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REVIEW

Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019

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Background: Aspirin has been associated with a reduced risk of colorectal cancer, and possibly of a few other digestive tract cancers. The quantification of risk reduction and the optimal dose and duration of aspirin use for the prevention of colorectal and other digestive tract cancers remains unclear.

Methods: To provide an up-to-date quantification of this association, we conducted a systematic review and meta-analysis of all observational studies on aspirin and cancers of the digestive tract sites published through March 2019. We estimated the pooled relative risk (RR) of cancer for regular aspirin use versus non-use using random-effects models, and, whenever data were available, we investigated the dose- and duration-risk relations.

Results: Regular aspirin use is associated with a reduced risk of colorectal cancer [RR = 0.73, 95% confidence interval (CI) = 0.69–0.78, 45 studies], squamous-cell esophageal cancer (RR = 0.67, 95% CI = 0.57–0.79, 13 studies), adenocarcinoma of the esophagus and gastric cardia (RR = 0.61, 95% CI = 0.49–0.77, 10 studies), stomach cancer (RR = 0.64, 95% CI = 0.51–0.82, 14 studies), hepato-biliary tract cancer (RR = 0.62, 95% CI = 0.44–0.86, five studies), and pancreatic cancer (RR = 0.78, 95% CI = 0.68–0.89, 15 studies), but not of head and neck cancer (RR = 0.94, 95% CI = 0.76–1.16, 10 studies). The associations are somewhat stronger in case-control than in cohort and nested case-control studies and are characterized by some between-study heterogeneity. Risk estimates are consistent across sex, geographical areas, and other selected covariates. For colorectal cancer, an aspirin dose between 75 and 100 mg/day conveys a risk reduction of 10%, and a dose of 325 mg/day of 35%. For all neoplasms, except head and neck cancer, inverse duration-risk relations with aspirin use are found.

Conclusion: The present comprehensive meta-analysis supports and further quantifies the inverse association between regular aspirin use and the risk of colorectal and other digestive tract cancers, including some rare ones. The favorable effect of aspirin increases with longer duration of use, and, for colorectal cancer, with increasing dose.

Key words: aspirin, colorectal neoplasm, digestive tract neoplasm, dose, duration, meta-analysis, risk factor

INTRODUCTION

Aspirin has long been associated with a reduced risk of colorectal and possibly a few other cancers.[1] The evidence comes mainly from a large number of observational studies,[2] but has been corroborated by the results of pooled analyses of randomized clinical trials (RCTs) for the primary or secondary prevention of vascular events.[3–5]

In a meta-analysis of observational studies published up to September 2011, significant risk reductions were reported for colorectal [relative risk (RR) 0.73], and esophageal and stomach cancer (RRs between 0.61 and 0.67) for regular aspirin use versus non-use.[2] Consistent risk reductions were reported in a few other meta-analyses on the same topic conducted over the last few years.[6–8]

The role of aspirin in other cancers of the digestive tract is, however, still controversial. Moreover, the optimal dose and duration of aspirin use for the prevention of colorectal and other digestive tract cancers remains unclear.

In order to provide the most up-to-date and comprehensive estimates for the chemopreventive role of aspirin on cancers of the digestive tract (i.e. colorectal, head and neck, esophageal, stomach, hepato-biliary, and pancreas), we updated the systematic review and meta-analysis of observational studies published in 2012,[2] including information from several case-control and cohort studies published over the last few years. We also further investigated the dose- and duration-risk relations of aspirin use and colorectal cancer, and, whenever sufficient data were available, other digestive cancers.

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MATERIALS AND METHODS

Search strategy

The present systematic review and meta-analysis was conducted according to the PRISMA guidelines[9,10] and its protocol was registered on the International Prospective Register of Systematic Review (PROSPERO; No. CRD42019132359). Briefly, we carried out an updated literature search to identify all original study publications from observational studies on aspirin use and cancer risk published between 1 January 2011 (i.e. year of publication of the meta-analysis by Bosetti et al.[2]) and 18 March 2019, and indexed in PubMed/Medline, Embase, and the Cochrane Library. The search strings used in each database are provided in supplementary Table S1, available at *Annals of Oncology* online. Additional articles were identified through a manual check of the references of selected papers or other systematic reviews/meta-analyses.

Eligibility criteria

In the present meta-analysis, we included studies which satisfied the following eligibility criteria: (i) they were case-control (including pooled analyses of case-control studies), nested case-control, or cohort studies (including pooled analyses of cohort studies); (ii) they provided data on humans in the general population; (iii) they provided information on regular aspirin use (i.e. use at least one or two tablets per week) or, alternatively, on any use; (iv) they focused on at least one of 14 major malignant neoplasms (i.e. head and neck cancer, squamous-cell esophageal cancer, adenocarcinoma of the esophagus and gastric cardia, colorectum, stomach, hepato-biliary, pancreas, lung, breast, endometrium, ovary, prostate, bladder, and kidney); (v) they reported RR estimates—including odds ratios, hazard ratios, or mortality rate ratios—for the selected neoplasms, in relation to aspirin use versus non-use, and the corresponding 95% confidence interval (CI), or provided sufficient information to compute them; and (vi) they were published as original articles in English. We excluded articles based on patients with specific diseases, as well as those evaluating cancer survival and recurrence. We also excluded studies reporting information on the use of other anti-inflammatory drugs or combinations of aspirin with other anti-inflammatory drugs. We did not assign quality scores to the studies and no study was excluded *a priori* for weakness of design or data quality.

Two reviewers (CS and MM) independently screened the titles and/or abstracts of the identified publication records, in order to exclude those that did not meet the eligibility criteria. Subsequently, they retrieved and assessed the full-text of the selected articles. Any disagreement was solved by consensus between the two reviewers, or with the help of a third reviewer (CB).

Data extraction

For each eligible study, we abstracted the following relevant information: first author, publication year, study design, country, cancer site and/or subsite, end point, type of controls, number of cases and controls (or subjects at risk/person years for cohort studies), and RR estimates for aspirin use versus non-use, with the corresponding 95% CI. When available, we also retrieved information on aspirin formulation (low dose, i.e. 75—100 mg, regular dose, i.e. 325 mg, or high dose, i.e. 500 mg), daily dose (mg), frequency (times per month, week, or day), and duration (years) of aspirin use.

When the results of the same study were published in multiple publications, we abstracted data only from the most recent and informative one. We also checked overlapping information between pooled analyses and original studies and, for some pooled analyses, we only included information not provided in separate study publications.

Statistical analysis

For each neoplasm of interest, we derived pooled RRs for regular aspirin use versus no use, overall, and by study design. These estimates were obtained using random-effects models, to take into account heterogeneity of risk estimates.[10,11] For cohort studies providing estimates both for incidence and mortality, in the main analysis we pooled data on incidence, unless the results on mortality were more recent and included a larger number of cases. We assessed heterogeneity between studies using the Cochran's χ^2 test and quantified the inconsistencies using the I^2 statistic.[12] To identify possible sources of heterogeneity between studies, we carried out stratified analyses considering selected *a priori* variables, such as study design, year of publication, geographic area, sex, end point, type of controls. When required, we computed estimates of the RR for regular aspirin use by pooling the RRs for various categories of frequency or duration of use, using the method described by Hamling et al.[13] To evaluate publication bias, we examined the funnel plots and applied the Egger's and Begg's tests for funnel plot asymmetry.[10,12]

For cancers with sufficient information, we investigated linear and nonlinear relations between daily dose and duration of aspirin use and the log-RR of cancer. When information on the daily dose of aspirin was not available, we computed it by combining information on aspirin formulation and frequency of use. We tested the log-linearity using the Wald test; we then used one-stage random-effects log-linear models in the case of linearity, or restricted cubic splines with three knots when linearity was rejected.[14—17]

All statistical analyses were carried out using the software SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.4.1 (R Development Core Team, 2017; in particular, the 'meta' and 'dosresmeta' packages[18]).

