

SPECIAL REPORT

Increased Risk of Melanoma in Organ Transplant Recipients: Systematic Review and Meta-analysis of Cohort Studies

Adèle C. GREEN^{1–3} and Catherine M. OLSEN¹

¹QIMR Berghofer Medical Research Institute, Brisbane, Australia, ²Institute of Inflammation and Repair, University of Manchester, and ³Cancer Research UK Manchester Institute, Manchester, United Kingdom

Transplant recipients have a raised risk of melanoma but the relative magnitude is uncertain. We undertook a systematic review by searching major databases for relevant publications to June 2014. Cohort studies quantifying the association between transplantation and melanoma were included and data were pooled using the weighted average method. Among 20 eligible studies the pooled relative risk (pRR) of melanoma was 2.71 (95% confidence interval (CI), 2.23–3.30) with significant heterogeneity ($p < 0.001$). There was no indication of publication bias. Sub-group analyses by study design, follow-up period, adjustment for confounding and quality score did not materially alter results. Among liver and heart transplant patients pRR for melanoma was 5.27 (95% CI 4.50–6.62), higher than the pRR of 2.54 (95% CI 2.18–2.96) among kidney transplant patients. Transplant recipients are at more than double the risk of melanoma overall compared with the general population. Key words: melanoma; organ transplant recipients; immunosuppression; meta-analysis.

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Professor Adèle C. Green, QIMR Berghofer Medical Research Institute, Locked Bag 2000, Royal Brisbane Hospital, Queensland, 4029 Australia. E-mail: adele.green@qimrberghofer.edu.au

Organ transplant recipients are at substantially raised risk of diverse cancer types such as lymphomas and anogenital cancers linked to infection and cancers of the lung, lip and thyroid linked to other exposures (1, 2). The commonest type of cancer affecting organ transplant recipients are the keratinocyte skin cancers (1, 3), a proportion of which may be associated with the β papillomavirus (4). Alongside the known high risk of these common skin cancers, evidence suggests that cutaneous melanoma, the most serious type of skin cancer, is also raised among organ recipients. Two systematic reviews have examined the issue, but both were based on a limited number of studies. The first assessed the literature to March 2007 with the aim of estimating the risk of all cancers, melanoma included, among organ transplant recipients (1). The authors identified 4

relevant population-based cohort studies whose pooled results suggested a significant doubling of the melanoma incidence rate (standardised incidence ratio (SIR) 2.34) compared with the rate in the background population. For 3 of the 4 studies (5–7) the follow-up of melanoma ended in the mid-1990s and in 2003 for the fourth (8). In the one to two decades since these studies, longevity of transplant recipients has steadily risen along with the incidence of melanoma in most countries (9). The other systematic review (10) assessed studies published to January 2012, and again reported a doubling of risk of melanoma (SIR 2.4), very similar to the previous estimate (1). Published data from several eligible cohort studies were not included in the second review (10) however. Because melanoma is a potentially fatal malignancy, it deserves particular attention in susceptible groups such as today's organ transplant recipients whose increased melanoma risk remains to be calculated based on the totality of available evidence. We therefore evaluated all relevant published literature to date to quantify the magnitude of the increase as precisely as possible.

MATERIALS AND METHODS

The systematic review and meta-analysis was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines for reviews of observational Studies (11), and we followed the PRISMA statement (12) to guide reporting.

Literature search

Eligible studies up to June 2014 were identified by searching the Medline 1950 (U.S. National Library of Medicine, Bethesda, MD) database using PubMed software as the search interface; Embase 1966 database (Elsevier Science, Amsterdam, Holland) using the Embase search interface; and the ISI Science Citation Index using the ISI Web of Science search interface, and by hand-searching the reference lists of the retrieved articles.

For computer searches, we used the following medical subject headings terms or text words (both United States and United Kingdom spellings): melanoma, cancer, neoplasms, transplant, transplants, transplantation, aetiology, cohort (Search strategy; see Appendix S1¹). Studies that had been commonly cited in the literature and review articles were also included as citation search terms in the ISI Science Citation Index (1990 to present) to identify subsequent studies that had referenced them. The search was not limited to studies published in English. We read

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the abstracts of all identified studies to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine if they met study inclusion criteria.

Inclusion and exclusion criteria

Cohort studies, including population-based record linkage studies, that permitted quantitative assessment of the association between solid organ transplantation and melanoma with reported measures of relative risk (RR), namely Hazard Ratio (HR), Incidence Rate Ratio (IRR), or Standardised Incidence Ratio (SIR) were included. Any discrepancies between investigators about inclusion of a study were resolved by joint evaluation of the manuscript. When multiple reports were published on the same population or subpopulation, we included in the meta-analysis the report with the longest follow-up duration or the most comprehensive data.

