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Protocol for Sex and melanoma incidence, treatment response, survival and lesion characteristics; a systematic review with meta-analysis

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ADMINISTRATIVE INFORMATION

Support - Salary suppoert for GJW is through Melanoma Institute Australia.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025120044

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 December 2025 and was last updated on 12 December 2025.

INTRODUCTION

Review question / Objective To determine whether sex impacts incidence, characteristics, treatment efficacy and death after adjusting for age at diagnosis, histopathological subtype and type of treatment.

Rationale Global data on melanoma incidence shows that in some countries there is a higher incidence of melanoma in males compared to females while for other regions, females have a higher incidence (Table 1.)[1]. World cancer registry data[1] also shows that the differing incidence of melanoma between the sexes is not constant across age groups, but appears to change with age (Table 2.). For the four countries listed, incidence in females below 44 years of age at diagnosis is higher than in men under 44 years, whereas as age at diagnosis increases, male incidence overtakes that of females.
Histopathological subtypes of melanoma also appear to differ between the sexes; US data suggests females have somewhat lower rates of superficial spreading melanoma, nodular melanoma and lentigo maligna melanoma than men[2] but similar rates of acral lentiginous melanoma. Pooled analysis of data from Australia, the US and Scotland show females have signficantly lower rates of melanoma on head and neck sites, similar rates on the trunk and upper limbs and a trend towards lower rates on lower limbs compared to males when age at diagnosis was not considered[3]. When age and site were analysed together, Queensland males aged 40 or older when diagnosed had much higher rates of melanoma on head and neck sites and the trunk, while females aged below 60 at diagnosis, had higher rates of melanoma on their upper and lower limbs compared to males. This pattern was similar in the US and Scotish sample although ages at which rates reversed for males and females differed somewhat[3].
Survival after a melanoma diagnosis also shows differences between the sexes, with females in many countries having a lower mortality rate than

is seen for men (Table 3.)[1]. When mortality rates are expressed within age group categories, in all but the youngest age group (≤44 years at diagnosis) females have lower mortality rates from melanoma compared to males (Table 4.).
Response to immune check point inhibitor (ICI) therapy also appears to differ between the sexes, with a lower efficacy for preventing death in females. A meta-analysis of 20 randomised controlled trials of ICI therapy, 7 specifically in melanoma, that reported risk of death separately for males and females showed a significant difference between the sexes[4]. The hazard ratio of death from disease in ICI treated males compared to not-treated males was 0.72 (95%CI 0.62, 0.79) and in ICI treated females compared to non-treated females; 0.86 (0.79, 0.93). The difference in risk between males and females was statistically signficant. Analysis limited to melanoma only, gave hazard ratios of death in ICI treated and untreated males of 0.66 (95%CI 0.55, 0.79) and in ICI treated and untreated females; 0.79 (95%CI 0.70, 0.90). There was however greater heterogeneity in analysis of the risk for males; I2 60% compared to I2 0% for females and the confidence intervals overlapped suggesting no significant difference is the risk estimates.
It thus appears that sex impacts melanoma incidence, anatomical site of the lesion, the type of melanoma, risk of death and possibly also response to treatment but further exploration of these patterns with more extensive data would further consolidate these patterns. If differences remain evident with further analyses, it may become necessary for health promotion strategies around melanoma prevention to include some sex specific information and discussion around treatment efficacy may also need to be adjusted for the sex of the patient.

Condition being studied Cutaneous melanoma.

METHODS

Search strategy

1 Melanoma, cutaneous malignant/
2 Cutaneous melanoma.mp
3 *Melanoma/
4 1 or 2 or 3
5 *Risk factors/
6 Risk factor.mp
7 *Prognosis/
8 Prognosis.mp
9 Adjusted analyses.mp
10 Exp Multivariate Analysis/
11 Multivariate analyses.mp
12 Multivariable analyses.mp
13 5-12/OR
14 Exp Sex/
15 Sex.mp
16 Gender.mp
17 14 or 15 or 16
18 4 and 13 and 17.

Participant or population Adults with cutaneous melanoma, excluding acral lentiginous melanoma.

Intervention None.

Comparator None.

Study designs to be included No study design or language restrictions will be applied.

Eligibility criteria Articles will be included if they report an adjusted risk of melanoma (incidence), and risk of death from melanoma after considering features such as age at diagnosis, sex and histopathological subtype for incidence risks and for risk of death; age, sex and treatment type with 95% confidence intervals (CIs).

Information sources Medline, Embase, the Cochrane CENTRAL register of trials will be searched.

Main outcome(s) Outcomes; incidence (risk of melanoma), death from melanoma, response to treatment.

Additional outcome(s) The information of interest to this review is 1. the risk of melanoma, in males and females, after adjustment for other important prognostic features, 2. the risk of death from melanoma in males and females, after adjustment for other important features and 3. the response to treatment rates for males and females after adjustment for other important features.

Data management Searches will be conducted using the OVID interface. Titles will be downloaded into Endnote software and sorted into folders for inclusion and exclusion reasons. Data will be extracted from eligible studies and stored in Excel worksheets. Review Managers software will be used for Forest plot analyses and figures. SPSS will be used for Eggers test for publication bias.

Quality assessment / Risk of bias analysis Risk of bias assessment will use the Cochrane framework for RCTs, and the Newcastle-Ottawa scale for non-randomised studies.

Strategy of data synthesis Cochrane Review Manager will be used to produce forest plots for analyses where there is MVA risk data for three or

more studies. Risk data will be log transformed and standard errors estimated from 95% CIs or p-values then analysed using the data type generic inverse variance, generating a pooled HR. A fixed effects model will be used and heterogeneity assessments will use the I2 measure. Summary risks will be reported only when the I2 value is ≤60%, indicating that the level of heterogeneity is low to moderate.

Subgroup analysis Sub-group analyses will be performed by country of patients recruitment, subtype (SSM, Nodular, Others), publication year and use of systemic therapies.

Sensitivity analysis Sensitivity analyses will be performed when any single study contributes a weighting of 20% or greater.

Language restriction None, articles were translated using Google Translate.

Country(ies) involved Australia.

Keywords Cutaneous melanoma, Sex, Gender, Multivariable analyses.

Dissemination plans Publication in a peer reviewed medical journal.

Contributions of each author

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