

# Methotrexate and Risk of Cutaneous Melanoma

Akademisk avhandling

Som för avläggande av Sam Polesies medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i hudklinikens föreläsningssal, Gröna stråket 16, Göteborg, den 5 december 2019, klockan 09.00

av Sam Polesie

Fakultetsopponent:

**Docent Åke Svensson, Lunds universitet**

Avhandlingen baseras på följande delarbeten:

- I. Polesie S, Gillstedt M, Sönnergren HH, Osmančević A, Paoli J. *Methotrexate treatment and risk for cutaneous malignant melanoma: a retrospective comparative registry-based cohort study*. Br J Dermatol. 2017 Jun;176(6):1492-1499.
- II. Polesie S, Gillstedt M, Paoli J, Osmančević A. *Methotrexate Exposure and Risk of Cutaneous Malignant Melanoma: No Evidence of a Dose-response Relationship*. Acta Derm Venereol. 2018 Oct 10;98(9):888-895.
- III. Polesie S, Gillstedt M, Paoli J, Osmančević A. *Methotrexate and melanoma-specific mortality*. J Eur Acad Dermatol Venereol. 2019 Mar; 33(3):e123-e125 Oct 25.
- IV. Polesie S, Gillstedt M, Paoli J, Osmančević A. *Methotrexate treatment in patients with a history of cutaneous melanoma and the risk of a consecutive primary melanoma: A national retrospective registry-based cohort study*. J Am Acad Dermatol. 2017 Jul;77(1):161-163.
- V. Polesie S, Gillstedt M, Paoli J, Osmančević A. *Methotrexate treatment for psoriasis patients and risk of cutaneous melanoma: a nested case-control study*. In manuscript.
- VI. Polesie S, Gillstedt M, Zaar O, Osmančević A, Paoli J. *Dermoscopic Features of Melanomas in Organ Transplant Recipients*. Acta Derm Venereol. 2019 Jul 12. [Epub ahead of print].

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**Sam Polesie**

Department of Dermatology and Venereology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Methotrexate (MTX) is an anti-inflammatory and immunosuppressive drug commonly used to treat psoriasis, psoriatic arthritis and rheumatoid arthritis. Cutaneous malignant melanoma (CMM) is a common and dangerous type of skin cancer and in recent decades a noteworthy increase in incidence has been observed. In Sweden, CMM is the fifth most common form of cancer in both men and women. This type of cancer is more frequent among patients with an impaired immune system such as organ transplant recipients (OTRs) who are treated with immunosuppressive drugs to prevent rejection of the transplanted organ. The use of MTX, has previously been associated with an increased risk of CMM in an Australian investigation.

The purpose of this thesis was to study the association between MTX and the risk of CMM.

In *Paper I*, a retrospective comparative cohort study was conducted, comprising all Swedish individuals over 18 years with at least one filled MTX prescription in the time period 2005-2014 (MTX-exposed). For each MTX-exposed patient, five age- and sex-matched MTX-unexposed individuals were selected (MTX-unexposed). The risk of CMM was elevated among MTX-exposed subjects, but this risk increase was lower than previously observed and hardly relevant in clinical practice.

To further investigate a possible association between MTX and CMM, a dose-response analysis was performed. *Paper II* used the cohort above and analyzed whether increased MTX doses elevated the risk. In summary, no conclusive dose-response relationship between MTX and CMM was observed.

*Paper III* investigated whether CMM that occurred in MTX-exposed patients caused an increased mortality compared to CMM occurring among the MTX-unexposed individuals. MTX-exposed patients had an increased risk of melanoma mortality. This observation was robust, after adjusting for melanoma stage at diagnosis.

*Paper IV* investigated patients who had already had CMM and exposed to MTX after the first CMM diagnosis. The risk of a new CMM among these patients was not increased compared to a corresponding MTX-unexposed group.

*Paper V* was performed using individuals from a cohort of psoriasis patients. Previously cancer-free psoriasis patients who developed CMM and psoriasis patients who had not developed CMM at the corresponding date were compared. The proportion exposed to MTX in each group did not differ significantly.

In *Paper VI*, the dermoscopic appearance of CMM that occurred in OTRs was investigated. The melanoma-specific features in this group were compared to age- and sex-matched controls. When analyzing the results, no differences could be observed. Nevertheless, these results are limited due to a small sample size and should instead be regarded as an invitation to more investigations.

In conclusion, this thesis has shown that CMM is unlikely to be associated with the use of MTX and the dermoscopic appearance of CMM in immunosuppressed patients does not seem to differ from those of immunocompetent individuals.

**Keywords:** methotrexate; cutaneous melanoma; risk; organ transplant recipients; dermoscopy