Acetylsalicylic acid (ASA) in prevention of cancer

Report from Kunnskapssenteret (Norwegian Knowledge Centre for the Health Services)
No 18–2013
Systematic review

kunnskapssenteret
Norwegian Knowledge Centre for the Health Services

Background: Acetylsalicylic acid (ASA), also named aspirin, has antipyretic, analgesic and anti-inflammatory properties as well as anti-platelet properties. Low doses of ASA are being used for prevention of cardiovascular disease. Based on its pharmaceutical properties, it has been debated for several years whether ASA may have a role in cancer prevention. **Main findings:** • Lower overall mortality associated with ASA use. • Lower cancer mortality associated with ASA use. • Lower cancer incidence associated with ASA use. • A clear increase in bleeding events associated with ASA usevide evidence of serious harmful consequences from FGM/C.

Title	Acetylsalicylic acid (ASA) in prevention of cancer
Norwegian title	Acetylsalicylsyre (ASA) som kreftforebyggende tiltak
Institution	Norwegian Knowledge Centre for the Health Services (NOKC, Nasjonalt kunnskapssenter for helsetjenesten) Magne Nylenna, *Director*
Authors	Ringerike, Tove *(Project leader), senior researcher, NOKC* Couto, Elisabeth, *senior researcher, NOKC* Klemp, Marianne, *Head of unit, NOKC*
ISBN	978-82-8121-639-6
ISSN	1890-1298
Report	No. 18 – 2013
Project number	900
Type of report	Hurtigoversikt
No. of pages	30 (41 including appendices)
Client	The Norwegian Directorate of Health
Subject headings (MeSH)	ASA, acetylsalisylic acid, aspirin, cancer
Citation	Ringerike T, Couto E, Klemp M. Acetylsalicylic acid (ASA) in prevention of cancer. Report from Kunnskapssenteret no. 18–2013. Oslo: Norwegian Knowledge Centre for the Health Services, 2013.

Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Knowledge Centre is organized under The Norwegian Directorate of Health, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

We would like to thank all contributors for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, November 2013

Key messages

Acetylsalicylic acid (ASA), also named aspirin, has antipyretic, analgesic and anti-inflammatory properties as well as anti-platelet properties. Low doses of ASA are being used for prevention of cardiovascular disease. Based on its pharmaceutical properties, it has been debated for several years whether ASA may have a role in cancer prevention.

The Directorate of Health asked us to examine the potential effect of ASA use on overall mortality, cancer mortality, cancer incidence and possible side effects, in patients without prior history, or increased risk, of cancer.

We included 12 systematic reviews. None of the included systematic reviews had examined the effect of ASA in the intended population. All identified studies were originally designed and performed to examine the role of ASA use in primary and secondary prevention of vascular events. The results:

- indicated a lower overall mortality associated with ASA use
- showed lower cancer mortality associated with ASA use
- showed lower cancer incidence associated with ASA use
- showed a clear increase in bleeding events associated with ASA use

Title:
Acetylsalicylic acid (ASA) in prevention of cancer

Type of publication:

Rapid review

A rapid review is a review that makes use of less comprehensive methods than a systematic review due to limited timeframe, e.g. less comprehensive search strategy, search in fewer databases, no grading of the quality of selected studies, no external peer review, and simpler quality check of both project plan and final manuscript.

Doesn't answer everything:

- Not evaluted effect on cardiovascular outcomes
- No recommendations

Publisher:

Norwegian Knowledge Centre for the Health Services

Updated:

Last search for studies: February 2013

Executive summary

Background

Acetylsalicylic acid (ASA), also named aspirin, belongs to the non-steroidal anti-inflammatory drugs (NSAIDS). It has the antipyretic, analgesic and anti-inflammatory properties of other NSAIDs, as well as antiplatelet properties. Low doses of ASA are being used for prevention and treatment of cardiovascular disease.

It has been reported that higher level of prostaglandins were found in tumors than in normal tissue, and hypothesized that prostaglandins may play a role in cancer. NSAIDs target the cyclooxygenase enzyme that is responsible for forming prostaglandins, and it has been debated for several years whether ASA may have a role in cancer prevention.