Data extraction

Two researchers independently abstracted data from identified studies using a standardised data abstraction form, with inconsistencies resolved by consensus. The following information was recorded for each study: study design, location, years of data collection, source and definition of cohort, number of cases, person-year duration of follow-up, age of study population, variables used for statistical adjustment, point estimates (RR, HR, IRR or SIR), and 95% confidence intervals (95% CI). Where several risk estimates were presented, we abstracted those adjusted for the greatest number of potential confounders.

Quality assessment

Two researchers independently evaluated the quality of the studies by using a scoring system that was designed with reference to MOOSE (11), QATSO (13) and STROBE (14), where a total score of 5–7 was considered high quality, 3–4 moderate quality, 0–2 poor quality. One point each was allocated for (a) representativeness of the exposed cohort (i.e. population-based); (b) melanoma histologically confirmed; (c) description of calculation of person-years at risk; (d) mean/median follow-up reported (e) adjustments made for age, sex and time period; (f) adjustments made for ethnicity, and (g) time period between graft failure if it occurred and re-transplantation excluded from calculation of person-years. Single-institution studies and those with selected patient representation were classified as non-population-based. Disagreements about any item were resolved through discussion.

Data synthesis and analysis

To pool individual study estimates for the risk of melanoma in transplant patients, we used the weighted average method where the weight of each study is inversely proportional to the study variance. We determined *a priori* to use random effects models in the presence of significant heterogeneity (15), assessed using the Q statistic (16) (significance level at $p < 0.05$), and quantified using the I² statistic (17). We performed a sensitivity analysis by omitting one study at a time, and calculated the pooled relative risk (pRR) for the remaining studies to evaluate whether the results could have been affected markedly by a single study. Subgroup analyses were carried out according to important study features: design (cohort or record linkage); representativeness (population-based or single clinic-based); geographic region; adjustment for age, sex and time period; adjustment for ethnicity; type of transplant (kidney/mostly kidney or other); follow-up time (0–5 years; > 5 years) and whether follow-up time accounted for time between graft failure and

re-transplantation; and quality score. The extent to which one or more of these study design characteristics explained heterogeneity was then explored in meta-regression models for all studies combined (18). Finally, publication bias was evaluated through visual inspection of a funnel plot and with Begg's and Egger's tests (19, 20). All statistical analyses were performed using Stata Version 10 (Stata Corporation, College Station, TX).

RESULTS

A total of 20 eligible studies were identified and included in our systematic review (2, 3, 7, 21–37) (Fig. S1[†]). Two were conducted in Australia (3, 27), 6 in Northern Europe (21, 24, 25, 28, 31, 34), 2 in Central Europe (22, 29), 4 in Mediterranean Europe (23, 30, 33, 36) and 6 in North America (2, 7, 26, 32, 35, 37), and all were published between 1996 and 2013 (Table S1[†]). Of the 20 studies, 10 were cohort studies (3, 22, 23, 28–30, 33, 35–37) and the remaining 10 were record-linkage studies (2, 7, 21, 24–27, 31, 32, 34). Two studies reported on single-clinic patient cohorts (22, 35); the remaining 18 reported on population-based patient cohorts. Most of the studies reported on cohorts of renal transplant patients only (or all solid organ transplants with a high proportion of renal transplant patients); 5 reported on liver transplant patients (23, 28, 35–37), and one on heart transplant patients (26). Mean or median follow-up time ranged from 3.5 to 16 years. Thirteen (65%) of the 20 studies included in the meta-analysis were classified as high quality; the remaining 7 studies as moderate quality (Table S1[†]).

Outcomes

All 20 studies reported a positive association between organ transplantation and melanoma. Using a random effects model, the pRR for this association was 2.71 (95% CI, 2.23–3.30) (Fig. 1), with evidence of significant heterogeneity ($p < 0.001$, $I^2 = 78.1\%$). Sensitivity analyses removing each study in turn resulted in pRRs ranging from 2.57 (95% CI 2.24–2.95) with the omission of Chatrath et al. (37) to 2.81 (95% CI, 2.31–3.42), with the omission of Jensen et al. (25). The funnel plot was close to symmetrical and there was no evidence of publication bias using the Egger weighted regression method (p for bias = 0.50) or the Begg rank correlation method (p for bias = 0.64).