RESULTS

Supplementary Figure S1, available at *Annals of Oncology* online, shows the flowchart for study selection. From 1575 records published between 2011 and 2019 on aspirin and cancer risk, after excluding duplicate or not eligible records, we identified 92 articles. Considering 150 additional articles

published before 2012 (already included in Bosetti et al.[2] or identified from manual searches), we ended up with 242 eligible articles. Of these, 113 focused on colorectal and other digestive tract cancers and were included in the present meta-analysis. The main characteristics of the cohort, nested case-control, and case-control studies included are given in supplementary Tables S2—S8, available at *Annals of Oncology* online. Eligible studies excluded from the meta-analysis, since their information was already included in more recent or complete papers, are provided in supplementary Tables S9—S14, available at *Annals of Oncology* online.

Colorectal cancer

Sixty-six studies provided information on aspirin and colorectal risk (supplementary Tables S2 and S9, available at *Annals of Oncology* online). Of these, 45 studies (15 cohort, 11 nested case-control, and 19 case-control studies, of which four were derived from a pooled analysis[19]) contributed to the estimate of regular aspirin use versus non-use, including a total of 156 019 cases (Table 1). A significant reduced risk was observed for regular aspirin use (RR = 0.73, 95% CI = 0.69—0.78), with a stronger inverse relation in case-control (RR = 0.62, 95% CI = 0.56—0.69) than in cohort (RR = 0.77, 95% CI = 0.72—0.82) and nested case-control studies (RR = 0.86, 95% CI = 0.78—0.94; *P* for heterogeneity across study design <0.001; Table 1 and Figure 1). For all pooled estimates, there was significant between-study heterogeneity ($P < 0.001$). The RRs were similar for colon (RR = 0.77, 95% CI = 0.71—0.84) and rectal (RR = 0.74, 95% CI = 0.66—0.84) cancer (*P* for heterogeneity =0.61; data not shown). The funnel plot pointed out some publication bias, confirmed by the Egger's test ($P = 0.002$), but not the Begg's test ($P = 0.358$; supplementary Figure S2, available at *Annals of Oncology* online). Publication bias was found in case-control studies (Egger's test $P = 0.06$), but not in cohort or nested case-control ones (data not shown). Risk estimates were consistent across strata of all covariates considered, except for year of publication (RR = 0.59 before 2000, 0.77 in 2000—2009, and 0.75 in 2010—2018; *P* for heterogeneity =0.038; supplementary Table S15, available at *Annals of Oncology* online).

Eleven studies provided estimates of the colorectal cancer risk in relation to dose of aspirin (Figure 2). Overall, they indicated that there was a linear dose-risk relation, the RR being 0.90 (95% CI = 0.85—0.96) for 75 mg/day, 0.89 (95% CI = 0.84—0.95) for 81 mg/day, 0.87 (95% CI = 0.80—0.94) for 100 mg/day, 0.64 (95% CI = 0.49—0.82) for 325 mg/day, and 0.50 (95% CI = 0.34—0.74) for 500 mg/day.

Table 1. Pooled relative risks (RR) and corresponding 95% confidence intervals (CI) for regular aspirin use versus non-use by cancer site and study design

Cancer site, study design	No. of studies	No. of cases	Pooled RR (95% CI)	*P* value[a]	I^2 (%)	*P* value[b]
Colorectum						
Cohort	15	33 126	0.77 (0.72—0.82)	<0.001	62	<0.001
Nested case-control	11	105 607	0.86 (0.78—0.94)	<0.001	88	
Case-control	19	17 286	0.62 (0.56—0.69)	<0.001	62	
Overall	45	156 019	0.73 (0.69—0.78)	<0.001	86	
Head and neck						
Cohort	1	316	0.78 (0.62—0.98)	—	—	0.106
Nested case-control	2	3940	1.03 (0.90—1.18)	0.196	40	
Case-control	7	6143	0.87 (0.58—1.31)	<0.001	87	
Overall	10	10 399	0.94 (0.76—1.16)	<0.001	83	
Esophagus (squamous-cell)						
Cohort	4	2873	0.65 (0.54—0.80)	0.233	30	<0.001
Nested case-control	2	2070	0.90 (0.78—1.03)	0.641	0	
Case-control	7	1268	0.54 (0.43—0.67)	0.970	0	
Overall	13	6211	0.67 (0.57—0.79)	0.006	57	
Esophagus/gastric cardia (adenocarcinoma)						
Cohort	2	481	0.88 (0.68—1.15)	0.575	0	0.015
Case-control	8	2540	0.56 (0.44—0.73)	<0.001	78	
Overall	10	3021	0.61 (0.49—0.77)	<0.001	76	
Stomach						
Cohort	6	6748	0.58 (0.44—0.76)	<0.001	84	<0.001
Nested case-control	1	980	1.17 (0.98—1.40)	—	—	
Case-control	7	2191	0.63 (0.48—0.83)	<0.001	77	
Overall	14	9919	0.64 (0.51—0.82)	<0.001	91	
Hepato-biliary						
Cohort	2	10 251	0.66 (0.47—0.94)	<0.001	92	<0.001
Nested case-control	1	814	1.11 (0.86—1.44)	—	—	
Case-control	2	2491	0.34 (0.30—0.39)	0.450	0	
Overall	5	13 556	0.62 (0.44—0.86)	<0.001	95	
Pancreas						
Cohort	7	7759	0.79 (0.64—0.98)	<0.001	90	0.103
Nested case-control	1	1141	0.95 (0.81—1.12)	—	—	
Case-control	7	3293	0.73 (0.60—0.88)	0.110	64	
Overall	15	12 193	0.78 (0.68—0.89)	<0.001	84	

[a] *P* value for heterogeneity within strata.
[b] *P* value for heterogeneity across strata.

