Meta-analysis on the association between nonsteroidal anti-inflammatory drug use and lung cancer risk


CRD summary
The authors concluded that regular aspirin use (seven or more tablets weekly) may protect against lung cancer. Lung cancer risk was not associated with non-aspirin or overall non-steroidal anti-inflammatory drug use. Although the review was limited by the low quality of available evidence and large differences between included studies, the authors’ conclusions reflected the strength of available evidence.

Authors’ objectives
To evaluate the association between non-steroidal anti-inflammatory drugs (NSAIDs) and lung cancer risk.

Searching
PubMed, EMBASE and ScienceDirect were searched for articles published in any language up to January 2011. Search terms were reported. References of retrieved articles were hand-searched.

Study selection
Cohort, case-control or clinical studies that evaluated exposure to aspirin or other NSAIDs and measured the incidence of lung cancer were eligible for inclusion. Studies that did not provide raw data on exposure or incidence of lung cancer were excluded. Studies that did not provide data on gender, histology or dose exposure were excluded from subgroup analyses.

Included studies measured exposure to aspirin or non-aspirin NSAIDs. Level of exposure ranged from any use in the one to six months prior to study start date to use on more than 4.2 days a week for ten years. The smoking status of participants varied, including people who did not smoke, those who had stopped smoking and those who smoked (up to 260 pack years), where reported.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The authors did not state that they assessed the quality of included studies.

Data extraction
The number of events in each group were extracted and used to calculate risk ratios (RRs) with 95% confidence intervals (CIs). Odds ratios (ORs) and corresponding 95% confidence intervals were also extracted.

The duration and frequency of NSAID exposure, histology type, and smoking pack-years/status were extracted for subgroup analyses.

Two reviewers independently extracted the data for review using a standardised form. Disagreements were resolved by consensus.

Methods of synthesis
For cohort studies, pooled risk ratios with 95% confidence intervals were calculated separately for aspirin use and non-aspirin NSAIDs. The clinical trial was combined with cohort studies for the meta-analysis of aspirin use and lung cancer risk. For case control studies, pooled odds ratios were calculated separately for aspirin use, non-aspirin NSAIDs and overall NSAIDs.

Statistical heterogeneity was assessed using X² and I². Where significant heterogeneity was found (I² over 50%), a random-effects model was used, otherwise a fixed-effect model was used.

Subgroup analyses were performed according to frequency of NSAID use, duration of NSAID use, gender, histological
type and smoking status. Sensitivity analyses were carried out excluding one study at a time.

Publication bias was assessed using funnel plots.

Results of the review

Nineteen studies were included for review (471,542 participants). These included one clinical trial (39,876 participants), seven cohort studies (348,079 participants), six case-control studies (15,343 participants) and five nested case-control studies (68,244 participants).

There was no significant association between aspirin use and lung cancer risk in cohort and clinical trials (RR 0.96, 95% CI 0.78 to 1.19; eight studies; 387,936 participants) or with case-control studies (OR 0.87, 95% CI 0.69 to 1.09; nine studies; 31,266 participants). Excluding the clinical trial did not significantly alter the results. There was evidence of substantial heterogeneity for cohort studies ($I^2=88\%$) and case-control studies ($I^2=92\%$).

There was no significant association between non-aspirin NSAID (non-steroidal anti-inflammatory drug) use and lung cancer risk with cohort studies (RR 0.93, 95% CI 0.77 to 1.12; two studies; 104,287 participants) or case-control studies (OR 0.88, 95% CI 0.67 to 1.16; five studies; 26,310 participants). There was evidence of moderate heterogeneity for cohort studies ($I^2=52\%$) and substantial heterogeneity for case-control studies ($I^2=93\%$).

Overall NSAID use was not associated with lung cancer risk in case-control studies (OR 0.80, 95% CI 0.63 to 1.03; six studies; 52,913 participants). There was evidence of substantial heterogeneity ($I^2=94\%$).

Consuming seven or more NSAID tablets a week was associated with a significantly reduced risk of lung cancer (OR 0.80 95% CI 0.67 to 0.95; three studies; 15, 507 participants). There was no evidence of heterogeneity ($I^2=0\%$).

Gender, histology and duration of use were not associated with lung cancer risk.

Risk ratios or odds ratios with 95% confidence intervals were reported for individual studies according to smoking status.

Sensitivity analyses did not significantly alter the results of the meta-analyses.

Examination of funnel plots found no evidence of publication bias.

Authors’ conclusions

Regular use of aspirin (seven or more tablets a week) may protect against lung cancer. Lung cancer risk was not associated with non-aspirin NSAID or overall NSAID use.

CRD commentary

The review addressed a clear question with well-defined inclusion criteria for study design, intervention and outcomes. Criteria for participants were less clear. Three relevant databases were searched. No language limitations were applied, which minimised the risk of language bias. Attempts do not appear to have been made to identify unpublished data, but publication bias was assessed and ruled out. Suitable methods were used to minimise reviewer error and bias in the data extraction process, but it was unclear whether these steps were taken for the study selection process.

The quality of included studies was not assessed. Due to unclear reporting, there was some uncertainty around the number of participants. However, most included studies were of weaker methodological design. Use of NSAIDs was largely self-reported and could have been prone to error or bias. Exposure to NSAIDs varied widely between and within studies; meta-analyses were carried out for use versus no use of NSAIDs. The wide range of dose exposure may weaken any possible association between NSAIDS and lung cancer risk. For some outcomes, it was unclear whether the results related to all NSAID use or aspirin only. Data was not reported on the reason for aspirin use, so participants may have been using aspirin for comorbid conditions which could have confounded the results. Heterogeneity was assessed and was high for the most outcomes, so it was unclear whether the data were suitable for combining in a meta-analysis.

The review was limited by the low quality of available evidence and high levels of heterogeneity. However, the authors’ conclusions reflected the strength of available evidence.
Implications of the review for practice and research

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further research was needed to investigate the lowest optimal aspirin dose and the optimal duration needed to reduce lung cancer risk. Further research is also needed to investigate the role of selective cyclooxygenase-2 (COX-2) inhibitors in lung cancer. Future research should identify which patients could benefit from aspirin use and assess the risk benefit profile.

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