Aspirin and cancer risk: a quantitative review to 2011

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Background: Aspirin has been associated to a reduced risk of colorectal and possibly of a few other common cancers.

Methods: To provide an up-to-date quantification of this association, we conducted a meta-analysis of all observational studies on aspirin and 12 selected cancer sites published up to September 2011.

Results: Regular aspirin is associated with a statistically significant reduced risk of colorectal cancer [summary relative risk (RR) from random effects models = 0.73, 95% confidence interval (CI) 0.67–0.79], and of other digestive tract cancers (RR = 0.61, 95% CI = 0.50–0.76, for squamous cell esophageal cancer; RR = 0.64, 95% CI = 0.52–0.78, for esophageal and gastric cardia adenocarcinoma; and RR = 0.67, 95% CI = 0.54–0.83, for gastric cancer), with somewhat stronger reductions in risk in case–control than in cohort studies. Modest inverse associations were also observed for breast (RR = 0.90, 95% CI = 0.85–0.95) and prostate cancer (RR = 0.90, 95% CI = 0.85–0.96), while lung cancer was significantly reduced in case–control studies (0.73, 95% CI = 0.55–0.98) but not in cohort ones (RR = 0.98, 95% CI = 0.92–1.05). No meaningful overall associations were observed for cancers of the pancreas, endometrium, ovary, bladder, and kidney.

Conclusions: Observational studies indicate a beneficial role of aspirin on colorectal and other digestive tract cancers; modest risk reductions were also observed for breast and prostate cancer. Results are, however, heterogeneous across studies and dose–risk and duration–risk relationships are still unclear.

Key words: aspirin, epidemiology, neoplasm, nonsteroidal anti-inflammatory drugs, meta-analysis, risk factors

Introduction

Aspirin has been associated to a reduced risk of colorectal and possibly of a few other cancers [1–3]. The chemopreventive effect of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been attributed to their inhibition of cyclooxygenase (COX), the enzymes responsible for the synthesis of prostaglandins. COX—in particular the isoform COX-2—has been reported to be abnormally expressed in many cancer cell lines and has been implicated in the process of carcinogenesis, tumor growth, apoptosis, and angiogenesis [4–9]. Additional mechanisms of the anticarcinogenic effect of aspirin and other NSAIDs include the induction of apoptosis through COX-independent pathways, the inhibition of NFκB factor, and the up-regulation of tumor suppression genes [8, 9].

A quantitative review of epidemiological studies considering the association between aspirin and cancer risk published up to 2005 [2] reported a 30% reduction in the risk of colorectal cancer [relative risk (RR) = 0.71]. It also found evidence—although more limited and mainly from case–control studies—that aspirin has a favorable effect on cancer of the esophagus (RR = 0.72), stomach (RR = 0.84), breast (RR = 0.90), ovary (RR = 0.89), and lung (RR = 0.94). No significant associations were found for pancreatic, prostate, and bladder cancer, while an increase in risk has been suggested for kidney cancer.

A few subsequent reviews and meta-analyses also reported an inverse association between aspirin and cancers of the esophagus and gastric cardia [10], stomach [11], breast [12–15], but not with pancreatic [16], lung [17], and prostate [18] cancer.

In order to provide an up-to-date quantification of the association between aspirin use and cancer risk, we conducted a meta-analysis of all observational studies on the issue published up to September 2011. Information on the relation with frequency, dose, and duration of use was considered in order to better understand the causal role, if any, of aspirin on cancer risk.

Material and methods

Search strategy and selection criteria

The meta-analysis was conducted following the PRISMA guidelines [19]. Papers were identified through a search of the literature using PubMed/ Medline and the following keywords: [aspirin or ‘nonsteroidal anti-inflammatory drugs’ or NSAID] and [neoplasms or cancer or carcinoma] and risk and [‘case-control study’ or ‘cohort study’ or ‘prospective study’ or

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meta-analysis. We retrieved and assessed potentially relevant articles and checked the reference lists of all papers of interest to identify additional relevant publications. Studies were considered eligible if (i) they provided information on aspirin use in relation to the cancers considered separately from other NSAIDs; (ii) they included original data from case-control or cohort studies; (iii) they were not based on selected patients with specific diseases (adenomas, ulcerative colitis, Barrett’s oesophagus, prior cancer); (iv) they were published in English language; (v) their publication date was before 30 September 2011. We did not include a few selected cohorts of subjects with rheumatoid arthritis [20–22]; a study on users on low-dose aspirin only was also excluded [23]. Randomized controlled trials of aspirin, usually with cardiovascular events as the primary endpoint, have not been included and have been meta-analyzed elsewhere [24–26]. When multiple reports were published on the same population or subpopulation, we included in the meta-analysis only the most recent and the informative one. We did not assign quality scores to studies and no study was excluded a priori for weakness of design or data quality.