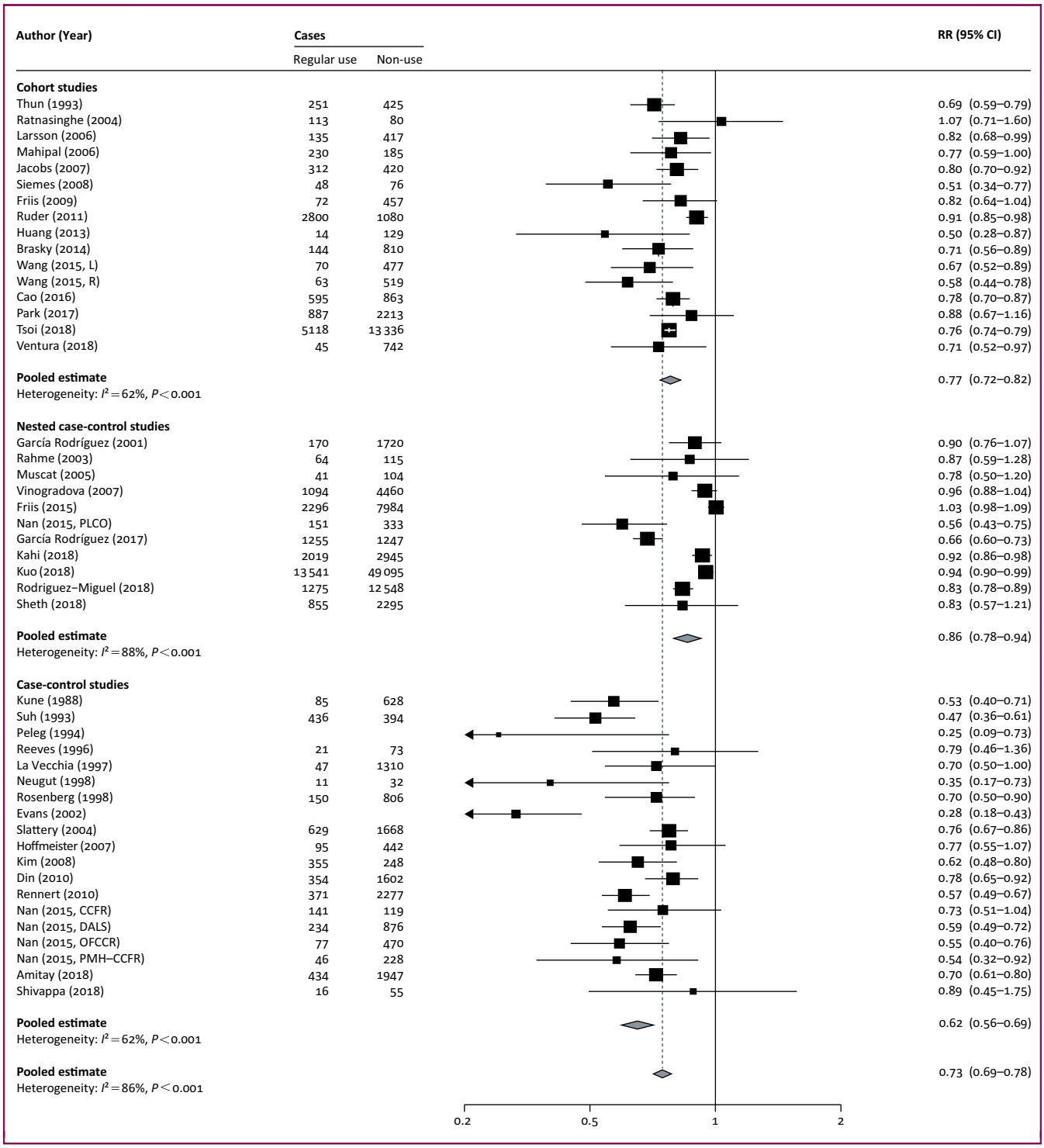

Figure 1. Forest plot of study-specific and pooled relative risk (RR) of colorectal cancer, and corresponding 95% confidence interval (CI), for regular aspirin use versus non-use, overall and by study design.

CCFR, Colon Cancer Family Registry; DALS, Diet, Activity and Lifestyle Study; L, low dose aspirin; OFCCR, Ontario Familial Colorectal Cancer Registry; PLCO, Prostate, Lung, Colorectal, and Ovarian cancer screening trial; PMH-CCFR, Postmenopausal Hormone Study—Colon Cancer Family Registry; R, regular dose aspirin.

Twenty-two studies provided estimates of the colorectal cancer risk in relation to duration of aspirin use (Figure 3). The RR declined up to 10 years of use (RR = 0.96, 95% CI = 0.95—0.98, for 1 year, 0.89, 95% CI = 0.85—0.93, for 3 years, 0.81, 95% CI = 0.76—0.88, for 5 years, and 0.71, 95% CI = 0.63—0.80, for 10 years).

Head and neck cancer

Ten studies (one cohort study, two nested case-control studies, and seven case-control studies) reported information on aspirin use and the risk of head and neck cancer (oral, pharyngeal, nasopharyngeal, and laryngeal cancer), including a total of 10 399 cases (Table 1 and supplementary Table S3, available at

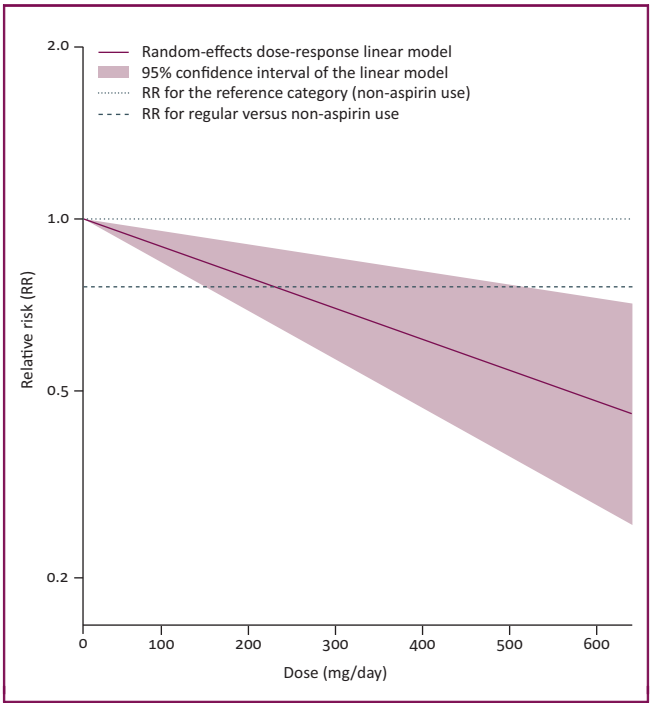

Figure 2. Relative risk (RR) function describing the relation between dose (mg/day) of aspirin use and colorectal cancer.
Thick line: random-effects dose-response linear model. Thin lines: 95% confidence interval of the linear model. Dashed line: RR for regular versus non-aspirin use. Dotted dashed line: RR for the reference category (non-aspirin use).

Annals of Oncology online). Overall, there was no significant association between regular aspirin use and the risk of head and neck cancer (RR = 0.94, 95% CI = 0.76—1.16, *P* for heterogeneity <0.001). Only the cohort study reported a significant risk reduction (RR = 0.78, 95% CI = 0.62—0.98), while no significant association was observed in nested-case-control studies (RR = 1.03, 95% CI = 0.90—1.18; *P* for heterogeneity =0.196) nor in case-control ones (RR = 0.87, 95% CI = 0.58—1.31; *P* for heterogeneity <0.001; Table 1 and Figure 4). There was no evidence of publication bias (Egger's test *P* = 0.421; Begg's test *P* = 0.245; supplementary Figure S3, available at *Annals of Oncology* online). Risk estimates were consistent across strata of year of publication and type of controls, but not of geographic area (*P* for heterogeneity <0.001), largely due to one case-control study conducted in China which reported a significant excess risk (RR = 1.91, 95% CI = 1.52—2.41; supplementary Table S16, available at *Annals of Oncology* online).

