1 **Article type:** Review

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3 **Title: Survival in Patients with Multiple Primary Melanomas: Systematic Review and Meta-**
4 **analysis**

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6 Genevieve Peek MBBS¹, Catherine M. Olsen PhD^{2,3}, Peter Baade PhD^{4,5,6}, Danny R Youlden
7 PhD^{4,5}, Joanne F Aitken PhD^{4,5,7,8}, Adele C Green MBBS PhD^{2,9}, Kiarash Khosrotehrani MD PhD
8 FACD^{1,10,11}

9

10 1-Queensland Skin and Cancer Foundation, Queensland Institute of Dermatology, South-Brisbane,
11 Queensland, Australia

12 2-QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia.

13 3-Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia

14 4- Cancer Council Queensland, Brisbane, Queensland, Australia.

15 5- Menzies Health Institute Queensland, Griffith University, Gold Coast, Queensland, Australia

16 6- School of Mathematical Sciences, Queensland University of Technology, Brisbane, Queensland,
17 Australia

18 7- School of Public Health and Social Work, Queensland University of Technology, Brisbane,
19 Queensland, Australia.

20 8- School of Public Health, The University of Queensland, Brisbane, Queensland, Australia

21 9-CRUK Manchester Institute and Faculty of Biology, Medicine and Health, University of
22 Manchester, Manchester, United Kingdom.

23 10-The University of Queensland, UQ Diamantina Institute, Translational Research Institute,
24 Brisbane, Queensland, Australia

25 11-Princess Alexandra Hospital, Department of Dermatology, Brisbane, Queensland, Australia

26

27 **Correspondence:**

28 Prof Kiarash Khosrotehrani, The University of Queensland Diamantina Institute, Translational
29 Research Institute, 37 Kent Street, Woolloongabba, QLD 4102, Australia. E-mail:
30 k.khosrotehrani@uq.edu.au

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32 **Funding sources:**

33 KK was supported by a National Health and Medical Research Council (NHMRC) Fellowship
34 (1125290), AG was supported by a NHMRC Program Grant (#552429)

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36 **Conflicts of interest:** none declared

37 **Manuscript word count** [excluding capsule summary, abstract, references, figures, tables]: 2414

38 **Capsule summary word count:** 50

39 **Abstract word count:** 189

40 **References:** 33

41 **Figures:** 2

42 Supplementary figures: 2

43 **Tables:** 3

44 Supplementary text: 2

45 **Attachments:** PRISMA checklist

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47 **Mendeley link for supplementary materials:** <http://dx.doi.org/10.17632/5t9b5vpx7b.2>

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Abstract

Background: The literature surrounding survival of patients with multiple primary melanomas (MPM) yields variable and opposing findings, constrained by statistical challenges.

Objectives: To critically examine the available literature regarding survival of patients with MPM compared with single primary melanomas (SPM) and detail statistical methods employed.

Methods: Electronic searches of Pubmed, Embase, Web of Science and Scopus, with cross-checking of references, for the period January 1956 - June 2019 were carried out. All studies published in English examining survival in patients with multiple melanoma were included. Case studies and small case series were excluded.

Results: Fourteen studies were eligible for inclusion. Conclusions on survival varied markedly depending on the statistical method used. Four studies that accounted for survival bias by partitioning the survival time were included in the quantitative review, with three of these reporting a survival disadvantage for MPM, while the fourth showed no difference in survival. Pooled HR was 1.39 (1.07-1.81) but with significant heterogeneity ($I^2 = 96.8\%$ $P_{\text{het}} < 0.001$).

Limitations: Studies showed significant heterogeneity in methodology.

Conclusions: When data was analysed with robust statistical methods, patients with MPM had a survival disadvantage compared with patients with SPM.

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Capsule Summary

- Literature regarding survival of patients with multiple primary melanoma (MPM) compared with single primary melanoma (SPM) is varied according to the method of calculation of the survival interval.
- Studies employing delayed-entry or time-varying statistical analyses address survival bias. A meta-analysis of such studies demonstrates survival disadvantage of MPM.