For each study, we abstracted information on study design, country, number of subjects (cases, controls, or cohort size), RR (approximated by the odds ratio (OR) for case-control studies), and the corresponding 95% confidence interval (CI) for ‘regular’ aspirin use (at least 1–2 tablets per week) or alternatively ever/any use. If available, information related to frequency, dose, and duration of aspirin use was also retrieved. Whenever available, estimates adjusted for multiple potential confounding factors were used. When the RR—or the corresponding 95% CI—was not given, it was derived from tabular data. Two investigators (CB and VR) independently reviewed and cross-checked the data, and disagreements were resolved by consensus.

**statistical analysis**

We derived summary estimates of the RR for each neoplasm—overall and separately for case-control and cohort studies—using both fixed effects models (i.e. as weighed averages on the inverse of the variance of the log RR) and random effects models (i.e. as weighed averages on the sum of the inverse of the variance of the log RR and the moment estimator of the variance between studies) [27]. Only the results from the latter models were, however, presented in order to take into account the heterogeneity of risk estimates (thus being more conservative). We assessed heterogeneity between studies using the $I^2$ test (defining a significant heterogeneity as a $P$ value $< 0.10$) [28] and quantified the inconsistencies using the $I^2$ statistic, which represents the percentage of the total variation across studies that is attributable to heterogeneity rather than chance [29]. The primary analysis concerned regular aspirin use; for some studies, the estimate for regular use was computed pooling the RRs for various categories of frequency or duration of use. Whenever possible, we also computed summary estimates for different aspirin doses (low-dose/baby aspirin used for cardiovascular prevention, $\sim$100 mg regular strength aspirin, between 300 and 500 mg) and duration (short-term use, approximately $\leq 5$ years; long-term use, approximately $\geq 5$ years). We carried out sensitivity analyses excluding studies based on prescription databases, where some misclassification of aspirin use was possible, since the frequent over-the-counter aspirin use may not have been accounted for.

For selected neoplasms, we provided a forest plot, in which a square was plotted for each study, whose center projection on the underlying scale corresponds to the study-specific RR. The area of the square is proportional to the inverse of the variance of the log RR and thus gives a measure of the amount of statistical information available. A diamond was used to plot the summary RR, whose center represents the RR and its extremes the corresponding 95% CI.

Publication bias was evaluated using funnel plots and quantified by the Egger’s and Begg’s test [30, 31].

### results

From the original literature search, we identified and screened 450 papers; of these, 195 were considered of interest and their full text was retrieved for detailed evaluation. Thirty-two additional studies were identified through the references of the retrieved papers. Eighty-eight papers were subsequently excluded from the meta-analysis (reviews, papers on patients with specific diseases, duplicate reports on the same study population). A total of 139 studies were considered in the present meta-analysis (Supplemental Appendix Figure S1, available at *Annals of Oncology* online).

The main characteristics and findings of case–control and cohort studies on aspirin and the risk of cancer at 12 sites are given in the supplemental Appendix Tables S1–S12 (available at *Annals of Oncology* online). Table 1 gives the corresponding pooled results overall and by study design. For seven major cancer sites, forest plots are also given in Figures 1–7. Risk estimates shown in these figures may differ from those presented in the corresponding supplemental Appendix Tables and in the original study publications, since they were computed on the basis of RRs for various categories of exposure. We present results on colorectal cancer first and then other selected neoplasms.

### colorectal cancer

Thirty studies considered the association between aspirin use and colorectal cancer, including 15 case–control studies on a total of 21 414 cases and 15 cohort studies including a total of 16 105 cases (supplemental Appendix Table S1, available at *Annals of Oncology* online, Figure 1).

Overall, there was evidence of a 27% reduced risk of colorectal cancer for regular aspirin use (RR = 0.73, 95% CI 0.67–0.79, $P < 0.001$), with stronger risk reductions in case–control studies (RR = 0.63, 95% CI 0.56–0.70, $P < 0.001$) than in cohort ones (RR = 0.82, 95% CI 0.75–0.89, $P < 0.001$) ($P$ for heterogeneity < 0.001, Table 1, Figure 1). Most studies reported an inverse relation for regular aspirin use, although the strength of the association varied across studies, with a few small studies reporting particularly strong inverse associations. A significant heterogeneity was thus observed both in case–control ($P < 0.001$) and in cohort studies ($P < 0.001$), but only two cohort studies reported RRs above unity. There was an indication of publication bias, both from visual inspection of funnel plot and from statistical tests (Egger’s test $P = 0.003$; Begg’s test $P = 0.053$).