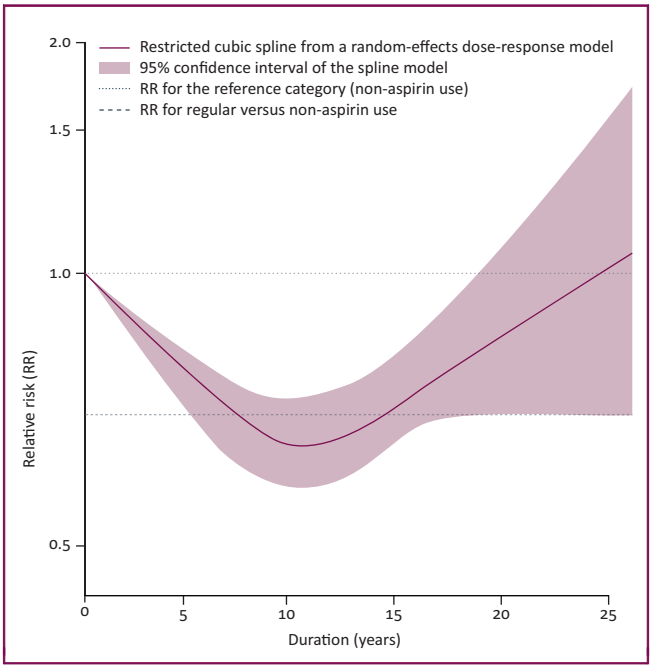

Figure 3. Relative risk (RR) function describing the relation between duration (years) of aspirin use and colorectal cancer.
Thick line: restricted cubic spline from a random-effects dose-response model. Thin lines: 95% confidence interval of the spline model. Dashed line: RR for regular versus non-aspirin use. Dotted dashed line: RR for the reference category (non-aspirin use).

Squamous-cell esophageal cancer

Among 15 studies providing information on squamous-cell esophageal cancer risk (supplementary Tables S4 and S10, available at *Annals of Oncology* online), 13 studies, including 6211 cases, contributed to the risk estimate of regular aspirin use versus non-use (Table 1). A significant reduced risk was reported overall (RR = 0.67, 95% CI = 0.57—0.79). The RR was 0.65 in four cohort studies, 0.54 (95% CI = 0.43—0.67) in seven case-control studies, and 0.90 (95% CI = 0.78—1.03) in two nested case-control studies (Table 1 and Figure 5). There was a significant heterogeneity between studies (*P* = 0.006), which was explained by study design (*P* for heterogeneity <0.0001). No evidence of publication bias was detected (Egger's test *P* = 0.459; Begg's test *P* = 0.272; supplementary Figure S4, available at *Annals of Oncology* online). The risk estimates were consistent across strata of all covariates considered (i.e. geographic area, type of controls, end point, and year of publication; supplementary Table S17, available at *Annals of Oncology* online).

Supplementary Figure S5, available at *Annals of Oncology* online, indicated a linear relation between duration of aspirin use and squamous-cell esophageal cancer risk on the basis of five studies providing information, with RRs of 0.88 (95% CI = 0.77—0.99) for 5 years of use and 0.77 (95% CI = 0.60—0.99) for 10 years of use.

Esophageal and gastric cardia adenocarcinoma

Out of 12 studies providing information on aspirin use and esophageal and gastric cardia adenocarcinoma (supplementary Tables S5 and S11, available at *Annals of Oncology* online), 10 studies, including 3021 cases, contributed to quantify the risk among regular aspirin use compared with non-use (Table 1). A significant inverse relation was found overall (RR = 0.61, 95% CI = 0.49—0.77), and in eight case-control studies (RR = 0.56, 95% CI = 0.44—0.73), while the RR was 0.88 (95% CI = 0.68—1.15) in two cohort studies (*P* for heterogeneity across study design =0.015; Table 1 and Figure 6). There was significant between-study heterogeneity overall and among case-control studies (*P* < 0.001), but not among cohort studies. There was no evidence of publication bias (Egger's test *P* = 0.085; Begg's test *P* = 0.151; supplementary Figure S6, available at *Annals of Oncology* online). The RRs were consistent across strata of all covariates considered (i.e. geographic area, type of controls,

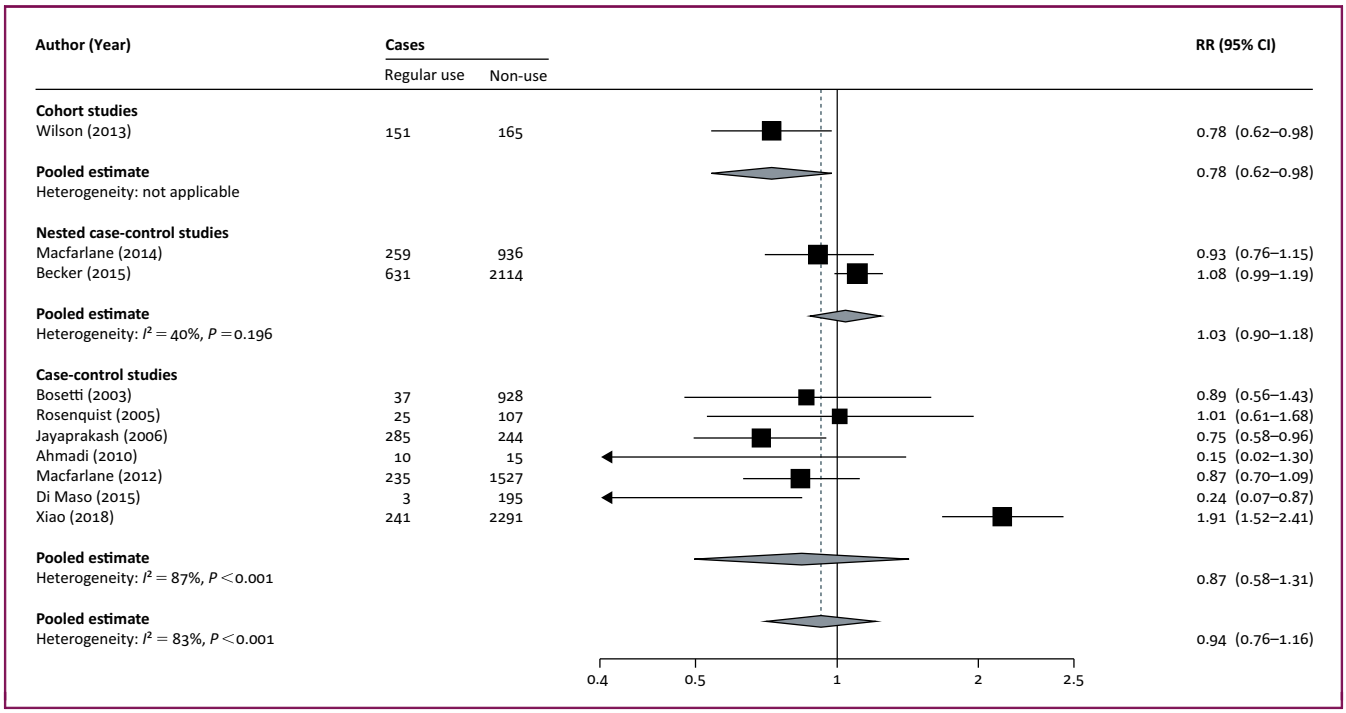

Figure 4. **Forest plot of study-specific and pooled relative risk (RR) of head and neck cancer, and corresponding 95% confidence interval (CI), for regular aspirin use versus non-use, overall and by study design.**

and year of publication; supplementary Table S18, available at *Annals of Oncology* online).

