International Agency for Research on Cancer

World Health Organization

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Regular use of pharmaceutical opioids and subsequent risk of cancer: a prospective cohort study and Mendelian randomization analysis

Questions and Answers (Q&A)

A large-scale study led by the International Agency for Research on Cancer (IARC) has found that regular use of pharmaceutical opioids is associated with a higher risk of developing several cancer types. In this study, published today in *eClinicalMedicine*,[1] regular use of pharmaceutical opioids was linked to a higher risk of developing cancers previously known to be associated with opium consumption, including cancers of the lung, bladder, larynx, pancreas, and oesophagus.

1. What is the position of the World Health Organization regarding opioids for pain management?

The World Health Organization (WHO) maintains its current position, which recognizes opioids as essential medicines for managing moderate to severe pain, particularly for cancer pain, palliative care, and acute pain (such as post-surgical or trauma-related pain). In addition, WHO recognizes specific opioids as essential for the treatment of opioid dependence in the form of opioid agonist maintenance treatment (OAMT). WHO emphasizes that opioids should continue to be available and accessible to patients who require them to ensure effective treatment of pain and of opioid use disorders.

At the same time, WHO highlights the importance of opioid stewardship, which involves a coordinated systems-level approach to ensure that opioids are accessible when needed and are used safely, rationally, and responsibly across the health system. Opioids should be prescribed using evidence-based guidelines to minimize risks of misuse, dependence, and adverse effects. WHO advocates for careful assessment, monitoring, and regulation to prevent both over-restriction, which can lead to untreated pain, and under-restriction, which can contribute to misuse, diversion, and opioid-related harm.

2. What do these findings mean for the long-term safety of pharmaceutical opioids, especially in non-cancer populations?

The findings suggest that regular use of pharmaceutical opioids may be associated with a higher risk of developing certain cancer types. From a public health perspective, the study's results provide further evidence highlighting the ongoing concerns about the long-term use of opioids in non-cancer populations, in which opioids

[1] Sheikh M, Domingues A, Alcala K, Langdon R, Mariosa D, Feng X, et al. (2025). Regular use of pharmaceutical opioids and subsequent risk of cancer: a prospective cohort study and Mendelian randomization analysis. *eClinicalMedicine*. Published online 11 November 2025; https://doi.org/10.1016/j.eclinm.2025.103439

are sometimes prescribed for chronic, non-cancer pain. However, it is important to note that these findings do not show that pharmaceutical opioids cause cancer. Further studies in humans and mechanistic investigations are needed to determine whether pharmaceutical opioids actually play a role in the development of some types of cancer.

3. What was the methodology used to obtain these results?

Two complementary approaches were combined. First, the study analysed data from nearly 473 000 adults who participated in the UK Biobank cohort study. Participants were recruited between 2006 and 2010 from 22 centres across the United Kingdom and were asked at baseline about medications they used regularly (weekly, monthly, or every 3 months). They were then followed up for more than 10 years to record health outcomes, including cancer. Cancer diagnoses during the follow-up period were compared between participants who reported regular use of pharmaceutical opioids and those who did not. To minimize potential bias from other cancer risk factors that may be more prevalent among people who use opioids (confounding), all analyses were adjusted for age, sex, smoking history, alcohol use, body mass index, socioeconomic status, chronic pain, and medical history.

Second, to further address potential biases in observational epidemiological studies, such as reverse causation (i.e. participants might be prescribed opioids because of pain from undiagnosed cancer) and confounding, genetic analyses were conducted using a method called Mendelian randomization. This method uses genetic variants associated with regular opioid use as proxies, allowing the researchers to test whether a genetic predisposition to regular opioid use is linked to cancer risk across 14 large independent genome-wide association studies of various cancer types.

Both approaches consistently indicated an increased risk of cancer types already known to be linked to opium consumption (cancers of the lung, pancreas, bladder, oesophagus, and larynx) and showed no overall increase in risk for other cancer types.

4. Can the increase in risk be put into perspective?

It is important to clarify that this study reports relative risks, not absolute risks. A relative risk increase means that people who regularly use opioids are more likely to develop certain cancer types compared with those who do not, but it does not mean that everyone who uses opioids will develop cancer, and the absolute risk increase remains small.

For example, in this study, regular opioid use overall was linked to about a 30% higher risk of specific cancer types, such as lung, bladder, and pancreatic cancers. In practical terms, if 10 out of every 100 000 people in the general population developed one of these cancers, then among regular opioid users one might expect that about 13 out of every 100 000 people would develop that cancer. The risk was even greater for people who used strong opioids, for which the study observed about an 80% higher risk. Using the same example, instead

of 10 out of every 100 000 people developing a cancer, in strong opioid users it could be closer to 18 out of every 100 000 people.

Although the increase in risk for an individual may appear modest, the widespread use of opioids means that even small differences in risk could translate into a substantial number of additional cancer cases at the population level.