Objective

This project was commissioned, as a rapid review, by The Directorate of Health and is aimed at examining the use of ASA as possible primary prevention of cancer in persons without prior history, or increased risk, of cancer. We examined the potential effect of ASA use on overall mortality, cancer mortality, cancer incidence and side effects.

Method

We performed a systematic search for systematic reviews in electronic databases. The most recent publication(s) reporting results according to our objective was selected and results summarized.

Results

In this rapid review, we have systematically reviewed and summarized 12 systematic reviews of ASA use compared with no such treatment or placebo in patients without prior diagnosis of cancer or increased risk of cancer.

Based on studies originally designed and performed to examine the role of ASA use in primary and secondary prevention of vascular events, the results indicated a lower overall mortality associated with ASA use. Results also showed that ASA use resulted in lower cancer mortality and cancer incidence. This benefit, however, came at a cost of a clear increase in bleeding events.

Discussion

This is a rapid review summarizing systematic reviews. Hence, its format is compact and without the level of detail normally found in full systematic reviews of individual studies.

Although the possible role of ASA in cancer prevention has been discussed for several years, none of the included systematic reviews identified any long-term randomized controlled studies designed purposely to investigate ASA use for cancer prevention. The estimates of the association between ASA use and the risk of cancer or cancer mortality resulted from randomized controlled trials which analyzed ASA use in primary or secondary prevention of cardiovascular disease.

Hovedfunn (norsk)

Acetylsalisylsyre (ASA), også kalt aspirin, har febernedsettende, smertestillende og betennelseshemmende egenskaper, samt hindrer dannelse av blodpropp. Lave doser av ASA blir brukt til forebygging av hjerte- og karsykdommer. Basert på sine farmasøytiske egenskaper, har det vært diskutert i flere år om ASA også kan ha en rolle i kreftforebygging.

Helsedirektoratet ba oss om å undersøke effekten av ASA på total dødelighet, kreftdødelighet, kreftforekomst og mulige bivirkninger hos pasienter uten tidligere kreft eller økt risiko for kreft.

Vi inkluderte 12 systematiske oversikter. Ingen av oversiktene hadde undersøkt effekten av ASA i den ønskede populasjonen. Basert på studier opprinnelig laget og utført for å undersøke ASA i primær og sekundær forebygging avhjerte- og karsykdommer, viste resultatene:

• indikasjon på lavere total dødelighet forbundet med ASA-bruk
• lavere kreftdødelighet forbundet med ASA-bruk
• lavere kreftforekomst i forbindelse med ASA-bruk
• en klar økning i blødninger assosiert med ASA-bruk

Tittel:
Acetylsalicylsyre (ASA) som kreftforebyggende tiltak

Publikasjonstype:

Hurtigoversikt

En hurtigoversikt er resultatet av å sammenfatte forskningsbasert kunnskap
- med kort tidsfrist og
- med mindre omfattende metode enn ved systematisk kunnskapsoppsummering.

Svarer ikke på alt:

- Har ikke undersøkt effekt av ASA på hjerte- og karsykdomer
- Ingen anbefalinger

Hvem står bak denne rapporten?

Kunnskapssenteret har skrevet rapporten på oppdrag fra Helsedirektoratet.

Når ble litteratursøket utført?

Søk etter studier ble avsluttet Februar 2013.

Sammendrag

Bakgrunn.

Acetylsalisylsyre (ASA), også kalt aspirin, tilhører ikke-steroide antiinflammatoriske legemidler (NSAIDs). ASA har febernedsettende, smertestillende og betennelseshemmende egenskaper som de andre antiinflammatoriske legemidler, så vel som antitrombotiske egenskaper. Lave doser av ASA blir brukt til forebygging og behandling av hjerte- og karsykdommer.

Det har blitt rapportert at tumorer (kreftceller) har et høyere nivå av prostaglandiner enn normalt vev, og dermed har det fremkommet en hypotese om at prostaglandiner kan spille en rolle ved kreft. Antiinflammatoriske legemidler innvirker på cyklooksygenaseenzymet som er ansvarlig for å danne prostaglandiner, og det har vært diskutert i flere år om ASA kan ha en rolle i kreftforebygging.