There was a non-significant linear RR reduction with increasing years of regular aspirin use, based on three studies (RR = 0.94, 95% CI = 0.79—1.04, and 0.82, 95% CI = 0.62—1.09, for 5 and 10 years of use, respectively; supplementary Figure S7, available at *Annals of Oncology* online).

Stomach cancer

Sixteen studies reported information on aspirin use and stomach cancer (supplementary Tables S6 and S12, available at *Annals of Oncology* online), of which 14 (six cohort studies, one nested case-control, and seven case-control studies) contributed to estimating the association for

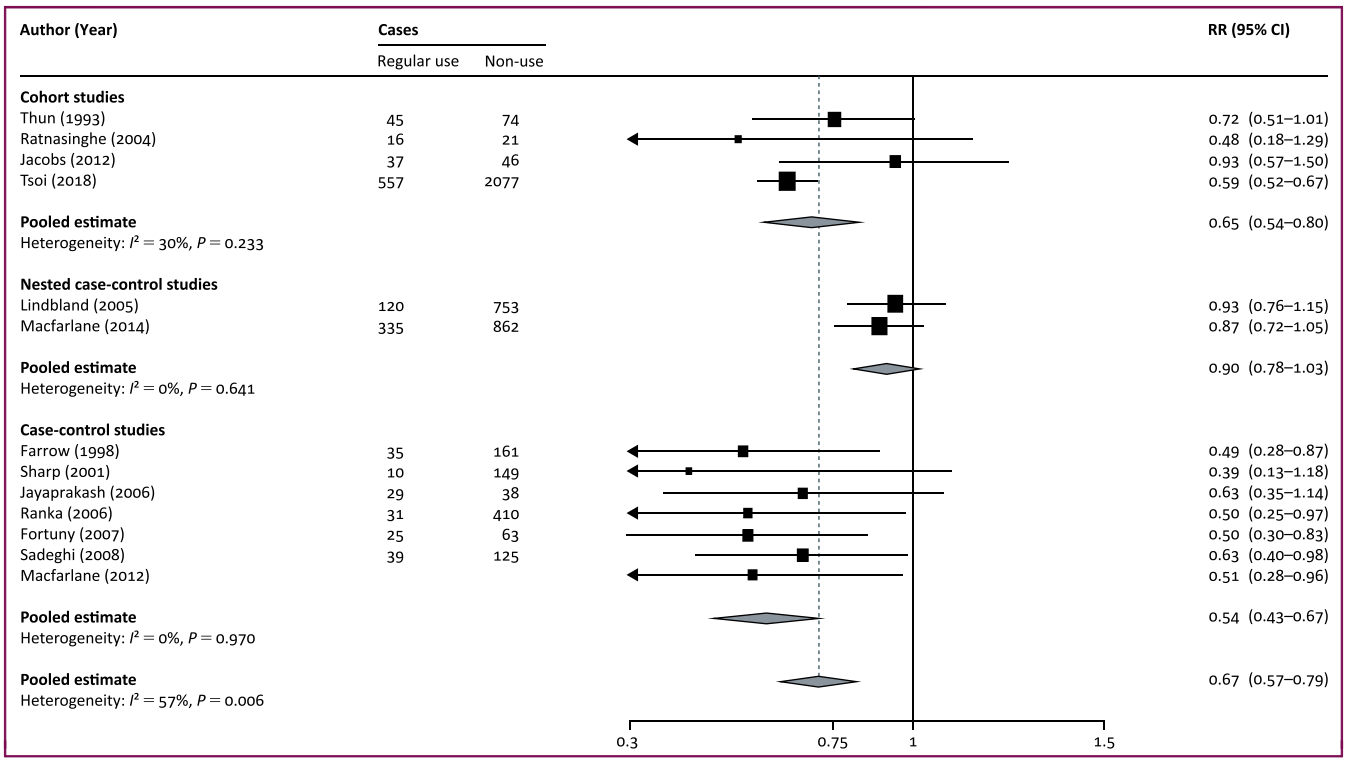

Figure 5. **Forest plot of study-specific and pooled relative risk (RR) of squamous-cell esophageal cancer, and corresponding 95% confidence interval (CI), for regular aspirin use versus non-use, overall and by study design.**

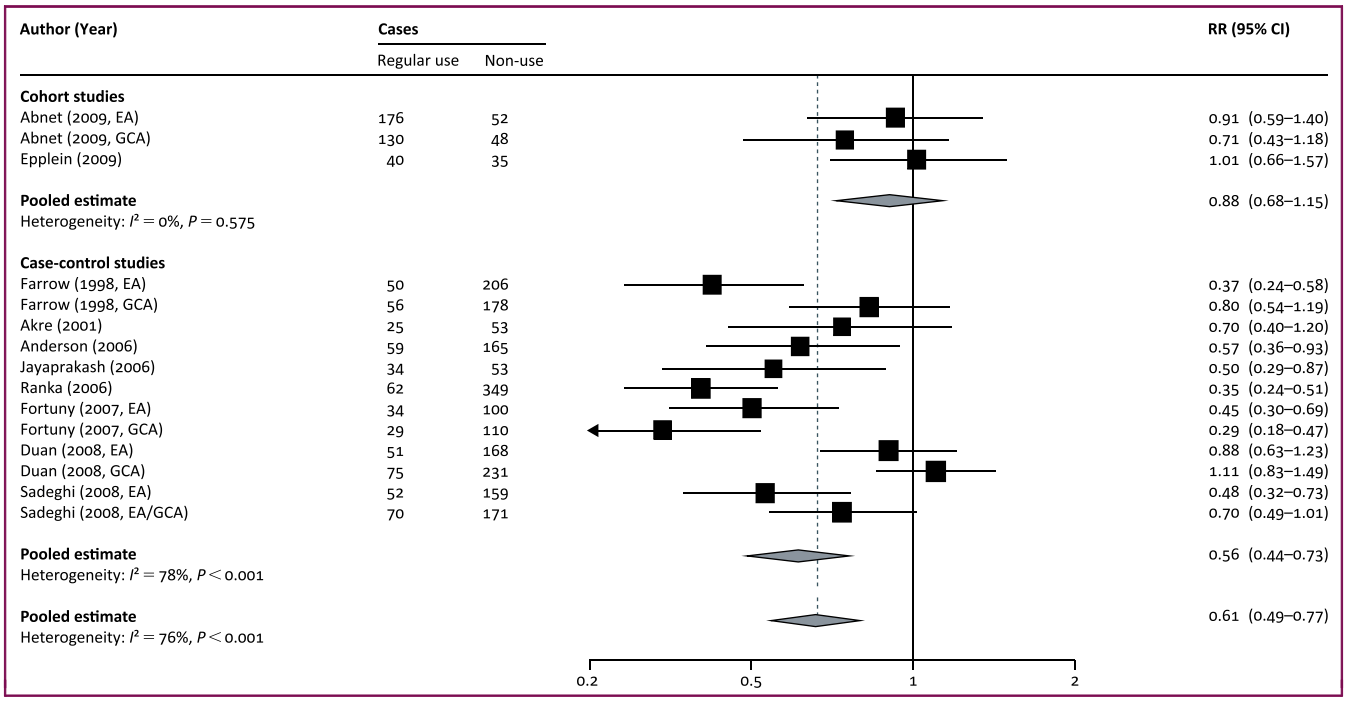

Figure 6. Forest plot of study-specific and pooled relative risk (RR) of adenocarcinoma of the esophagus and gastric cardia, and corresponding 95% confidence interval (CI), for regular aspirin use versus non-use, overall and by study design.
EA, esophageal adenocarcinoma; GCA, gastric cardia adenocarcinoma.

