td>–</td>
<td>Age, post-hoc NS for subtype, thickness, vascular invasion</td>
<td>2</td>
<td>1.7</td>
<td>30</td>
<td>36</td>
<td>5 years</td>
</tr>
<tr>
<td>Silipo et al. [25]</td>
<td>Dermatological Institute Rome</td>
<td>Case-control</td>
<td>OS, DSS</td>
<td>40</td>
<td>During pregnancy</td>
<td>10</td>
<td>30</td>
<td>All</td>
<td>Age, localization, histotype and stage of melanoma</td>
<td>1.08</td>
<td>0.84</td>
<td>32</td>
<td>–</td>
<td>5 years</td>
</tr>
<tr>
<td>Houghton et al. [26]</td>
<td>Connecticut Tumour Registry</td>
<td>Case-control</td>
<td>OS</td>
<td>187</td>
<td>During pregnancy</td>
<td>12</td>
<td>175 (24 matched)</td>
<td>All</td>
<td>Age, anatomic site of primary melanoma, and stage</td>
<td>–</td>
<td>–</td>
<td>31.1</td>
<td>31.2</td>
<td>5 years</td>
</tr>
<tr>
<td>Sutherland et al. [27]</td>
<td>Tulane University School of Medicine</td>
<td>Case-control</td>
<td>OS</td>
<td>30</td>
<td>During pregnancy</td>
<td>18</td>
<td>12</td>
<td>1.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>275</td>
<td>25.6</td>
<td>5 years</td>
</tr>
</tbody>
</table>

Quality of included observational studies was evaluated using the NOS [8].

DFS, disease-free survival; DSS, disease-specific survival; MM, malignant melanoma; NOS, Newcastle–Ottawa scale; NS, no significant differences; OS, overall survival; PAM, pregnancy-associated malignant melanoma; TNM, tumor nodes metastasis.

*In longitudinal (cohort) studies, matching is rare, whereas adjustment for thickness or other factors is more common. Median follow up is reported where mean is not available.

Strength of recommendation (GRADE – see summary of findings Table 2): [8] very low.
Table 2  GRADE profile summary of findings recommendation

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk</th>
<th>Corresponding risk (95% CI)</th>
<th>Relative effect (HR)</th>
<th>Number of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>93/1000</td>
<td>108/1000 (96–122)</td>
<td>1.17 (1.03–1.33)</td>
<td>34 217 (14 studies)</td>
<td>♦♦♦♦ very low&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Mean follow-up</td>
<td>8 years</td>
<td>5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-specific morbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>262/1000</td>
<td>366/1000 (303–438)</td>
<td>1.5 (1.19–1.9)</td>
<td>1630 (four studies)</td>
<td>♦♦♦♦ very low&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Mean follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GRADE Working Group grades of evidence: high quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate.

<sup>a</sup>The basis for the assumend risk are female melanoma patients not involved in pregnancy. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
<sup>b</sup>Case–control and cohort study designs together.
<sup>c</sup>Large number of patients pooled.

Definition of pregnancy-associated melanoma

The definition of PAM was not unanimous among the studies included. Nine studies [13–18,22,24,25] defined PAM as melanoma arising during pregnancy (Tables 1 and 2). Six studies included melanomas diagnosed in the post-partum period in the PAM category [6,7,19–21,23]. Of these, two included melanomas occurring within 6 months post partum [20,21], another two included melanomas diagnosed within the first year post partum [19,23], Johansson et al. [7] included a 2-year post-partum period, whereas Moller et al. [6] used a ‘window’ of ‘pregnancy 0–1 year before cancer diagnosis’ to approach ‘cancers diagnosed during pregnancy or in the year following childbirth’.

Outcomes

All studies include crude survival Kaplan–Meier curves for groups of interest. We used the reported crude HRs, when the original report included them [6,7,22]. When HRs were not reported, we calculated HRs from indirect methods [13–17,19,23,24] using the methodology developed by Parmar et al. [11] and the approach to it by Tierney et al. [10]. When using curve data and follow-up intervals to calculate HRs from the slope of the curve, we corrected the O-E number to correspond to the reported log-rank P-value of the original report, to be more conservative. We replotted all curves used to extract HRs and compared the resulting curves with the originals in the reports.

Figure 2 presents the included studies, corresponding HRs, and 95% CIs for OS. We found that PAM is associated with a 17% higher mortality compared with melanoma diagnosed in female patients who were not pregnant (total HR = 1.17, 95% CI: 1.03–1.33, P = 0.02).

With respect to DFS, we found that PAM is associated with a 50% higher recurrence rate compared with melanoma diagnosed in female patients who were not pregnant (total HR = 1.50, 95% CI: 1.19–1.90, P < 0.001, Fig. 3). This effect is derived from four studies [13,16,17,24], with a mean follow-up or patients ranging from 5 to 10 years.

In the DSS analysis, only two studies were included [7,22] and the results were expectedly not significant (total HR = 1.12, 95% CI: 0.92–1.36, P = 0.24).