Introduction

Melanoma is a major public health issue worldwide^[1-3]. It is recognised that patients diagnosed with a first primary melanoma have an increased risk of developing a subsequent primary invasive melanoma^[1, 4], with a recent Australian study reporting a more than 5 fold increase in incidence compared to the general population^[5]. Although such estimates may vary between populations with different background incidence rates,^[6, 7] there is, overall, a significant subset of patients who develop multiple, nonsynchronous, primary melanomas^[5, 8]. The prognosis of patients with multiple invasive melanoma remains controversial.

While there is substantial literature examining the risk-factors associated with developing multiple primary melanomas (MPM), studies examining survival are sparse. In major prognostic studies, such as the ones performed by the American Joint Committee on Cancer (AJCC), analysis of survival is limited to a single (thickest) melanoma, neglecting the effects of other tumours in the same patient^[9]. In other studies that specifically examine the impact of multiple primary melanomas, survival outcomes have varied, and these studies have been constrained by statistical challenges and biases. This is a fundamental question pertaining to the biology of the host: is a preceding localised invasive melanoma of any importance for the survival of a host who newly develops a localised invasive melanoma?

Until recently, the issue of survival bias when examining the effect of multiple primary invasive melanoma on prognosis appears to have been underappreciated. Many studies have reported a survival benefit of MPM, however, a large number of these used the first melanoma^[10-14] as the index lesion. Indexing the first melanoma artificially increases survival interval and produces survival bias; that is, in order to be diagnosed with a second melanoma, the patient must survive until at least the time of the second diagnosis. Conversely, some groups have reported a survival disadvantage of MPM when using the most recent melanoma diagnosis as the index^[15, 16] - an analysis method that discounts survival time from the first diagnosis and produces bias in the opposite direction. Reported survival outcomes in patients with MPM are therefore strongly affected by the method of statistical analysis employed to estimate the survival interval. The delayed entry or the varying time entry methods minimize bias by allowing for consideration of total time between first and subsequent events^[17]. Although these methods have been established in other settings of repeated time-dependent events^[18] they have not been used for MPM survival until recently^[19-22].

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The aim of this systematic review was to analyse the published evidence regarding survival for patients with multiple melanoma, with an emphasis on the methodology of each study. A quantitative analysis of those studies that appropriately considered survival bias was subsequently performed.

Methods

Search strategy

We conducted a systematic review and meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines^[23]. Studies were identified from a search of electronic databases and cross checking with reference lists of articles. Databases included Pubmed, Embase, Web of Science and Scopus, for the period January 1956-June 2019. Search terms included ‘Melanoma’, ‘Multiple’, ‘Subsequent’, ‘Recur’, ‘Survival’, ‘Mortality’ and ‘Predictor’, with text works and MeSH words related to the key search terms (see supplementary material). Reference lists of selected articles were examined for additional studies.

Selection of studies and data extraction

Published articles written in English related to melanoma survival and prognosis were considered. Studies were deemed eligible if they related to melanoma survival and had compared patients with multiple versus those with a single primary cutaneous melanoma. Focusing on primary invasive melanoma, studies including solely stage III or IV disease were not considered given the major reduction of survival upon disease dissemination. Similarly, studies reporting only in situ melanoma were not considered. Both longitudinal retrospective and prospective studies were included. Articles relating to incidence or risk factors for developing multiple melanoma were excluded, as were case reports and small case series. Study eligibility and data extraction were assessed and performed by two authors. If two articles were based on the same study population only the study with the longest follow-up was included.

From each study we extracted the year of publication, data sources, study period and follow up length, study design, number of cases of MPM and SPM and stages of melanoma included. The index lesion, defined as the melanoma diagnosis from which survival was measured, was identified for each study and statistical methods used for survival analysis recorded. Overall results and study conclusions, sources of weakness and design bias were detailed. Included studies were reviewed to

determine if the authors had considered survival bias how it may have affected the outcomes. Studies were included in the meta-analysis if they considered survival bias by using a delayed entry or variable time survival analysis and if they reported a Hazard Ratio (HR) with a confidence interval. Other studies were summarised narratively.

Statistical methods

Individual study estimates were pooled using the weighted average method where the weight of each study is inversely proportional to the study variance. We determined a priori to conduct random effects meta-analysis^[24] in the presence of statistically significant heterogeneity, assessed using the Q statistic^[25] (significance level at $P < 0.05$), with inconsistencies quantified using the I^2 statistic^[26]. Publication bias was assessed using the Begg and Egger tests.