The RR for colon cancer was 0.71 (95% CI 0.63–0.80) overall, 0.61 (95% CI 0.50–0.76) in six case–control studies [32–38], and 0.77 (95% CI 0.67–0.89) in seven cohort ones [39–52]; corresponding estimates for rectal cancer were 0.68 (95% CI 0.55–0.83) overall, 0.52 (95% CI 0.35–0.77) from three case–control [32, 36, 53], and 0.78 (95% CI 0.63–0.98) from six cohort [40, 44, 46, 47, 51, 54] studies.

The summary estimate was 0.66 (95% CI 0.57–0.77) for daily aspirin use [32, 35, 37–39, 44, 47–49, 52, 54]. In relation to duration of aspirin use, the RR was 0.80 (95% CI 0.71–0.91) for $\leq 5$ years and 0.75 (95% CI 0.70–0.80) for $\geq 5$ years ($P$ for heterogeneity $= 0.369$) [33, 38, 44, 45, 48, 49, 54, 55]. A few
studies suggested that the protection was less strong (P for heterogeneity = 0.037) for low (RR = 0.95, 95% CI 0.76–1.19) as compared with regular/high strength aspirin (RR = 0.69, 95% CI 0.57–0.85) [42, 45, 55].

**Table 1.** Summary relative risk (RR) and 95% confidence interval (CI) for regular aspirin use by cancer site, and study design