Problemstilling

Denne hurtigoversikten ble bestilt av Helsedirektoratet og oppsummerer forskning om bruk av ASA som mulig primær forebygging av kreft hos personer uten tidligere kreft eller økt risiko for kreft. Vi undersøkte den potensielle effekten av ASA-bruk på utfallsmålene total dødelighet, kreftdødelighet, kreftforekomst og bivirkninger.

Metode

Vi utførte et systematisk søk i elektroniske databaser for å identifisere relevante systematiske oversikter. Vi valgte ut den nyeste og/eller mest omfattende publikasjonen som rapporterte resultater i henhold til våre utfallsmål og oppsummerte resultatene.

Resultat

I denne hurtigoversikten, har vi systematisk gjennomgått og oppsummert 12 systematiske oversikter av ASA-bruk sammenliknet med ingen slik behandling eller placebo hos pasienter uten tidligere kreft eller økt risiko for kreft.

Basert på studier som ble utført for å undersøke effekt av ASA-bruk i primær- og sekundær forebygging av vaskulære hendelser, indikerte resultatene en lavere total dødelighet forbundet med ASA-bruk. Resultatene viste også at ASA-bruk resulterte i lavere kreftdødelighet og kreftforekomst. Denne fordelen kom på bekostning av en klar økning i alvorlige blødninger.

Diskusjon

Dette er en hurtigoversikt som oppsummerer systematiske oversikter. Derfor er formatet kompakt og uten det nivået av detaljer som normalt finnes i systematiske oversikter over enkeltstudier.

Selv om den mulige rollen for ASA i kreftforebygging har vært diskutert i flere år, identifiserte ingen av de inkluderte systematiske oversiktene noen langsiktige randomiserte kontrollerte studier designet med hensikt å undersøke ASA-bruk for kreftforebygging. Anslagene for sammenheng mellom ASA-bruk og risiko for kreft eller kreftdødelighet, kommer fra randomiserte kontrollerte studier som har undersøkt ASA-bruk i primær- eller sekundærforebygging av hjerte- og karsykdommer.

Nasjonalt kunnskapssenter for helsetjenesten fremskaffer og formidler kunnskap om effekt av metoder, virkemidler og tiltak og om kvalitet innen alle deler av helsetjenesten. Målet er å bidra til gode beslutninger slik at brukerne får best mulig helsetjenester. Kunnskapssenteret er formelt et forvaltningsorgan under Helsedirektoratet, men har ikke myndighetsfunksjoner og kan ikke instrueres i faglige spørsmål.

Nasjonalt kunnskapssenter for helsetjenesten
PB 7004 St. Olavs plassN-0130 Oslo, Norway
Telefon: +47 23 25 50 00
E-mail: post@kunnskapssenteret.no
Hele rapporten (pdf): www.kunnskapssenteret.no/Publikasjoner

Table of contents

KEY MESSAGES 2

EXECUTIVE SUMMARY 3

HOVEDFUNN (NORSK) 5

SAMMENDRAG (NORSK) 6

TABLE OF CONTENTS 8

PREFACE 10
Objective 10
Project administration 10

BACKGROUND 11
A possible role for ASA in cancer prevention 11
Choice of outcomes 12

METHODS 13
Literature search 13
Inclusion criteria 13
Exclusion criteria 14
Selection of articles 14
Data extraction and analysis 14
Grading the quality of evidence 15

RESULTS 16
Results of the literature search 16
Description of included systematic reviews 17
Overall mortality in studies investigating ASA use 18
Cancer related mortality in studies investigating ASA use 19
Cancer incidence in studies investigating ASA use 21
Adverse events in studies investigating ASA use 22

DISCUSSION 24
Summary of results 24
Strengths and weaknesses of this review 25

CONCLUSION 28

Need for further research 28

REFERENCES 29

APPENDIX 31
Appendix 1 - Literature search 31
Appendix 2 - List of publications reviewed in full text 32
Appendix 3 - Checklist for systematic reviews and individual evaluations 39
Appendix 4 – Cancer incidence according to specific cancer sites 40

Preface

Objective

This project was commissioned, as a rapid review, by The Directorate of Health and is aimed at examining the use of ASA as possible primary prevention of cancer. We examined the effect of ASA use on overall mortality, cancer specific mortality, cancer incidence and side effects, in patients without prior history, or increased risk, of cancer.