Subset and meta-regression analyses

Excluding the two single clinic-based studies did not materially alter the summary estimate (pRR 2.71, 95% CI 2.21–3.33) (Table I). Summary estimates were lower for studies conducted in Europe (pRR 2.43, 95% CI 2.09–2.84) than those conducted in North America (pRR 3.09, 95% CI 2.10–4.54) or Australia (pRR 2.67, 95% CI 2.15–3.31); heterogeneity was evident only for the studies conducted in North America. For analyses

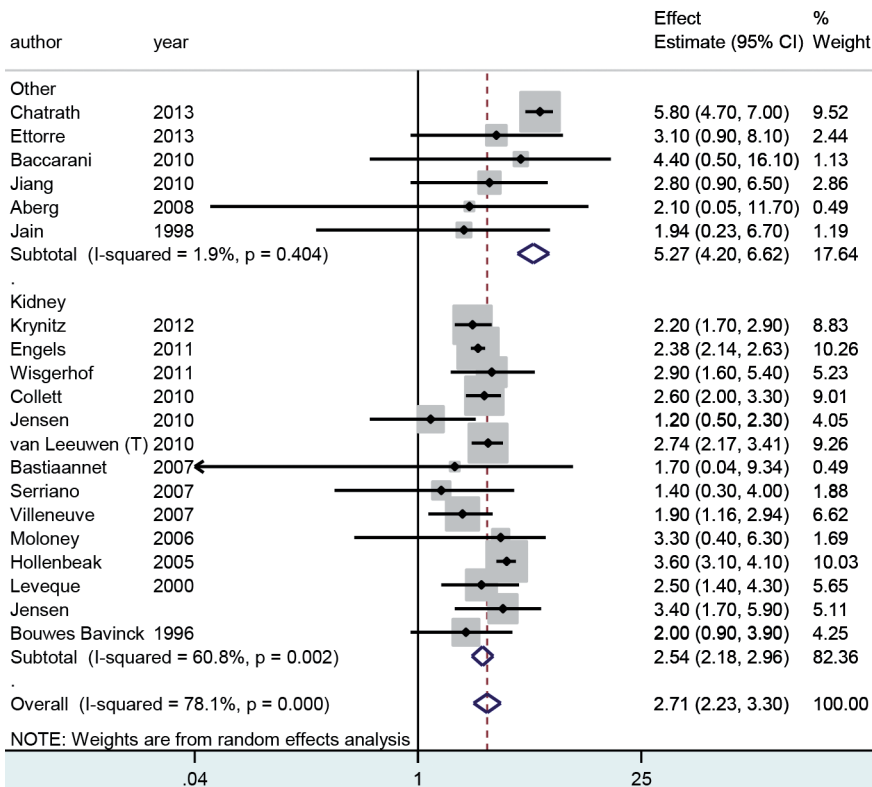


Fig. 1. Forest plot of the association between solid organ transplantation and melanoma stratified by study population (kidney/predominantly kidney or other). Each line represents an individual study result with the width of the horizontal line indicating 95% CI, the position of the box representing the point estimate, and the size of the box being proportional to the weight of the study.

Table I. Meta-analysis results using the weighted average method: organ transplantation and risk of melanoma

	Studies, n	Pooled effect estimate (95% CI)	I ² (%)	p heterogeneity	Weight, %
All studies	20	2.71 (2.23–3.30)	78.1	<0.001	100
Population-based					
Yes	18	2.71 (2.21–3.33)	80.3	<0.001	93.6
No	2	2.77 (1.56–4.91)	0.0	0.660	6.4
Study location					
Europe	12	2.43 (2.09–2.84)	0.0	0.787	46.0
North America	6	3.09 (2.10–4.54)	93.0	<0.001	40.5
Australia	2	2.67 (2.15–3.31)	0.0	0.421	13.5
Study quality					
High	13	2.95 (2.33–3.74)	84.3	<0.001	71.0
Moderate	7	2.24 (1.73–2.90)	2.7	0.405	29.0
Adjusted for age, sex and time period					
Yes	16	2.66 (2.02–3.51)	76.7	<0.001	71.8
No	4	2.75 (1.98–3.81)	82.4	<0.001	28.2
Ethnicity taken into account					
Yes	5	2.78 (2.25–3.44)	88.2	<0.001	88.2
No	15	2.31 (1.50–3.57)	0.0	0.727	11.8
Follow-up duration (mean/median)					
0–5 years	6	2.66 (2.00–3.55)	81.4	<0.001	38.0
>5 years	14	2.71 (2.02–3.65)	76.4	<0.001	62.0
Kidney (or mostly kidney)					
Yes	14	2.54 (2.18–2.96)	60.8	0.002	82.4
No	6	5.27 (4.20–6.62)	1.9	0.404	17.6
Excluded time period between graft failure and re-transplantation*					
Yes	3	2.43 (2.21–2.67)	0.0	0.470	33.1
No	11	2.53 (2.03–3.14)	58.6	0.007	66.9