5. Which types of pharmaceutical opioids were most strongly linked to increased cancer risk in this study?

The analyses showed that the increased cancer risk was more pronounced with regular use of strong and long-acting opioids, and the increase was more modest for weak and short-acting opioids. These findings suggest that cancer risk may vary depending on opioid strength and duration of action, although because of sample size limitations the study was not able to evaluate the risks of individual opioid molecules separately.

6. What are the limitations of the study, and what impact do these have on the findings?

First, both the cohort and genetic analyses relied on self-reported opioid use collected only once, at the beginning of the study. The study could not assess changes in dose, duration, cumulative use, or switching between opioid types over time. As a result, although the observed associations appear robust, the exact degree of risk increase for each cancer type may not be precise and should be clarified in future studies with more detailed exposure assessment.

Second, although the study carefully adjusted for many important factors such as smoking history, alcohol use, body mass index, and chronic pain, the possibility of residual confounding cannot be fully excluded. In other words, the underlying health conditions that led individuals to use opioids may still contribute to the observed associations. Replication of these findings in additional studies in humans, together with mechanistic investigations, will be essential before drawing conclusions about causality.

Third, the analyses were conducted at the drug-class level. Because of sample size constraints, the study was not able to evaluate the risks of individual opioid molecules separately, and it could not fully explore different patterns of use, such as short-term versus very long-term therapy. Future studies should aim to assess risks for specific opioid classes and examine how duration of therapy influences cancer risk.

7. What are the potential biological mechanisms that could explain a link between opioid use and cancer development?

The mechanisms by which pharmaceutical opioids may influence cancer development (e.g. initiation or promotion) remain unknown, and mechanistic studies are needed to clarify this potential link, but several pathways are biologically plausible. Unlike raw opium, pharmaceutical opioids do not contain known

carcinogens such as polycyclic aromatic hydrocarbons; however, a recently identified mutational signature in oesophageal tumours linked to opium consumption suggests mechanisms beyond known carcinogens. Some opium alkaloids have demonstrated genotoxicity in a few experimental studies, which could extend to natural and semi-synthetic opioids with similar chemical structures. More broadly, activation of opioid receptors, particularly the μ-opioid receptor, which is overexpressed in several opium-related cancers, can trigger intracellular pathways that drive cell-cycle progression, angiogenesis, and immune suppression, all of which are relevant to cancer biology. Opioids may also interact with non-opioid receptors and signalling cascades, further promoting tumorigenesis. At the same time, paradoxical tumour-inhibitory effects, such as enhanced apoptosis, have been reported in experimental studies, underscoring the complexity of opioid–cancer interactions and the need for dedicated mechanistic research.

8. Should people with cancer who are using opioids stop their treatment?

No. These findings should not be interpreted to mean that people with cancer should stop taking opioids when they are needed for pain control. Evidence-based WHO guidelines have identified opioids as an essential component of cancer pain management, with the priority being adequate pain control and quality of life under the guidance of trained health-care professionals. For these patients, the benefits of effective pain relief far outweigh any potential long-term risks, and no one should stop or reduce their prescribed pain medication on the basis of these findings.

It is also important to note that this study specifically excluded people with cancer at baseline, so the results do not apply to patients with cancer.

9. How might these findings influence current prescribing guidelines or regulatory policies around opioid use for chronic pain?

These findings should not be interpreted as grounds for immediate clinical application or changes to prescribing guidelines. Rather, they underscore the need for further research to determine whether the observed associations are causal, to quantify their magnitude, and to clarify their clinical relevance. Importantly, the analyses evaluated opioids as a class and did not study individual compounds or their effects on cancer progression among people already diagnosed with cancer, so clinical decision-making should not be altered on this basis. More broadly, opioid misuse is already associated with well-established harms, including dependence, toxicities, and overdose, which have shaped existing recommendations to use them cautiously and mainly for short-term indications.

10. How should health-care providers weigh the benefits of opioid pain relief against the potential long-term cancer risks suggested by this study?

Health-care providers should continue to prioritize effective pain relief, especially for severe acute and cancer-related pain and palliative care, for which opioids remain indispensable. The potential long-term cancer risks suggested by this study require further investigation and should not prompt immediate changes in prescribing. Instead, providers should weigh these potential risks alongside the already well-established harms of opioids, such as dependence, overdose, and other toxicities, by using them at the lowest effective dose, for the shortest necessary duration, and when clinically indicated. Ultimately, these findings reinforce the importance of appropriate prescribing, following evidence-based guidelines, and highlight the urgent need for further research to guide future practice.

11. What further research is needed to clarify the risks of individual opioid drugs and confirm these findings in other populations?

Further research is needed to assess the cancer risks of individual opioid compounds, because this study evaluated opioids as a class. Replication in diverse populations is essential to confirm these findings and ensure that they are generalizable. Studies with more detailed exposure assessment, including dose, duration, and changes in opioid use over time, will be critical to understand dose–response relationships. In parallel, mechanistic and experimental studies are needed to clarify the biological pathways by which opioids might contribute to cancer development. Large-scale international collaborations, such as the Opioid Cohort Consortium (OPICO), will play a key role in addressing these questions.

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