Project administration

Tove Ringerike led the project. Elisabeth Couto contributed to defining the aim, and to carrying out the systematic review (selection of articles, data extraction and writing the report). Research librarian Ingrid Harboe performed the systematic search.

Åse Skår, Rigmor Berg, Steinar Madsen and Per Olav Vandvik performed peer review of the report.

The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

Gro Jamtvedt	Marianne Klemp	Tove Ringerike
Department director	*Head of Unit*	*Project leader*

Background

A possible role for ASA in cancer prevention

Acetylsalicylic acid (ASA), also named aspirin, belongs to the non-steroidal anti-inflammatory drugs (NSAIDS). ASA, which is the most commonly consumed NSAIDs drug, has been used for a very long time with possible use back to ancient Egypt (1). It has the antipyretic, analgesic and anti-inflammatory properties of other NSAIDs, as well as antiplatelet properties (2). ASA, which is easily available and relatively cheap, is commonly used in Norway, as in many other countries. It is primarily used as an anti-inflammatory, analgesic and antipyretic drug (3). Furthermore, low doses of ASA are being used for primary and secondary prevention of cardiovascular disease (3-5).

Bennett et al. reported that more prostaglandins (PG) were found in human tumors than in normal tissue, and hypothesized that PGs may play an important role in growth of tumors and their ability to metastasize(6). NSAIDs target the cyclooxygenase enzyme that is responsible for forming PGs from arachidonic acid (7), and several animal studies have been carried out to test whether the use of ASA and other NSAIDSs would prevent malignant tumors. Most of these studies have found that ASA (and other NSAIDs) inhibited colorectal tumors. In 1988, the first published observational study reported a statistically significant reduced risk of developing colorectal cancer with ASA use (8). In 1997, the WHO International Agency for Research on Cancer (IARC) summarized the evidence on ASA use and cancer (4). The published evidence was mainly from observational studies with a reported lack of randomized prospective trials. The IARC report concluded that while ASA showed promising evidence for protection against colorectal cancer, further research was needed, in particular randomized controlled trials.

In most developed countries, cancer is the second largest cause of death after cardiovascular disease, with the number of global cancer deaths projected to increase by 45% from 2007 to 2030. In the same period, the number of new cancer cases is predicted to increase from 11.3 in 2007 to 15.5 million in 2030 (9). In Norway, the cancer incidence rate increased by 7% in men and 3% in women from the period 2001-2005 to the period 2006-2010 (10). This is partly due to a population that is aging and predicted to increase also in the future. Drugs that could possibly prevent cancer

cases and cancer mortality would have a significant public health impact now and in the future.

However, severe adverse effects such as gastrointestinal hemorrhage have been reported for ASA use (11). Therefore, as proposed in the IARC evaluation of ASA use as possible chemoprevention for cancer: “Detailed consideration of the total benefits of the prevention of cancer (…) in contrast to toxicity will be required before the use of ASA for the prevention of cancer in asymptomatic humans can be recommended.”

Since IARC summarized the evidence on ASA use and cancer in 1997, several clinical trials have been conducted that may clarify this association. The Norwegian Directorate of Health requested an assessment of the general use of ASA as a possible cancer prevention intervention. In particular, they asked us to examine the possible effect of ASA use on cancer prevention and mortality, with careful consideration also given to ASA’s safety profile.

While the effect of ASA use on other diseases such as cardiovascular is important, and should be considered if implementing a nationwide policy aiming at preventing cancer through ASA use, this rapid review is limited to the effects of ASA with regards to cancer.