regular aspirin use, including 9919 cases (Table 1). The RR was 0.64 (95% CI = 0.51—0.82) overall, 0.58 in six cohorts, and 0.63 (95% CI = 0.48—0.83) in seven case-control studies, while one nested case-control study reported an RR of 1.17 (95% CI = 0.98—1.40; *P* of heterogeneity across study design <0.001; Table 1 and Figure 7). Significant between-studies heterogeneity was found overall and among case-control or cohort studies ($P < 0.001$). There

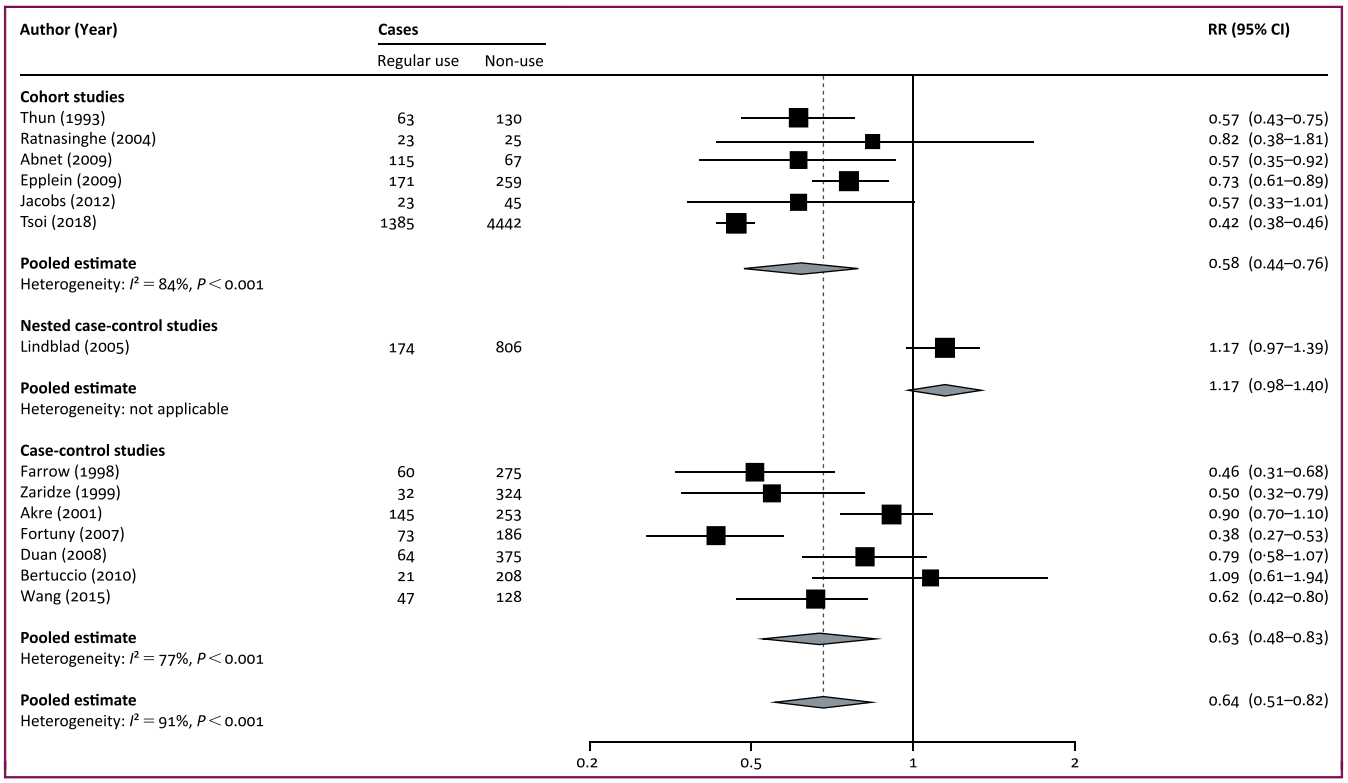

Figure 7. Forest plot of study-specific and pooled relative risk (RR) of stomach cancer, and corresponding 95% confidence interval (CI), for regular aspirin use versus non-use, overall and by study design.

was no evidence of publication bias (Egger's test $P = 0.268$; Begg's test $P = 0.784$; supplementary Figure S8, available at *Annals of Oncology* online). The RRs were consistent across strata of all covariates considered, except geographic area (RR = 0.58, 95% CI = 0.48—0.71, in the USA, 0.89, 95% CI = 0.65—1.23, in Europe, and 0.49, 95% CI = 0.34—0.72, in other areas; *P* for heterogeneity =0.034; supplementary Table S19, available at *Annals of Oncology* online).

Eight studies indicated that the risk of stomach cancer linearly decreased with increasing years of regular aspirin use (RR = 0.81, 95% CI = 0.71—0.92, for 5 and 0.65, 95% CI = 0.50—0.85, for 10 years of use; supplementary Figure S9, available at *Annals of Oncology* online).

Hepato-biliary cancer

Eight studies provided information on aspirin use and risk of hepato-biliary cancer (including hepatocellular carcinoma and cholangiocarcinoma; supplementary Tables S7 and S13, available at *Annals of Oncology* online) of which five studies contributed to the estimate of regular aspirin use compared with non-use (Table 1). The RR was 0.62 (95% CI = 0.44—0.86) overall (*P* for heterogeneity <0.001), 0.66 (95% CI = 0.47—0.94) in two cohort studies (*P* for heterogeneity <0.001), 0.34 (95% CI = 0.30—0.39) in two case-control studies, and 1.11 in a nested case-control one (*P* for heterogeneity across study design <0.001; Table 1 and Figure 8). The RRs were 0.71 (95% CI = 0.46—1.09) for liver cancer and 0.53 (95% CI = 0.24—1.14) for cholangiocarcinoma (*P* for heterogeneity =0.51; data not shown).

No evidence of publication bias was observed (Egger's test $P = 0.540$; Begg's test $P = 0.624$; supplementary Figure S10, available at *Annals of Oncology* online). After stratifying studies for geographic area, risk estimates were not consistent across strata (RR = 0.34, 95% CI = 0.30—0.39, in the USA, 0.75, 95% CI = 0.31—1.81, in Europe, and 0.49, 95% CI = 0.45—0.53, in other areas; *P* for heterogeneity <0.001; supplementary Table S20, available at *Annals of Oncology* online).

Supplementary Figure S11, available at *Annals of Oncology* online, shows a linear duration-risk relation, although the 95% CI are extremely wide, since it was based on three studies only.

Pancreatic cancer

Twenty original publications reported risk estimates for pancreatic cancer (supplementary Tables S8 and S14, available at *Annals of Oncology* online). Fifteen studies (seven cohort studies, one nested case-control study, and seven case-control studies) were considered in the estimate of regular aspirin use, including a total of 12 193 cases (Table 1). An inverse association was found overall (RR = 0.78, 95% CI = 0.68—0.89), in cohort (RR = 0.79, 95% CI = 0.64—0.98, *P* for heterogeneity <0.001), in case-control studies (RR = 0.73), but not in one nested case-control study (RR = 0.95, 95% CI = 0.81—1.12; Table 1 and Figure 9). There was no evidence of publication bias (Egger's test $P = 0.136$; Begg's test $P = 0.216$; supplementary Figure S12, available at *Annals of Oncology* online). The RRs were consistent across strata of all covariates (i.e. geographic area, type of controls, and year of publication; supplementary Table S13, available at *Annals of Oncology* online).