Limitations – sensitivity analyses

Definition of pregnancy-associated melanoma

We carried out sensitivity analyses to examine whether the definition of PAM in the studies included would alter the total effect size. The HR for studies defining PAM as melanoma diagnosed during or within 6 months after pregnancy (HR = 1.20, 95% CI: 0.97–1.50, P = 0.10) was not different from the HR of studies defining the peri-partum period differently (HR = 1.15, 95% CI: 0.98–1.35, P = 0.08). It is evident that there is no real change in the total effect size, apart from the marginal loss of significance because of the loss of patients included.

Case–control versus cohort studies

We carried out sensitivity analyses to calculate the total HR separately for cohort (HR = 1.16, 95% CI: 0.99–1.35, P = 0.06) [6,7,18,19,23] and case–control (HR = 1.20, 95% CI: 0.95–1.52, P = 0.13) [13–17,20,21,24,25] studies. These HRs show that there is no real change in the total effect size, apart from the marginal loss of significance because of the reduction in the number of studies included.
Sample overlap
Both the Lens et al. [18] and Johansson et al. [7] studies use the Swedish Cancer Registry, with a 10-year time frame difference. However, the difference in the PAM group should be more emphatic as Johansson et al. [7] included 1019 PAM patients as opposed to 185 in the Lens et al.’s [18] study. Given that the initial pool of obtaining MM controls exceeded 19,000 patients, some patient overlap between the two studies cannot be ruled out, especially for the MM group. For this, a sensitivity analysis excluding the Lens et al.’s [18] study was carried out; the results (HR = 1.17, 95% CI: 1.02–1.34, P = 0.03, I² = 43%) were identical to the results in Fig. 2.

Contribution of each study toward the outcome when removed
In a sensitivity analysis, we excluded each included study to determine how the total result was affected. The only study that, when excluded, renders the total HR of the meta-analysis nonsignificant is the study by Moller et al. [6] (total HR = 1.08, 95% CI: 0.94–1.24, P = 0.25) in the OS analysis. No study altered the statistical significance of the total HR for DFS, when excluded.

Inclusion of adjusted instead of crude hazard ratios
The three late cohort studies [6,7,22] included adjusted HRs, in addition to crude HRs. We carried out a sensitivity analysis, using these adjusted HRs, combined with the rest of the data from the other studies (from Moller and Johansson: HR = 1.17, 95% CI: 1.02–1.33, P = 0.02, Fig. 5, also including Stensheim: HR = 1.18, 95% CI: 1.04–1.33, P = 0.01, Fig. 6).
Effect of thickness stage on the total outcome

To examine the possible effect of stage in the results of the meta-analysis, we excluded the studies by O’Meara, MacKie, Miller, Reintgen and Travers [13,17,19,20,23], for which we have no evidence (Table 1 and 2) that in fact thickness was not significantly different between groups (acknowledging that some of them would have been not significantly different – thus comparable groups). We also excluded the Johansson study, which is not adjusted for stage or thickness. We used the adjusted HRs for Moller (for stage); for Stensheim, we used the adjusted for thickness and localization HR. The total HR was significant using either fixed-effects or random-effects models (fixed: HR = 1.36, Fig. 7; random: HR = 1.37, Fig. 8). We carried out a secondary sensitivity analysis in the analysis of Fig. 7, separating case–control and cohort studies. It is noteworthy that the result from the three largest and recent [6,18,22] studies further amplifies the effect size, with moderate heterogeneity (HR = 1.46, 95% CI: 1.18–1.82, P < 0.001, I² = 44%).

Heterogeneity was low to moderate in all analyses (Figs. 2–8). Publication bias was examined by funnel plot.
with no notable asymmetry (Fig. 9, Egger’s test for small-study effects $P = 0.586$).

**Discussion**

**Limitations**

A limitation of our analysis was that the definition of PAM was not unanimous among studies with the post-partum period included. This might result in some overlap between the PAM and the non-PAM groups. We addressed this limitation by a large number of sensitivity analyses. We could not include two studies in the quantitative syntheses [26,27]. Houghton et al. [26] reported a slightly, not significant worse survival in PAM as opposed to matched case-controls. Sutherland et al. [27] reported that
10/18 PAM died, as opposed to 2/12 controls. Therefore, the effect from both studies not eligible for the quantitative syntheses was in the same direction with the total effect of the meta-analyses.

Publication bias was examined through funnel plot asymmetry and we believe it to be not important. We used fixed-effects estimates for the main analyses. Heterogeneity was low to moderate in all the above comparisons.

### Outcomes

Outcomes show that PAM is associated with a worse prognosis than melanoma not related to pregnancy, both in terms of OS and DFS. Such an association has not been yet established on the basis of a quantitative meta-analytical approach [2–4,28]. A systematic review by Byrom et al. [29], using pooled HRs, also concluded that PAM appears to have a poorer outcome than other melanomas. However, the latter review failed to quantify data from studies that did not report HRs, resulting in a considerable selection bias [30,31]. In contrast, the current meta-analysis integrates data from more studies, including those not reporting HRs, thereby minimizing selection bias. A population-based cohort study in Norway concluded that melanoma is the only cancer that, when diagnosed during pregnancy, is associated with a slightly increased risk of disease-specific death, compared with tumors diagnosed in nonpregnant women [22]. Similarly, using epidemiologic data from UK, Moller et al. [6] provided evidence on a significant association between pregnancy and melanoma mortality and by carrying out a stage-adjusted analysis, suggested this association to be stage independent.