Choice of outcomes

The aim of this report was to investigate the possible association between ASA use and cancer, therefore we only examined the clinical outcomes that were the most relevant to this issue to allow us to carry this rapid review in the most efficient manner. These outcomes are; overall mortality, cancer mortality and cancer incidence as well as adverse events. It is believed that these outcomes will cover the aspects most relevant to both patients and health decision makers when deciding whether ASA should be offered as cancer prophylaxis. The selected outcomes ascertain different aspects of the examined association. With cancer incidence, we investigated whether the occurrence of new cancers differs in patients taking ASA compared to others. Finally, it is important to investigate if a potential difference in cancer related mortality also affects the overall mortality. We evaluated adverse events experienced after ASA use since it is important to know if a potential benefit has also a detrimental effect.

Methods

Literature search

The research librarian planned and executed all systematic searches in collaboration with the project group. Searches were limited to systematic reviews published in the last 20 years. We used a combination of subject terms and text words and, when available in the databases, filters for systematic reviews. The search was adapted to each database. We searched Embase, Ovid Medline, Cochrane Database of Systematic Reviews (CDSR), Centre for Reviews and Disseminations (CRD) and Pubmed. The search was performed on the 26th February 2013. The complete search strategies are listed in appendix 1.

Inclusion criteria

Population: Persons ≥18 years old taking ASA
If possible, we specify age- and sex distribution of the study participants

Intervention: ASA, as oral mono-therapy or as part of multi-therapy
The main focus was on low-dose ASA, defined as doses 75-100 mg/daily. If available, we specify the dosage and the treatment duration of ASA and report follow-up period.

Comparison: No treatment
Other pharmaceutical treatment
If available, we specify what the comparators are.

Outcomes: Overall mortality
Cancer related mortality
Cancer incidence
Adverse events/side effects (total and specific e.g. gastrointestinal bleedings, ulcers)

Study design: Systematic reviews including information on how the literature search was conducted, and on criteria for inclusion/exclusion. The systemtic review had to be of high or moderate quality.

Language: No limitation in languages during the search, but we only includ-

ed articles written in English, a Scandinavian language and articles with at least an English abstract.

Exclusion criteria

We excluded systematic reviews/studies that focused on patients with established cancer, pre-cancerous states or increased risk. We also excluded systematic reviews/studies that focused on sporadic and very short-term use of ASA, or considered ASA for topical use.

Selection of articles

Two persons independently inspected all the citations generated by the search to identify potentially relevant articles based on title and/or abstract. Full text versions were obtained for articles appearing to meet our inclusion criteria or when insufficient information was available in the abstract to make a decision. Two persons independently assessed whether the full-text articles were relevant according to our list of inclusion criteria. Disagreements were resolved by discussion or by consulting a third person. A list of articles assessed in full text is available in appendix 2.

Articles meeting our inclusion criteria were assessed for quality according to a predefined check list for systematic reviews (appendix 3). All assessments were performed and agreed upon by two persons. Final assessments are available in appendix 3.

Data extraction and analysis

Data were collected from the systematic reviews and presented as they appeared in the published reviews. Data were extracted by one reviewer and checked for accuracy by another. We extracted data presented as relative risks (RR) or odds ratios (OR), including the corresponding 95% confidence interval (CI). We present these data in Summary of findings tables, which also calculated illustrative absolute effect estimates based on baseline risk in the control groups of the included studies.

As we were asked to provide a rapid review of the literature, we have not performed any analyses to identify, for example, potential differences by subgroups, (e.g. different doses used or different treatment duration). We do however present data on subgroups if they have been reported in the included systematic reviews.

Grading the quality of evidence

Two persons assessed the overall documentation for each outcome by using GRADE (Grading of Recommendations, Assessment, Development and Evaluation, www.gradeworkinggroup.org). The method used involves an evaluation of factors influencing our confidence in the reported estimates. It includes an evaluation of study type, study quality/risk of bias, consistency of results between trials, directness (how similar the population, intervention, and outcomes are among the trials and the objectives of this report), precision of the estimates and publication bias. GRADE may also take into account whether there are strong associations between the intervention and the outcome/very large effect, dose-response associations or if all confounding variables would have reduced the effect. Finally the overall quality, or confidence in the estimate, was categorized as high, moderate, low or very low.