Results

Database searches and cross-checking of reference lists yielded 440 unique articles, after duplicates were removed (Figure 1). These articles were screened by title and abstract, and studies not of direct relevance were excluded ($n = 391$) leaving fourteen articles for inclusion. Studies were classified based on the method used to calculate the survival interval (supplemental Fig 1). Four studies addressed the issue of survival bias using a delayed entry or a variable entry method and were included in the meta-analysis^[19-22].

Qualitative review:

Among ten studies not retained in the meta-analysis, 7 used the first melanoma to calculate the survival interval^[10, 12-14, 27-29] (Table 1) and 1 used the last or the thickest melanoma^[15]. 2 studies performed multiple analyses using a combination of models – the first, last or thickest melanoma^[11, 16]. Analysis of bias revealed a high level of bias in 3 of the studies^[13, 14, 29] and an unknown level in an additional four^[10, 12, 21, 27]. Details of the types of bias per study^[30] are provided in supplemental text and supplemental Fig 2.

Among the studies using the first melanoma as an index lesion, 5 showed an improved prognosis for MPM patients^[10, 12-14, 29]. Bower et al.^[10] studied 48 MPM patients with Stage I and II disease and reported a 5-year survival of 95.3% vs 80% for MPM compared with SPM, respectively. Similarly, Savoia et al.^[12] demonstrated improved survival in 270 MPM patients with Stage 0-II disease with a HR of death of 0.546 (95% CI = 0.39-0.77, $p = 0.001$). Schiebner et al.^[13] demonstrated improved survival for men with MPM in a cohort of 90 patients with Stage I

240 melanoma. 283 MPM patients from the Duke Cancer Centre^[14] had improved survival over their
241 SPM counterparts, though it was unclear if *in situ* lesions were included in this study. Moseley et
242 al^[29] performed a retrospective analysis of 38 MPM patients with Stage I and II disease and
243 reported a poorer survival compared to SPM patients, though statistical details were lacking. In a
244 similar set of studies, Grossman et al^[28] utilised single matched controls from the SPM cohort for
245 MPM cases (n=887), provided the control survived as long as the interval between first and second
246 diagnoses for the MPM, and showed no significant survival difference between the groups even
247 after exclusion of *in situ* cases (615 SPM vs 504 MPM, HR=0.99). Burden et al^[27] demonstrated no
248 survival advantage in 108 MPM patients compared to 216 SPM controls matched for age, sex, site
249 and melanoma thickness.

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251 Krickler et al^[15] performed a large retrospective study of 1206 MPM patients indexing the last
252 melanoma and reported no difference in survival for MPM compared with SPM. Rowe et al^[16] and
253 Doubrovsky^[11] et al employed a combination of models for analysis (Table 2). Rowe et al^[16]
254 employed 4 models – the first MM, last MM, thickest MM and the first MM with thickest Breslow
255 as a covariate. They found a survival disadvantage for MPM using the last MM model with HR =
256 2.76 (95% CI = 1.20-6.32, p = 0.017). The findings neared significance when using the first MM as
257 the index lesion (HR = 1.80, 95% CI = 0.91-3.55, p = 0.092), overall supporting a worse prognosis
258 for MPM patients. Doubrovsky et al^[11] employed three models – indexing the first MM, thickest
259 MM and last MM and demonstrated poorer survival when indexing the last lesion and improved
260 prognosis when indexing with the first MM or thickest lesion.