<table>
<thead>
<tr>
<th>Cancer, study design</th>
<th>No. of studies</th>
<th>No. of cases</th>
<th>RR (95% CI)</th>
<th>Heterogeneity, I² (%)</th>
<th>Heterogeneity between study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>15</td>
<td>21 414</td>
<td>0.63 (0.56–0.70)</td>
<td>&lt;0.001</td>
<td>65.4</td>
</tr>
<tr>
<td>Cohort</td>
<td>15</td>
<td>16 105</td>
<td>0.82 (0.75–0.89)</td>
<td>&lt;0.001</td>
<td>66.0</td>
</tr>
<tr>
<td>Overall</td>
<td>30</td>
<td>37 519</td>
<td>0.73 (0.67–0.79)</td>
<td>&lt;0.001</td>
<td>75.3</td>
</tr>
<tr>
<td>Esophageal (SCC/NOS)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>7</td>
<td>1075</td>
<td>0.54 (0.44–0.67)</td>
<td>0.970</td>
<td>0</td>
</tr>
<tr>
<td>Cohort</td>
<td>4</td>
<td>1118</td>
<td>0.73 (0.51–1.07)</td>
<td>0.083</td>
<td>55.1</td>
</tr>
<tr>
<td>Overall</td>
<td>11</td>
<td>2193</td>
<td>0.61 (0.50–0.76)</td>
<td>0.060</td>
<td>43.6</td>
</tr>
<tr>
<td>Esophageal and gastric cardia adenocarcinoma</td>
<td></td>
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</tr>
<tr>
<td>Case-control</td>
<td>9</td>
<td>3222</td>
<td>0.60 (0.48–0.75)</td>
<td>&lt;0.001</td>
<td>76.7</td>
</tr>
<tr>
<td>Cohort</td>
<td>2</td>
<td>499</td>
<td>0.88 (0.68–1.15)</td>
<td>0.576</td>
<td>0</td>
</tr>
<tr>
<td>Overall</td>
<td>11</td>
<td>3721</td>
<td>0.64 (0.52–0.78)</td>
<td>&lt;0.001</td>
<td>74.3</td>
</tr>
<tr>
<td>Gastric</td>
<td></td>
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</tr>
<tr>
<td>Case-control</td>
<td>7</td>
<td>2411</td>
<td>0.60 (0.44–0.82)</td>
<td>&lt;0.001</td>
<td>80.3</td>
</tr>
<tr>
<td>Cohort</td>
<td>6</td>
<td>2108</td>
<td>0.77 (0.58–1.04)</td>
<td>&lt;0.001</td>
<td>80.3</td>
</tr>
<tr>
<td>Overall</td>
<td>13</td>
<td>4519</td>
<td>0.67 (0.54–0.83)</td>
<td>&lt;0.001</td>
<td>81.6</td>
</tr>
<tr>
<td>Pancreatic</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Case-control</td>
<td>3</td>
<td>1406</td>
<td>0.82 (0.68–1.00)</td>
<td>0.309</td>
<td>15.0</td>
</tr>
<tr>
<td>Cohort</td>
<td>7</td>
<td>6471</td>
<td>0.95 (0.85–1.05)</td>
<td>0.213</td>
<td>28.2</td>
</tr>
<tr>
<td>Overall</td>
<td>10</td>
<td>7877</td>
<td>0.91 (0.83–1.01)</td>
<td>0.136</td>
<td>34.0</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
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</tr>
<tr>
<td>Case-control</td>
<td>5</td>
<td>4863</td>
<td>0.73 (0.55–0.98)</td>
<td>0.002</td>
<td>76.2</td>
</tr>
<tr>
<td>Cohort</td>
<td>15</td>
<td>11 356</td>
<td>0.98 (0.92–1.05)</td>
<td>0.176</td>
<td>25.2</td>
</tr>
<tr>
<td>Overall</td>
<td>20</td>
<td>16 219</td>
<td>0.91 (0.84–0.99)</td>
<td>0.001</td>
<td>57.3</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Case-control</td>
<td>10</td>
<td>25 835</td>
<td>0.83 (0.76–0.91)</td>
<td>0.080</td>
<td>41.7</td>
</tr>
<tr>
<td>Cohort</td>
<td>22</td>
<td>27 091</td>
<td>0.93 (0.87–1.00)</td>
<td>&lt;0.001</td>
<td>65.9</td>
</tr>
<tr>
<td>Overall</td>
<td>32</td>
<td>52 926</td>
<td>0.90 (0.85–0.95)</td>
<td>&lt;0.001</td>
<td>63.0</td>
</tr>
<tr>
<td>Endometrial</td>
<td></td>
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</tr>
<tr>
<td>Case-control</td>
<td>4</td>
<td>1657</td>
<td>0.86 (0.70–1.06)</td>
<td>0.374</td>
<td>3.7</td>
</tr>
<tr>
<td>Cohort</td>
<td>5</td>
<td>1824</td>
<td>0.94 (0.82–1.07)</td>
<td>0.597</td>
<td>0</td>
</tr>
<tr>
<td>Overall</td>
<td>9</td>
<td>3481</td>
<td>0.92 (0.82–1.02)</td>
<td>0.613</td>
<td>0</td>
</tr>
<tr>
<td>Ovarian</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>11</td>
<td>7923</td>
<td>0.90 (0.79–1.02)</td>
<td>0.065</td>
<td>42.7</td>
</tr>
<tr>
<td>Cohort</td>
<td>4</td>
<td>1017</td>
<td>0.91 (0.71–1.17)</td>
<td>0.165</td>
<td>41.1</td>
</tr>
<tr>
<td>Overall</td>
<td>15</td>
<td>8940</td>
<td>0.91 (0.81–1.01)</td>
<td>0.060</td>
<td>39.1</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
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<tr>
<td>Case-control</td>
<td>9</td>
<td>5795</td>
<td>0.87 (0.74–1.02)</td>
<td>0.012</td>
<td>59.3</td>
</tr>
<tr>
<td>Cohort</td>
<td>15</td>
<td>31 657</td>
<td>0.91 (0.85–0.97)</td>
<td>&lt;0.001</td>
<td>66.3</td>
</tr>
<tr>
<td>Overall</td>
<td>24</td>
<td>37 452</td>
<td>0.90 (0.85–0.96)</td>
<td>&lt;0.001</td>
<td>63.1</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
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</tr>
<tr>
<td>Case-control</td>
<td>3</td>
<td>2848</td>
<td>0.81 (0.63–1.05)</td>
<td>0.183</td>
<td>41.2</td>
</tr>
<tr>
<td>Cohort</td>
<td>6</td>
<td>4134</td>
<td>1.02 (0.94–1.11)</td>
<td>0.413</td>
<td>0.5</td>
</tr>
<tr>
<td>Overall</td>
<td>9</td>
<td>6982</td>
<td>0.95 (0.83–1.07)</td>
<td>0.122</td>
<td>37.1</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Case-control</td>
<td>5</td>
<td>4546</td>
<td>1.14 (0.94–1.39)</td>
<td>0.051</td>
<td>57.6</td>
</tr>
<tr>
<td>Cohort</td>
<td>5</td>
<td>792</td>
<td>1.22 (0.82–1.83)</td>
<td>0.006</td>
<td>72.1</td>
</tr>
<tr>
<td>Overall</td>
<td>10</td>
<td>5338</td>
<td>1.14 (0.95–1.37)</td>
<td>0.004</td>
<td>63.3</td>
</tr>
</tbody>
</table>

aSummary estimates from random effects models.
NOS, not otherwise specified; SCC, squamous cell carcinoma.

squamous cell esophageal cancer

With reference to squamous cell esophageal cancer (or esophageal cancer not otherwise specified), seven case–control and four cohort studies were identified, including a total of 1075 and 1118
An overall 39% reduction in the risk of squamous cell esophageal cancer (RR = 0.61, 95% CI 0.50–0.76, \( P < 0.001 \)) was observed for regular aspirin users, the protective relation being non-significantly stronger (\( P \) for heterogeneity = 0.165) in case–control studies (RR = 0.54, 95% CI 0.44–0.67, \( P < 0.001 \)) than in cohort ones (RR = 0.73, 95% CI 0.51–1.07, \( P = 0.105 \), Table 1, Figure 2). All risk estimates were below unity; some heterogeneity was found among cohort studies (\( P = 0.083 \)), with a small study reporting a particularly strong inverse association. Publication bias was observed both from visual inspection of funnel plot and from statistical tests (Egger’s test \( P < 0.001 \); Begg’s test \( P = 0.073 \)).