In contrast, a recent population-based cohort study from Sweden found no difference in melanoma stage between women with PAM and non-PAM, nor any evidence of worse prognosis of PAM [7]. In addition, several reviews reported lack of quality evidence to document an adverse effect on survival in women diagnosed with melanoma during pregnancy [2,28]. An older review by Lens et al. summarized data from all available studies at that time in a comprehensive table, suggesting that the survival of pregnant women with melanoma is not worse than the survival of nonpregnant female melanoma patients [30]. However, the authors did not carry out a meta-analysis of the data, whereas new evidence came to light after the
publication of the latter review. Some overlap between the Johnasson et al. [7] and Lens et al. [18] studies cannot be ruled out. This has been addressed through sensitivity analysis: we found that it is unlikely to have altered the overall effect of the present analysis.

These controversial data had led experts to conclude that existing evidence is insufficient to establish any impact of pregnancy on melanoma prognosis. The increased thickness of PAM, reported in several studies, was mainly attributed to a delayed diagnosis, which possibly results from the belief that nevi normally change during pregnancy. This leads to an underestimation of clinical characteristics that should be otherwise assessed as worrisome. Accordingly, the overall suggestion was that the management of PAM should be similar to melanoma not related to pregnancy, with the exception of some steps during the staging process, which should be avoided during pregnancy or postponed until delivery. In terms of the continuance of pregnancy after PAM diagnosis, the suggestion was that it should only be discussed on a social basis, taking into consideration the prognosis as determined by the disease stage.

On the background of the unresolved controversy on the possible effect of pregnancy on melanoma prognosis, our results might be highly relevant from a clinical aspect. Our meta-analysis combines the results of older studies that did not achieve to document a significant association between pregnancy and melanoma mortality, along with the results of recent studies that could establish an unfavorable prognosis for melanoma diagnosed during pregnancy, to some extent. Using a quantitative approach, combining data from all the available studies, we could detect a small but significant survival difference for both OS and DSS, favoring melanoma controls compared with PAM patients. For OS, this result is a 17% increased probability of mortality for PAM patients, which ranges between 3 and 33%. For DFS, the result is a 50% increased probability of disease recurrence for PAM patients, which ranges between 19 and 90%. The heterogeneity among the studies included in the current meta-analysis was low for DFS (P=0.69) and moderate (P=0.07) for OS.

Interestingly, in a sensitivity analysis, we included only those studies that controlled for the effect of melanoma thickness (Breslow, TNM, or Clark’s) and/or staging of melanoma. In this subgroup of studies, the result is more robust as statistical significance is achieved with either fixed-effects or random-effects models (Figs 7 and 8). Although the latter analysis was associated with the limitation of several excluded studies, because of insufficient information provided, it further supports the conclusions by Moller et al. [6], who suggested that the worse prognosis of PAM is independent of the tumor thickness. It is noteworthy that in these analyses, heterogeneity was low; thus, one can anticipate this difference in survival we report here to be further amplified with the addition of future well-carried out studies that will control for stage/thickness. Until such studies emerge, clinicians dealing with PAM patients should take into consideration that existing evidence suggests a worse prognosis compared with nonpregnant melanoma patients. Although this certainly justifies a very close and careful monitoring, no evidence indicates that early termination of pregnancy could improve the prognosis of the patient. Subsequently, the current strategy of discussing the pregnancy continuance on a social and family basis remains the optimal approach.

Clinicians should be aware of the risk of missing melanoma because of the general belief that a changing mole during pregnancy is a normal finding. In this context, the usefulness of dermoscopy in evaluating pigmented skin lesions of pregnant women is unquestionable, and the detection of even one melanoma criterion should immediately warrant excision.

Acknowledgements
Athanassios Kyrgidis and Aimilios Lallas had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Giuseppe Argenziano, Aimilios Lallas, Athanassios Kyrgidis contributed to the study concept and design; Athanassios Kyrgidis and Aimilios Lallas carried out acquisition, analysis, and interpretation of data; Athanassios Kyrgidis, Aimilios Lallas, Elvira Moscarella, Caterina Longo, Giuseppe Argenziano drafted the manuscript; Elvira Moscarella, Roberto Alfano carried out critical revision of the manuscript for important intellectual content; Athanassios Kyrgidis carried out the statistical analysis; Giuseppe Argenziano, Caterina Longo obtained funding; Caterina Longo, Elvira Moscarella, Athanassios Kyrgidis contributed to the administrative, technical, or material support; and Caterina Longo, Giuseppe Argenziano supervised the study. A.K., A.L. and G.A. had access to the raw data.

The study was supported in part by the Italian Ministry of Health (RF-2010-2316524).

Conflicts of interest
There are no conflicts of interest.

References