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262 Five studies^[19-22, 31] using a delayed entry or a variable entry method were identified and four were
263 included in the meta-analysis (Table 3)^[19-22]. One^[31] of two studies from the Dutch Cancer Registry
264 was omitted because of significant overlap in the study population^[19]. Of the remainder, three large
265 retrospective studies showed poorer survival for MPM patients compared with SPM controls^{[19, 20,}
266 ^{22]}. A lone smaller study (n=61 MPM patients) reported no significant survival difference between
267 the groups^[21]. All studies excluded *in situ* disease. The multivariate adjustments performed are
268 summarised in Table 3. There were no significant differences in the MPM and SPM groups with
269 regard to Breslow thickness, ulceration or melanoma subtype in three studies^[19, 21, 22]. Utjes found a
270 higher proportion of MPM patients with thicker lesions and a higher T class^[20]. Mostly, patients
271 with MPM were older^[20-22] and two studies found a greater proportion of males in this group^[19, 20].
272 The meta-analysis identified a pooled HR of 1.39 (1.07-1.81, p<0.05) showing poorer outcome in
273 MPM patients, with significant heterogeneity ($I^2 = 96.8\%$ $P_{het} = 0.000$) (Figure 2). Despite the small
274 number of studies, we found no evidence of publication bias (Begg P=0.734 and Egger P=0.051).

Discussion

Understanding the multitude of host or tumour-derived parameters that may affect survival in melanoma is important, as these factors strongly influence patient management. Stratification of patients for therapy and clinical trials is currently based on the AJCC stage at the time of diagnosis, though other factors are likely to be involved. Given improvements in early diagnosis of melanoma, resulting in improved survival outcomes, the increased risk of melanoma in survivors, a significant proportion of patients will develop multiple invasive melanomas. Therefore, understanding the influence of multiple events on prognosis is critical and of increasing clinical relevance.

Our systematic review has highlighted the variation in outcomes reported depending upon the statistical approach to survival analysis. Overall, of the 9 studies indexing the first melanoma to calculate the survival interval, 6 found a survival advantage for MPMs and 3 reported no survival difference. In contrast, in studies using the last melanoma to calculate the survival bias, 2 showed poorer survival for MPM and one reported no significant difference in survival. As previously described, statistical analyses which index the first melanoma have an inherent bias towards improved survival as these patients essentially have a longer period of time to develop a second primary melanoma, which may account for the findings in this group of studies. This was best illustrated by 2 studies that performed analyses on the same patients using either first, last or thickest melanoma. In these studies, models using the first melanoma systematically showed a better survival hazard for MPM patients while the converse was true for models using the most-recently diagnosed melanoma. Studies employing a time-dependent or adjusted model suggest either reduced or equivocal survival in the MPM patient group. This is further supported by the quantitative results of the meta-analysis (time dependent or adjusted models only) which showed an overall poorer survival for MPM with a HR of 1.39 (although with evidence of significant heterogeneity). Of note, aside from the statistical method used, most studies retained in the meta-analysis were population based cohorts with the highest number of cases and controls. All 3 of these large studies reported a poorer survival for MPM patients.

It is counterintuitive that a patient with multiple invasive melanomas would have an improved prognosis over a patient with a single malignancy. Some authors have proposed the reported improved survival may be due to an ‘immunization effect’^[11, 12]. In addition, it has been suggested

that patients with melanoma are closely followed-up and therefore, subsequent melanomas are detected at an earlier stage ^[12, 28]. We propose, however, that the improved survival is more an artefact of failing to use appropriate statistical models. In contrast, use of time dependent or adjusted models found reduced survival of patients with MPM. The influence of certain genetic mutations or biological characteristics of the tumour have been suggested as potentially playing a role in the deteriorated survival of these patients^[11]. Previous findings have highlighted different host factors in patients with MPM, such as older age and of male sex, both of which are associated with poorer survival^[22]. This illustrates the impact of host characteristics on melanoma outcomes in patients with MPMs.

This review was limited by the small number of included studies and the heterogeneity of the results. This is likely to be explained by the wide range of methods and settings used for individual studies with many relying on registry data or single institution cohorts. In many studies, survival analysis was not adjusted for classical prognostic indicators. In addition, we have previously reported the importance of stage of first and subsequent melanomas on the survival of MPMs^[32, 33], finding that in situ melanomas did not influence the survival of invasive tumours^[32]. Yet, many of the retained studies included in situ melanomas together with invasive disease in the case definition of MPM patients, diluting the opportunity to detect a real effect. Similarly, earlier stage melanomas have been shown not to affect later stage disease outcomes significantly^[33] irrespective of the order of diagnosis. The variation in modes of adjustment in multivariate analysis or follow-up length could represent additional factors that contributed to the observed heterogeneity in the meta-analysis.