Data on frequency and duration of aspirin use were limited but did not indicate any strong inverse risk for more frequent or longer use.

**esophageal and gastric cardia adenocarcinoma**

Nine case–control studies on a total of 3222 cases and two cohort studies including a total of 499 cases reported information on aspirin use and the risk of esophageal and gastric cardia adenocarcinoma (supplemental Appendix Table S3, available at *Annals of Oncology* online, Figure 3). Overall, the RR was 0.64 (95% CI 0.52–0.78, \( P < 0.001 \)), being...
0.60 (95% CI 0.48–0.75, \( P < 0.001 \)) from case–control studies, and 0.88 (95% CI 0.68–1.15, \( P = 0.357 \)) from cohort studies (\( P \) for heterogeneity = 0.029, Table 1, Figure 3). There was a significant heterogeneity among case–control studies (\( P < 0.001 \)), although only two of them reported risk estimates above unity.
Only a few studies gave information on daily use, reporting similar risk estimates than for overall regular use. Likewise, no difference was found according to duration of aspirin use.

**gastric cancer**

With reference to gastric cancer, seven case–control and six cohort studies were identified, including a total of 2411 and 2108 cases, respectively (supplemental Appendix Table S4, available at Annals of Oncology online, Figure 4).

The overall RR for gastric cancer for regular aspirin use was 0.67 (95% CI 0.54–0.83, \( P < 0.001 \)), being 0.60 (95% CI 0.44–0.82, \( P = 0.001 \)) from case–control studies, and 0.77 (95% CI 0.58–1.04, \( P = 0.089 \)) from cohort studies (\( P \) for heterogeneity = 0.252, Table 1, Figure 4). Significant heterogeneity was observed both among case–control \( (P < 0.001) \) and cohort \( (P < 0.001) \) studies, although only in one case–control and one cohort study, the risk estimate was above unity.

Similar inverse association was found in a few studies reporting information on daily use of aspirin, while there was a suggestion of stronger risk reduction \( (P \) for heterogeneity = 0.088) for longer aspirin use \( (RR = 0.80, 95\% CI 0.66–0.98, \text{ for } \geq 5 \text{ years}) \) \[56–59\].

**pancreatic cancer**

Three case–control studies including a total of 1406 pancreatic cancer cases and seven cohort studies including a total of 6471 cases provided information on aspirin use (supplemental Appendix Table S5, available at Annals of Oncology online).

A small nonsignificant inverse association was found with aspirin, with a RR of 0.91 (95% CI 0.83–1.01, \( P = 0.085 \)) overall, 0.82 (95% CI 0.68–1.00, \( P = 0.052 \)) from case–control studies, and 0.95 (95% CI 0.85–1.05, \( P = 0.321 \)) from cohort ones \( (P \) for heterogeneity = 0.190, Table 1).

No difference in risk was observed in relation to daily use versus less often or for duration of use, although data were limited.

**lung cancer**

Five case–control studies on a total of 4863 cases and 15 cohort studies including 11 356 cases included information on aspirin use and lung cancer risk (supplemental Appendix Table S6, available at Annals of Oncology online, Figure 5).

The RR of lung cancer for regular aspirin use was marginally significantly reduced overall \( (RR = 0.91, 95\% CI 0.84–0.99, P = 0.024) \), again being 0.73 (95% CI 0.55–0.98, \( P = 0.035 \)) from case–control studies, but only 0.98 (95% CI 0.92–1.05, \( P = 0.546 \)) from cohort studies \( (P \) for heterogeneity 0.051, Table 1, Figure 5). Some heterogeneity was observed, particularly among case–control studies \( (P = 0.002) \), four studies reporting inverse relations and a large one reporting a direct association. Moreover, visual inspection of funnel plot and statistical tests suggested the presence of publication bias (Egger’s test \( P = 0.003 \); Begg’s test \( P = 0.014 \)).

No difference in risk was observed in relation to frequency, dose, or duration of use, although again a limited number of studies analyzed the issue.