*restricted to studies including kidney (or largely kidney) transplant patients.

stratified by study quality, the summary estimates were higher for studies that had a received a high quality score ($n=13$) than those graded as of moderate quality ($n=7$), although only the former showed significant heterogeneity ($p<0.001$). The pooled estimate for studies with longer mean or median follow-up time (i.e. over 5 years), a proxy for duration of immunosuppression, was no higher than for those with shorter length of follow-up. The pRR for kidney transplant studies that had excluded the time period between graft failure and re-transplantation in the calculation of person-years was not materially different than for studies that did not specifically exclude it (Table I), although significant heterogeneity was evident only for the latter group of studies. The pRR of 5.27 (95% CI 4.50–6.62) for studies of liver and heart transplant patients was substantially higher than the pRR of 2.54 (95% CI 2.18–2.96) for studies of predominantly kidney transplant patients.

In meta-regression analyses, the association between melanoma risk and transplantation was not greatly altered by such study design features as the extent of adjustment for confounding factors, but did depend on geographic region ($p=0.002$) and whether time period between graft failure and re-transplantation was included in the calculation of person-years among kidney transplant recipients ($p<0.001$).

DISCUSSION

Physicians who treat today's organ transplant recipients into the long term need the most accurate estimates of their patients' risk of cancer. Based on all current available studies, the majority of which were classified as being of high quality, we have shown that melanoma risk is more than doubled in organ transplant recipients in general (comprising mostly kidney transplant recipients) compared with the general population. We have further shown new evidence from a small group of studies that the risk of melanoma in liver and heart transplant recipients, at over 5 times the risk of the background population, appears even higher than the risk in kidney transplant recipients. Studies included in the review had an average follow-up time that ranged between 3.5 to 16 years, though duration of follow-up as a proxy

for duration of immunosuppression did not appear to be directly associated with risk of melanoma. Previous reports have noted a reversal of melanoma risk following graft failure (27) and a higher risk in transplanted patients when compared with those on the waiting list (38). Thus, inclusion of time between graft failure and re-transplantation in the calculation of person-years could lead to an underestimate of the association between transplantation and risk of melanoma. This was not apparent in our sensitivity analyses, with a slightly lower pRR for studies that had specified the exclusion of time between transplants compared with those that did not (or did not state they had). It is possible that the background risk of melanoma is higher in renal failure patients following long-term exposure to immunosuppressive therapy, and these patients are known to be at higher risk of developing cutaneous squamous cell carcinoma (25).

Based on 20 studies, our meta-analysis results substantially extend the results of the previous two meta-analyses based on 4 cohort studies (1) and 12 studies (10), respectively. The magnitude of melanoma risk is now shown to be increased by around 2.7-fold rather than 2.3-fold (1) or 2.4-fold (10), with the likelihood that some organ transplant recipient subgroups like heart transplant patients may have higher melanoma risk due to more intensive immunosuppressive regimens.

Limitations of our meta-analysis include the potential for biases and confounding inherent in the original studies. Also the vast majority of the evidence arises from follow-up of patient cohorts dating back many decades, and this may somewhat diminish the generalizability of the evidence to current organ transplant recipients who are exposed to different treatment regimens. These limitations may detract from the precision of our estimate of melanoma risk in current transplant recipients, but their significantly increased risk remains a major concern.

There are feasible and effective screening and prevention strategies that can be put in place to decrease transplant patients' elevated risk of melanoma morbidity. Their medical carers should be aware that these patients require regular skin screening for early detection and treatment of any suspicious pigmented lesions. Also since melanoma is driven by high sun exposure (39), sun avoidance and sun protection can be advised by transplant physicians, dermatologists and other medical staff involved in the care of these patients. Studies that have evaluated the sun protection behaviour of organ transplant recipients show that it is inadequate in many cases, with around a third not using sunscreen when in the sun and two-thirds not wearing protective clothing (40, 41). Advice and encouragement to adopt sun protection measures routinely will help counter the increased risk of melanoma demonstrated here, as well as mitigating the better-known increased risk of other skin cancers that immunosuppression carries for organ transplant recipients.

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