Overall, this systematic review and meta-analysis addresses some of the controversy around survival in MPM patients in the literature by highlighting the impact of inherent biases according to the statistical methods used. Despite limited available literature, our results clearly indicate that, when appropriate methods are used, patients with a history of an invasive melanoma who are diagnosed with an additional invasive melanoma are at higher risk of death than is indicated by their tumour characteristics. Additional statistically robust and large population-based studies are required to confirm this conclusion.

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<i>Study, year</i>	<i>Data source, study period</i>	<i>Study Design</i>	<i>Number of patients MPM (total)</i>	<i>Stages included</i>	<i>Follow-up in months (range)</i>	<i>Index melanoma</i>	<i>Average time (years) between 1st and subsequent MM</i>	<i>Result</i>	<i>Survival outcome</i>
Grossman, et al 2018	Utah Cancer Registry, 1973-2011	Retrospective analysis	504 (1119)	I-IV	Mean 173.9	First MM	NOS (>1)	HR=0.99 (0.76-1.29, p = 0.97) *	No evidence of difference
Rowe et al, 2015	Queensland Study of Melanoma, 1982-2004	Retrospective analysis	190 (1022)	I, II	Median 292.8 (266.4 - 321.6)	Model 1: first MM	Mean 9.34	HR=1.80 (0.91-3.55, p = 0.092);	No evidence of difference
Savoia et al, 2012	Centro Melanomi of University of Turin, 1975-2009	Retrospective analysis	270 (4290)	0-II	NS	First MM	2nd MM within 1 year 16.7%; 1-5 years 28.9%; 5-10 years 20.8%' >10 years 11.1%	HR= 0.546 (0.39-0.77, p = 0.001)	MPM > SPM
Bower et al, 2010	Sunbelt Melanoma Trial, 1997-2003	Post hoc analysis	48 (2506)	I, II	Median 66	First MM	Median 2.4	5 yr survival 95.3% vs 80% (MPM vs SPM), p = 0.005	MPM > SPM
Burden et al, 1999	Scottish Melanoma Group 1979-1996	Retrospective analysis	108 (216)	I-IV	Mean 84 (0-250)	First MM	Median 1.91	RR 1.5 (0.8-2.7), p = 0.18	No evidence of difference
Doubrovsky and Menzies, 2003	Sydney Melanoma Unit, 1983-1999	Retrospective analysis	298 (5250)	I, II	44.4 (SPM), 68.4 (2 MM), 84 (3 MM)	First MM	2nd MM within 0-2 years 61%; within 2-5 years 17%, > 5 years 21%	Improved survival for patients with 3 MM	MPM > SPM
Slingluff et al, 1993	Duke Cancer Centre, 1972-1993	Retrospective analysis	283 (7530)	NS. Invasive included.	44.4 (MPM) and 57.6 (SPM)	First MM	51.6% within 1 year; 75.6% within 5 years	Improved survival for MPM, p = 0.03	MPM > SPM
Scheibner et al, 1982	Melanoma Unit, Sydney Hospital, 1951-1980	Retrospective analysis	90 (3128)	I	NS	First MM	Average 3-4 years (0-41)	5-year survival 88.9% (MPM) vs 66.8% (SPM) in men (p = 0.05). NS difference for women.	MPM > SPM (men only)

Moseley et al, 1979	Division of Surgical Oncology UCLA, 1971-1979	Retrospective analysis	38 (633)	Stage I and II	Median 31.2 (6-264)	First MM	45% 2nd MM within the 1st year of diagnosis	Survival advantage for MPM. No statistical details provided.	MPM>SPM
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Table 1: Studies using the entire survival time from the first melanoma or not otherwise specified

* Analysis excluding in situ disease

Follow up duration: median or mean with range if available, unless otherwise specified