![Figure 4. Summary relative risk (RR) of gastric cancer for regular aspirin use versus never use from case–control and cohort studies, and overall. CI, confidence interval.](https://academic.oup.com/annonc/article-abstract/23/6/1403/170389?download=true)
A few studies reported risk estimates in strata of tobacco smoking and lung cancer subsites but did not show any meaningful difference in risk.

### Breast Cancer

Ten case–control and 22 cohort studies, including a total of 25835 and 27091 breast cancer cases, respectively, analyzed the relationship with aspirin (supplemental Appendix Table S7, available at Annals of Oncology online, Figure 6).

Overall, they gave a highly significant summary RR of 0.90 (95% CI 0.85–0.95, \( P < 0.001 \)), significant in both case–control studies (0.83, 95% CI 0.76–0.91, \( P < 0.001 \)) and cohort studies (0.93, 95% CI 0.87–1.00, \( P = 0.043 \) for heterogeneity = 0.050, Table 1, Figure 6). Risk estimates were, however, heterogeneous, particularly among cohort studies (\( P < 0.001 \)), with six cohort studies providing risk estimates above unity, significant in a large one. There was also evidence of some publication bias from visual inspection of funnel plot and statistical tests (Egger’s test \( P = 0.032 \); Begg’s test \( P = 0.059 \)).

The summary RR was 0.89 (95% CI 0.82–0.98) for daily use [39, 48, 49, 51, 60–68]; the RR was 0.88 (95% CI 0.75–1.03) for low dose and 0.80 (95% CI 0.65–0.99) for regular/high dose (\( P \) for heterogeneity = 0.478) [69–72]; with reference to duration of aspirin use, the RR was 0.96 (95% CI 0.91–1.02) for <5 years and 0.93 (95% CI 0.84–1.03) for \( \geq 5 \) years of use (\( P \) for heterogeneity = 0.394) [48, 49, 60, 65, 67, 69, 71, 73–76].

In 10 studies providing information on breast cancer and aspirin use according to hormone receptor (HR) status, the RR was 1.01 (95% CI 0.91–1.14) for HR-negative women and 0.90 (95% CI 0.84–0.98) for HR-positive breast cancers (\( P \) for heterogeneity = 0.098) [23, 60, 65–68, 74, 75, 77, 78].

### Endometrial Cancer

At least nine studies were published over the last years on aspirin and endometrial cancer, including four case–control studies on a total of 1657 cases and five cohort studies on a total of 1824 cases (supplemental Appendix Table S8, available at Annals of Oncology online).

Overall, the RR for regular aspirin use was 0.92 (95% CI 0.82–1.02, \( P = 0.111 \), 0.86 (95% CI 0.70–1.06, \( P = 0.161 \)) from case–control studies, and 0.94 (95% CI 0.82–1.07, \( P = 0.327 \)) from cohort ones (\( P \) for heterogeneity = 0.479, Table 1).

No significant association was observed for daily use and no meaningful trend with duration of use was identified.

### Ovarian Cancer

Eleven case–control studies based on a total of 7923 ovarian cancer cases and four cohort studies including a total of 1017 cases (supplemental Appendix Table S9, available at Annals of Oncology online).
Oncology online) gave respectively a summary RR of 0.90 (95% CI 0.79–1.02, \(P = 0.097\)) and 0.91 (95% CI 0.71–1.17, \(P = 0.476\)) for regular aspirin use (\(P\) for heterogeneity = 0.938); overall the RR was 0.91 (95% CI 0.81–1.01, \(P = 0.076\), Table 1).

A few studies providing information on frequency and duration of use did not indicate meaningful patterns of risk.

prostate cancer

Twenty-four studies—nine case–control studies on a total of 5795 cases and 15 cohort studies including a total of 31,657 cases—investigated the relation between aspirin use and prostate cancer (supplemental Appendix Table S10, available at Annals of Oncology online, Figure 7).

The summary RR for regular aspirin use was 0.90 (95% CI 0.85–0.96, \(P = 0.001\)) overall, 0.87 (95% CI 0.74–1.02, \(P = 0.086\)) from case–control, and 0.91 (95% CI 0.85–0.97, \(P = 0.006\)) from cohort studies (\(P\) for heterogeneity = 0.612, Table 1, Figure 7). Results were significantly heterogeneous (particularly among cohort studies, \(P < 0.001\)), with 17 studies out of 24 reporting risk estimates below unity, of which only 8 were significant.

The RRs were similar for low (RR = 0.81, 95% CI 0.69–0.95) [79–84] and regular/high (RR = 0.83, 95% CI 0.70–0.97) [80–84] aspirin dose (\(P\) for heterogeneity = 0.834). Likewise, no trend in risk was found with increased exposure either measured by daily use (RR = 0.88, 95% CI 0.81–0.95) [39, 49, 79, 83, 85–88] or for long-term use (RR = 0.92, 95% CI 0.83–1.01, for ≥5 years.

