

What is the risk of cancer in patients who take methotrexate?

Case: 50-year-old patient is taking methotrexate for psoriatic arthritis. They were recently diagnosed with skin cancer and want to know whether methotrexate increases the risk of skin cancer or other types of cancer.

1. CIRT Trial (2018):

<https://www.nejm.org/doi/full/10.1056/NEJMoa1809798>

This cardiovascular prevention trial randomly assigned 4,786 patients with cardiovascular disease to low-dose methotrexate (≤ 20 mg/week) or placebo, with median follow-up of 23 months. **Cancers developed in 52 patients in the methotrexate group versus 30 in the placebo group.** This difference was mostly due to non-basal-cell skin cancers, with 31 cases compared to 10. This indicates that there is more than three times the rate of these types of skin cancers in this group, which was statistically significant.

2. Solomon 2014.

<https://www.sciencedirect.com/science/article/abs/pii/S0049017213001704?via%3Dihub>:

This study followed 6,806 DMARD courses in rheumatoid arthritis patients from 2001-2010. This study found that patients using methotrexate had a higher risk of developing cancer compared to those receiving other treatments. Specifically, when looking at non-biologic DMARDs (disease-modifying antirheumatic drugs), the hazard ratio (HR) was 0.17, meaning that the cancer risk in the methotrexate group was much higher (approximately 6 times higher) than in the non-biologic DMARDs group.

3. Polesie et al. (2023); <https://pubmed.ncbi.nlm.nih.gov/36739322/>

This study conducted in Denmark that looked at a large number of skin cancer cases from 2004 to 2018. The study found that using methotrexate (at a cumulative dose of 2.5 grams or more) was linked to an increased risk of three types of skin cancer:

- **Basal Cell Carcinoma (BCC):** The odds of developing this type of skin cancer were 29% higher in methotrexate users (adjusted odds ratio of 1.29).
- **Cutaneous Squamous Cell Carcinoma (cSCC):** The risk was even higher, with methotrexate users having a 61% increased risk (odds ratio of 1.61).
- **Melanoma:** There was also a 35% higher risk for melanoma (odds ratio of 1.35).

Additionally, the study indicated that higher cumulative doses of methotrexate were associated with an increased risk of BCC and cSCC.

However, when the analysis focused specifically on patients with psoriasis, the observed associations were weaker, suggesting that the increased risk of skin cancers may not be as pronounced in psoriasis patients using methotrexate compared to the general population.

4. Mabel Review (2022);

<https://jamanetwork.com/journals/jamadermatology/fullarticle/2795482>

- **Study Inclusion:** Seventeen studies were included in the analysis
- **Indications for Methotrexate:** Methotrexate was prescribed for various conditions including rheumatoid arthritis, psoriasis, psoriatic arthritis, and inflammatory bowel disease. The reasons for using methotrexate were not specified in 5 of the studies.
- **Risk of Melanoma:** When comparing individuals who were exposed to methotrexate with those who were not (unexposed), those using methotrexate had a small but statistically significant

increased risk of developing melanoma (pooled relative risk of 1.15, with a confidence interval of 1.08-1.22). This means that methotrexate users had a 15% higher risk of melanoma compared to non-users.

5. Inose et al. (2020); <https://pubmed.ncbi.nlm.nih.gov/31854294/>

This analysis of the FDA Adverse Event Reporting System database for rheumatoid arthritis patients found **methotrexate showed significant associations with all malignancies except liver cancer**. The study also found that adding biologic DMARDs to methotrexate further increased risk of breast, ovarian, and lung cancers.