<i>Study, year</i>	<i>Data source, study period)</i>	<i>Study design</i>	<i>Number of patients MPM (total)</i>	<i>Stages included</i>	<i>Follow-up in months (range)</i>	<i>Index melanoma</i>	<i>Average time (years) between 1st and subsequent MM</i>	<i>Result</i>	<i>Survival outcome</i>
Rowe et al, 2015	Queensland Study of Melanoma, 1982-2004	Retrospective analysis	190 (1022)	I, II	Median 292.8 (266.4 - 321.6)	Model 2: last MM	Mean 9.34	HR 2.76 (1.20-6.32, p = 0.017)	MPM < SPM
Kricker et al, 2013	Registries in Australia, Canada, Italy and USA, 1998-2003	Retrospective analysis	1206 (2372)	0-IV	Median 91.2 (4.8-127.2)	Last MM	NOS	HR 1.24 (0.91-1.69, p = 0.18)	No evidence of difference
Doubrovsky and Menzies, 2003	Sydney Melanoma Unit, 1983-1999	Retrospective analysis	298 (5250)	I, II	44.4 (SPM), 68.4 (2 MM), 84 (3 MM)	Last MM	2nd MM within 0-2 yrs 61%; within 2-5 years 17%, > 5 years 21%	Poorer survival when modelled from last lesion. P = 0.01	MPM < SPM

Table 2: Studies only using the survival interval from the second melanoma

Follow up duration: median or mean with range if available, unless otherwise specified

<i>Study, year</i>	<i>Data source, study period</i>	<i>Study design</i>	<i>Number of patients MPM (total)</i>	<i>Stages included</i>	<i>Follow-up (months)</i>	<i>Index melanoma</i>	<i>Multivariate adjustments</i>	<i>Survival analysis</i>	<i>Average time (years) between 1st and subsequent MM</i>	<i>Result</i>	<i>Survival outcome</i>
Sharouni et al, 2019 *	Dutch Nationwide Network and Registry of Histopathology and Cytopathology, 2000-2014	Retrospective analysis	1767 (37049)	Invasive only	Median 75.1	Time varying	Age, sex, thickness, ulceration, tumour characteristics a& site	Multivariate Cox	Median 2.2 (0-16.7)	1.31 (1.20-1.42, p < 0.01)	MPM < SPM
Utjes et al, 2017 *	Swedish Melanoma Register, 1990-2007	Retrospective analysis	700 (27,235)	Invasive only	Median 103.2	Second MM, time dependent model	Age, sex, education level, thickness, ulceration, tumour characteristics & site	Cox regression and Kaplan-Meier	Median 2.5 (0-16.6)	HR 1.48 (1.19-1.85, p<0.001)	MPM < SPM
Pardo et al, 2017	Netherlands Cancer Registry, 1994-2009	Retrospective analysis	1210 (41523)	Invasive only	NOS	Time varying	Age, sex, thickness, tumour characteristics, presence of nodal or distant metastases	Extended Cox model	NOS	HR 1.32 (1.17-1.50)	MPM < SPM
Youlden et al, 2016 *	Queensland Cancer Registry, 1995-2013	Retrospective analysis	2330 (32238)	Invasive only	111.6	Delayed entry	Age, sex, thickness, ulceration, tumour characteristics & site	Kaplan-Meier	2nd MM: 3.1; 3rd MM 5.1	HR 2.01 (1.57-2.59, p<0.001)	MPM < SPM
Hwa et al, 2012 *	Melanoma Cooperative Group Database, New York University, 2002-	Prospective study	61 (788)	Stages I - III	Median 38.4 (SPM), 44.4	Time dependent covariate	Unclear	Unclear	Cumulative incidence of 2nd MM 5 years after initial MM 8.7%	HR 1.01 (0.99-1.03; p = 0.31)	No evidence of difference

Table 3: Studies using specific statistical methods to address survival bias

* Included in meta-analysis

Follow up duration: median or mean with range if available, unless otherwise specified

Acknowledgements

KK was supported by a National Health and Medical Research Council (NHMRC) Fellowship (1125290), AG was supported by a NHMRC Program Grant (#552429)

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Figure legend

Figure 1: Article selection strategy and outcome: Systematic review of literature using PRISMA guidelines

Figure 2: Risk of death in patients with multiple primary melanomas: Forest plot indicating increased risk of melanoma death in MPMs

Capsule Summary

- Literature regarding survival of patients with multiple primary melanoma (MPM) compared with single primary melanoma (SPM) is varied according to the method of calculation of the survival interval.
- Studies employing delayed-entry or time-varying statistical analyses address survival bias. A meta-analysis of such studies demonstrates survival disadvantage of MPM.