Figure 6. Summary relative risk (RR) of breast cancer for regular aspirin use versus never use from case–control and cohort studies, and overall. CI, confidence interval.
as compared with RR = 0.92, 95% CI 0.86–0.99, for <5 years, P for heterogeneity = 1.00) [49, 80, 81, 83, 84, 88–91]. Risk estimates were similar for low-grade/less aggressive cancers (RR = 0.97, 95% CI 0.85–1.10) [83, 84, 86, 87, 90] and high-grade/more aggressive ones (RR = 0.87, 95% CI 0.80–0.95, P for heterogeneity = 0.169) [79, 81, 83, 84, 86–88, 90–92].

bladder cancer
Three case–control and six cohort studies, including respectively 2848 and 4134 cases, provided information on aspirin use and bladder cancer (supplemental Appendix Table S11, available at Annals of Oncology online).

No evidence of an association with regular aspirin use was found, with a summary RR of 0.95 (95% CI 0.83–1.07, P = 0.395) overall, 0.81 (95% CI 0.63–1.05, P = 0.110) from case–control studies, and 1.02 (95% CI 0.94–1.11, P = 0.671) from cohort studies (P for heterogeneity = 0.093, Table 1).

Likewise, no meaningful trends were shown either with frequency or with duration of aspirin use.

kidney cancer
Ten studies—five case–control studies on a total of 4546 cases and five cohort studies on a total of 792 cases—considered aspirin in relation to kidney cancer (supplemental Appendix Table S12, available at Annals of Oncology online).

The summary RR of kidney cancer for regular aspirin use was 1.14 (95% CI 0.95–1.37, P = 0.149) overall, 1.14 (95% CI 0.94–1.39, P = 0.183) from case–control studies, and 1.22 (95% CI 0.82–1.83, P = 0.330) from cohort studies (P for heterogeneity = 0.766, Table 1). The estimates from most studies were around unity. There was, however, significant heterogeneity between studies (P = 0.004), with one large case–control study and two cohort studies reporting a direct association.

Data on daily use, dose, and duration were scanty but did not indicate any meaningful association.

discussion
This updated analysis of observational studies on aspirin and cancer risk confirms the existence of a protective effect for colorectal cancer and other neoplasms of the digestive tract and supports a possible inverse association with cancers of the breast and the prostate. It also indicates that the relation with lung cancer is inconsistent and that there is no meaningful association of aspirin use with pancreatic, endometrial, ovarian, bladder, and kidney cancer.

Figure 7. Summary relative risk (RR) of prostate cancer for regular aspirin use versus never use from case–control and cohort studies, and overall. CI, confidence interval.

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Among the weaknesses of our meta-analysis are inherent limitations of observational studies on aspirin, related in particular to measurement errors in the exposure to aspirin. Estimates from cohort studies are considered to be more reliable than those from case–control ones since they are generally less prone to (differential) information or selection bias. However, case–control studies generally provide a more detailed lifelong history of aspirin and other NSAIDs use and allow to estimate long-term effects of drug use. Stronger inverse associations were generally found in case–control studies as compared with cohort ones. Some of the apparent differences may be due to the fact that case–control studies tend to collect particularly valid information on the short term before cancer diagnosis. Aspirin and other NSAIDs may cause gastrointestinal bleeding and heartburn [93, 94] and it is possible that patients with early symptoms of esophageal, gastric, and other digestive tract neoplasm selectively avoid using it. Prospective studies based on prescription databases may be limited by the lack of accounting for over-the-counter medication use, although we did not find meaningful differences in risk estimates when excluding those studies. Moreover, a limitation of summarizing this body of studies is the high variability of aspirin use definitions across studies—and the difficulty to have a homogeneous definition of ‘regular’ use—which may partly explain the heterogeneity in risk estimates across studies.

Evidence from at least 30 studies on colorectal cancer, including over 37 500 cases, indicates that risk reduction for (regular) aspirin use is around 20%–30%. Data suggest that a use of at least 5 years of regular/high strength aspirin is necessary to convey such a protection. The consistency of risk estimates in case–control and cohort studies supports the causality of this association, although there was some heterogeneity across studies and some evidence of publication bias, with various small studies reporting the strongest inverse associations. Data from randomized clinical trials (RCTs) showed that aspirin reduces the risk of colorectal adenomas in patients with a history of colorectal cancer or adenomas [95–99]. Additionally, a pooled analysis of four RCTs of aspirin use for the prevention of cardiovascular diseases showed a reduction in colorectal cancer incidence and mortality, but only after a latency period of at least 10 years and for treatments of ≥5 years [24, 25]. The beneficial effect of aspirin on colorectal cancer was evident for any dose over 75 mg/day. In a recent RCT of aspirin in the prevention of colorectal cancer in carriers of the Lynch syndrome, 600 mg of aspirin per day significantly reduced colorectal cancer incidence after a 3-year follow-up [100]. However, two RCTs of low-dose aspirin—including the Physicians’ Health Study (PHS) and the Women’s Heath Study (WHS)—with an average follow-up of ~10 years, did not show any reduction in the risk of colorectal cancer [101, 102].