Supplementary Figure S5, available at *Annals of Oncology* online, shows linear dose-response relations between duration of regular aspirin use and the risk of pancreatic cancer, based on seven studies. The RRs for 5 and 10 years

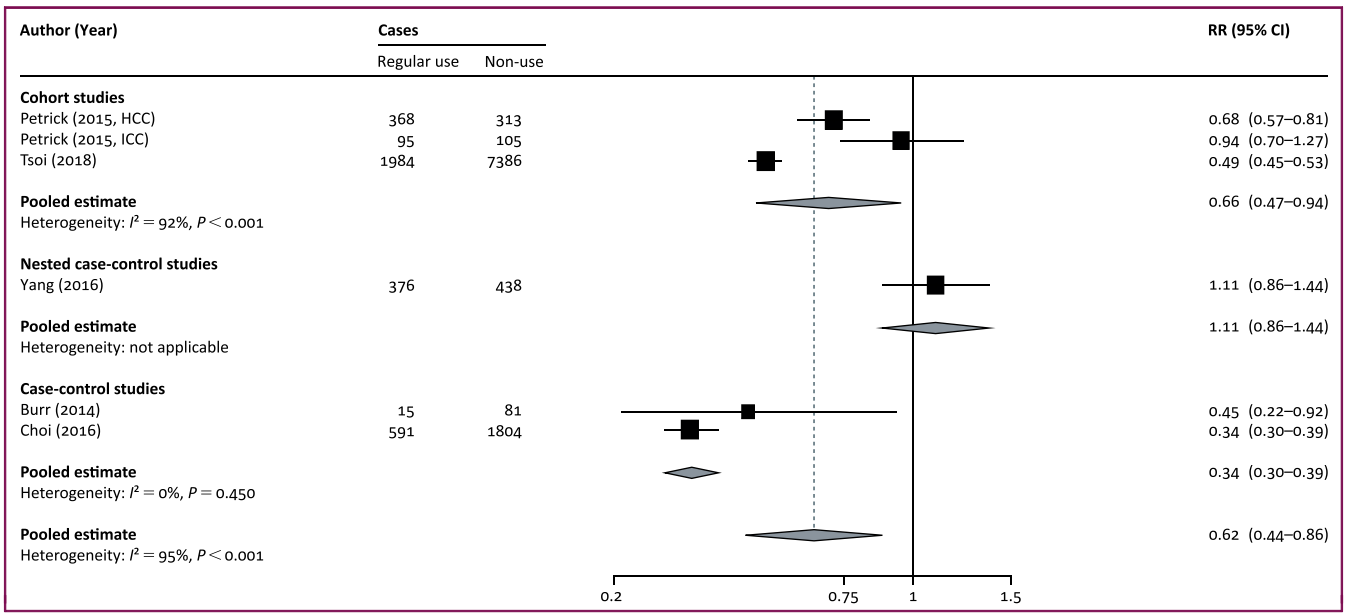

Figure 8. Forest plot of study-specific and pooled relative risk (RR) of hepato-biliary cancer, and corresponding 95% confidence interval (CI), for regular aspirin use versus non-use, overall and by study design.

HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

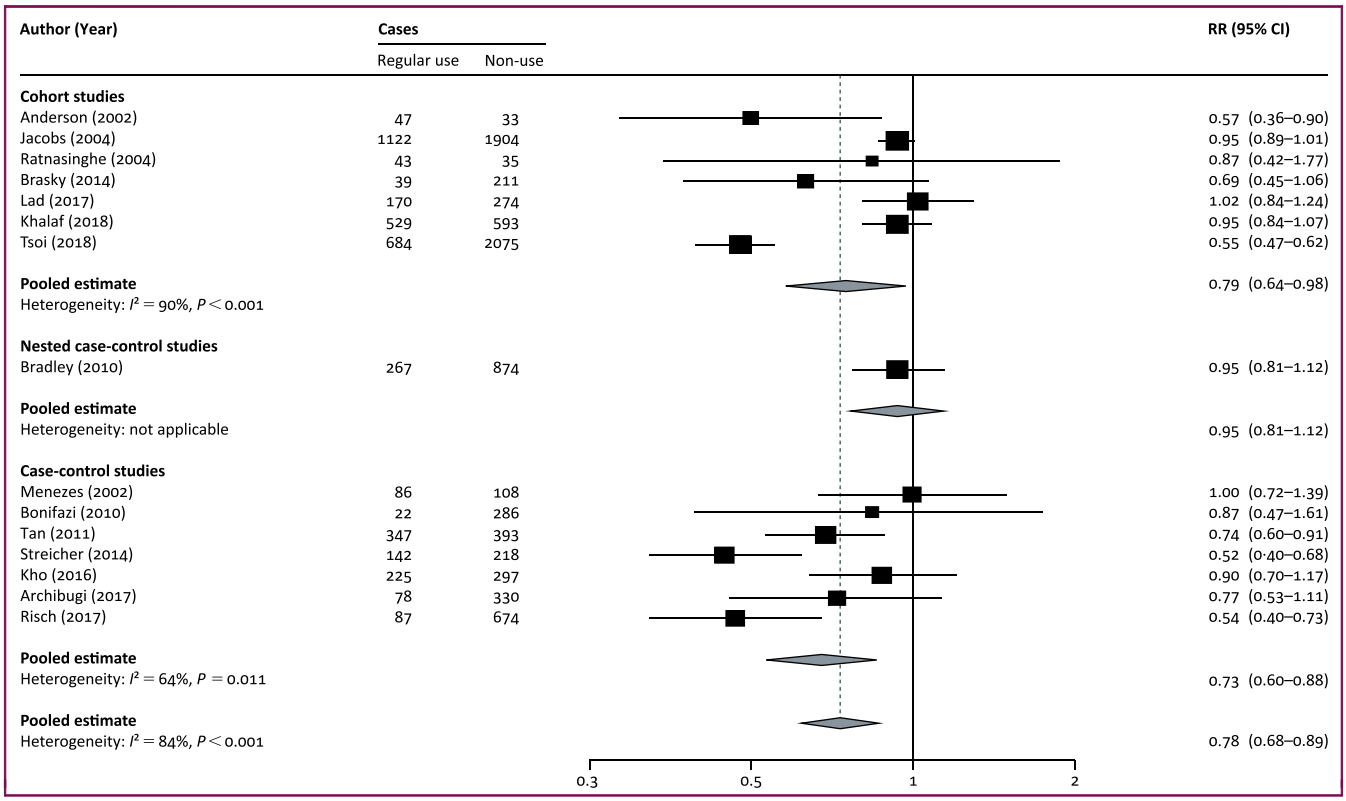

Figure 9. **Forest plot of study-specific and pooled relative risk (RR) of pancreatic cancer, and corresponding 95% confidence interval (CI), for regular aspirin use versus non-use, overall and by study design.**

of regular aspirin use were 0.75 (95% CI = 0.59—0.94) and 0.56 (95% CI = 0.35—0.89), respectively.