For other cancers of the digestive tract (i.e. esophageal and gastric cancer), risk reductions were around 30%. Data are too limited to evaluate dose–risk and duration–risk relationships. At least part of this inverse association may, however, be due to reverse causation, given also the stronger risk reduction observed in case–control studies than in cohort ones. Since aspirin and other NSAIDs may cause gastrointestinal bleeding [93, 94], it is possible that patients with early symptoms of esophageal and gastric cancer avoid using these drugs. However, it is also possible that aspirin use increases the likelihood of being diagnosed with a cancer of the upper aerodigestive tract, thus leading to an underestimate of the risk. In the pooled analysis of RCTs of aspirin use for the prevention of cardiovascular diseases, treatment with aspirin for at least 5 years conveyed a significant reduction in esophageal cancer death after a latent period of 5 years, while a nonsignificant reduction for stomach cancer mortality was observed even after a long period of latency [25].

Aspirin does not seem to modify the risk of pancreatic cancer, although evidence is too limited to draw any definite conclusion [46, 103].

A modest overall reduction (~10%) in lung cancer risk has been reported in 20 studies on ~16 000 cases, which, however, seems restricted to case–control studies. Moreover, there is evidence of publication bias, with several small studies reporting the strongest inverse associations. A recent meta-analysis also observed that the inverse relations were mainly observed in low-quality studies [17]. Among RCTs, the Women Health Initiative showed a nonsignificant benefit for daily low-dose aspirin on lung cancer incidence [102], and the pooled analysis of RCTs of aspirin for cardiovascular prevention [25] reported a reduction in mortality, which was significant only in patients with at least 5 years of treatment and after a latent period of ≥10 years.

A reduction of ~10% has also been found for breast cancer in over 30 studies on ~54 000 cases, with consistent results in case–control and cohort studies. Some heterogeneity in risk estimates was, however, observed, as well as evidence of publication bias. Moreover, there was no indication of dose–risk and duration–risk relationships. Similar findings have been reported also for other NSAIDs [14, 15]. Data from an RCT have not shown an effect of aspirin on breast cancer incidence [102].

With reference to endometrial and ovarian cancer, data are limited but do not seem to indicate any meaningful association with aspirin use. In particular, the inverse association suggested for ovarian cancer in some early studies [2] was not confirmed in recent ones.

At least 24 studies on >37 000 cases indicate that prostate cancer risk was reduced by 10% in regular aspirin users, with similar risk reductions in case–control and cohort studies, and for less aggressive versus more aggressive cancers. However, there was no evidence of a relation with frequency, dose, or duration of use. Moreover, detection bias is possible since men taking aspirin regularly may have had more frequent medical contacts and consequently prostate-specific antigen (PSA) measurements, thus increasing their probability of being diagnosed with prostate cancer. This, however, would have tended to bias the estimates toward the null, as suggested by a few studies that have tried to adjust for the possible confounding of PSA screening rate [18]. Epidemiological studies that examined the effect of non-aspirin NSAIDs or all NSAIDs combined also suggested a reduced risk of prostate cancer, although their results were scattered and less consistent [18]. In the pooled analysis of RCTs of daily aspirin use for the prevention of
cardiovascular diseases, a nonsignificant reduced risk of death from prostate cancer was observed after a latent period of 25 years [25].

Although a few case–control studies reported a favorable effect of aspirin and other NSAIDs on bladder cancer, most investigations did not find any meaningful association. In any case, overall evidence allows to exclude any material excess risk, as reported for phenacetin-based analgesics [104–108].

Regular use of aspirin is associated with a modest nonsignificant increased risk of kidney cancer. In particular, a large case–control [109] and two prospective [39, 43] studies reported a significant increased risk. The latter two studies, however, found a direct association also with colorectal cancer, in contrast with the evidence from most other studies [2, 3]. The apparent excess risk of kidney cancer may, however, not be real but due to residual misclassification of exposure or mixed exposure with other analgesics—such as phenacetin—which have been linked to an increased risk of renal cell cancer [110, 111].

In conclusion, observational studies indicate a beneficial role of aspirin for colorectal and other digestive tract cancers. Evidence from RCTs also gives some support of a beneficial role of aspirin for colorectal and other digestive tract cancers.

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references