DISCUSSION

The present comprehensive meta-analysis on aspirin and colorectal and other digestive tract cancers confirms and further quantifies the inverse association between aspirin use and the risk of cancer of the colorectum, esophagus, and stomach, and provides evidence of a protective effect on hepato-biliary and pancreas cancer risk, as well. The associations are consistent across sex, geographical areas, and other covariates. For all neoplasms, the favorable effect of aspirin tends to increase with longer duration of use, and for colorectal cancer, with increasing dose.

Data on over 150 000 colorectal cancer cases provide evidence of an about 30% reduced risk for regular aspirin use as compared with non-use. A significant risk reduction is reported for all study designs. There is, however, some heterogeneity between studies, although almost all studies provided RR estimates significantly below unity; moreover, there is some evidence of publication bias, with various small studies reporting stronger inverse associations. These results confirm those of previous meta-analyses of observational studies[6,8] and are consistent with the evidence provided by a pooled analysis of RCTs of aspirin for the prevention of cardiovascular diseases.[3,20,21]

Low dose aspirin (between 75 and 100 mg/day) conveys a reduction of risk by 10%, regular-dose aspirin (325 mg/day) by 35%, and high-dose aspirin (500 mg/day) by 50%. This latter estimate should be cautiously interpreted, since it is based on a limited number of studies. A previous meta-analysis of cohort studies reported an inverse relation between colorectal incidence, with significant and dose- and frequency-risk relations.[6] In a post-trial follow up of the randomized Physicians' Health Study, use of 325 mg of aspirin every other day was not associated with a significant reduction of colorectal cancer incidence.[22] Similarly, in the randomized Women's Health Study alternate day use of low dose aspirin (100 mg) for an average treatment of 10 years did not lower colorectal cancer incidence,[23] although in the post-trial follow-up colorectal cancer risk was significantly reduced.[24] A pooled analysis of two RCTs of high-dose aspirin use indicated that regular use of at least 300 mg/day is effective in the primary prevention of colorectal cancer.[25] Moreover, an RCT of aspirin in the prevention of colorectal cancer in carriers of the Lynch syndrome indicated that 600 mg of aspirin per day significantly reduced colorectal cancer incidence after a 3-year follow-up.[26]

With regard to the duration of aspirin use and colorectal cancer risk, the risk reduction is by 20% for 5 years of use and by 30% for 10 years of use. The risk levels off for longer duration of use, although this result is difficult to interpret as there are few studies that analyzed long-term aspirin use. The meta-analysis of cohort studies by Ye et al.[6] also suggested that long-term (at least 5 years) use of aspirin is required in order to show a protective effect on colorectal cancer risk. In the pooled analysis of RCTs of aspirin use for the prevention of cardiovascular diseases, the reduction in colorectal cancer incidence and mortality was evident for treatments of more than 5 years.[20,21,27,28]

Aspirin use is associated with about a 35%—40% risk reduction of cancers of the esophagus and stomach, confirming the findings of previous meta-analyses.[7,8] For squamous-cell and stomach cancers, consistent results are found in case-control and cohort studies, but the evidence is less clear in nested case-control studies, while for adenocarcinoma of the esophagus and gastric cancer, the only two cohort studies do not show a significant association. Since aspirin may cause gastrointestinal bleeding,[29] it is possible that at least part of the inverse association observed is due to the avoidance of aspirin use in patients with early symptoms of esophageal or stomach cancer. Data from a few studies suggest linear duration-risk relations between the use of aspirin and the risk of squamous-cell esophageal and stomach cancer. The duration-risk relation for adenocarcinoma of the esophagus and gastric cardia is less clear. In the pooled analysis of RCTs, treatment with aspirin for at least 5 years conveyed a significant protection on esophageal cancer death after a latent period of 5 years, while a non-significant reduction was observed for stomach cancer mortality even after a long latency.[21]

With regard to cancers of the hepato-biliary tract (mainly hepatocellular carcinoma), this meta-analysis provides some evidence of a possible favorable effect of aspirin, as reported in a previous meta-analysis.[8] Data for the duration of aspirin use are too limited to provide a meaningful duration-risk relation. A recent study also reported that aspirin is associated with a reduced risk of hepatocellular cancer in patients with hepatitis B infection,[30] although further studies should confirm these associations.

While in a previous meta-analysis[2] there was no evidence of a significant pancreatic cancer risk reduction with aspirin use, about a 20% significant reduction is observed in the present meta-analysis as in a previous one,[8] with a similar risk reduction in case-control and cohort studies. Moreover, an inverse duration-risk relation is found, with an RR of 0.56 for 10 years of regular aspirin use. The evidence accumulated over the last few years therefore points to a favorable effect of aspirin also on pancreatic cancer risk. In the pooled analysis of RCTs, treatment with aspirin for at least 5 years conveyed a significant protection on pancreatic cancer death after a latent period of 5 years.[21]

Overall evidence does not support an association of aspirin use with cancers of the head and neck.[8] However, this class includes different cancers, with variable characteristics and etiological factors. Additional studies are necessary to further assess the role of aspirin on each of those neoplasms.

Among the possible limitations of our study, there are inherent biases of observational studies. The inverse associations observed in the present meta-analysis are generally stronger in case-control than cohort studies. Although cohort studies are less prone to recall or selection bias than case-control studies, they generally collect data only at baseline and lack information on exposure changes over time, thus causing possible misclassification of aspirin exposure. In any case, potential recall bias in case-control studies—due to possible more careful reporting of aspirin use in cases than controls—should, if any, bias risk estimates towards the null. Confounding by indication—due to selective avoiding of aspirin use in patients with early symptoms of digestive tract cancers—may partly explain the stronger inverse associations observed in case-control than cohort studies. The lower inverse associations reported in nested case-control studies (often based on prescription databases) can be explained by misclassification of aspirin exposure in those studies, due to possible less precise assessment of the actual aspirin use and lack of information on over-the-counter use. For many of the pooled estimates, there is a between-study heterogeneity, which does not seem to be explained by the covariates considered. Different study populations, baseline cancer risks, prevalence of aspirin use, aspirin dose, inclusion of patients for primary and secondary cardiovascular disease prevention, and high variability in the definition of 'regular' use may be responsible of such heterogeneity. Finally, most studies included in our meta-analysis did not have data on other medications for cardiovascular prevention (such as statins), which may confound the association between aspirin and cancer risk.

From a biological point of view, the chemopreventive effect of aspirin has been attributed to the inhibition of cyclooxygenase (COX), the enzyme responsible for the synthesis of prostaglandins. COX-2 isoform is abnormally expressed in many cancer cell lines and is implicated in the process of carcinogenesis, tumor growth, apoptosis, and angiogenesis.[1,31—34] Additional mechanisms include the induction of apoptosis through COX-independent pathways, such as the inhibition of nuclear factor-kappa β, the PIK3CA pathway, and the up-regulation of tumor suppression genes.[33,34]

In conclusion, the present meta-analysis provides further evidence and quantification of a favourable effect of aspirin on colorectal and other digestive tract neoplasms. It also suggests that the protection tends to increase with longer duration of use, and for colorectal, with increasing dose. These results should be confirmed by the on-going primary prevention trials.[35—37]

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DISCLOSURE

The authors have declared no conflicts of interest.

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