GRADE gives the following definition of the different levels of evidence.

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Results

Results of the literature search

We identified 308 publications through the literature search (figure 1). Of these, 86 were found to be potentially relevant, and full text copies were assessed. In reviewing the full text publications, we confirmed whether or not the publications fulfilled our inclusion criteria. If several publications covered the same topic, we used the most recent, or the most detailed. A list of all the publications that were considered in full text is presented in appendix 2 with reasons for exclusion for excluded publications. We were unable to retrieve two references in full text (12;13). However, based on the publications' dates and titles, it appeared that the treated topics were covered in more recent publications. Finally, 12 systematic reviews met the prespecified inclusion criteria.

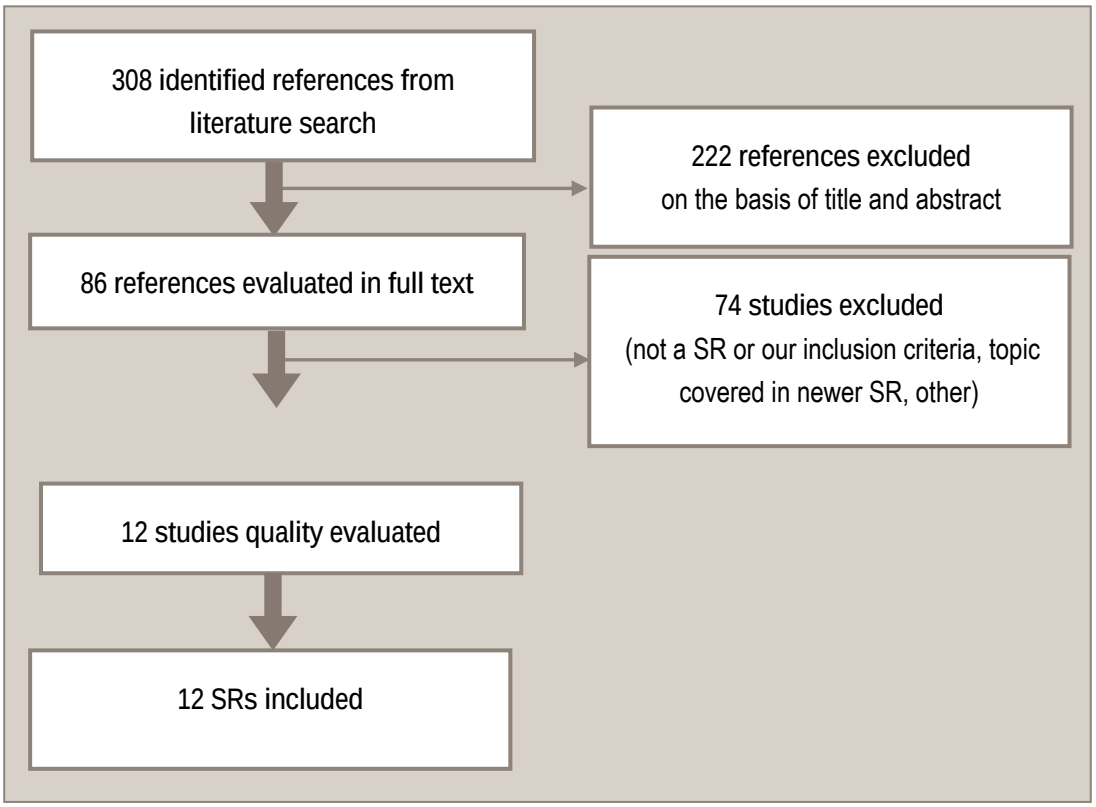

Figure 1 *Flowchart of selection process of systematic reviews.*

Description of included systematic reviews

We included 12 systematic reviews. They were all published during the last four years and covered different parts of this report's objectives. Most of the included studies were performed in North America and Europe. We rated the systematic reviews to be of high or moderate quality (see appendix 3).

Table 1 lists the included systematic reviews, gives a short summary of the outcomes reported, when the systematic search for literature was performed and the type of studies included. A more detailed description is presented when we report data for the different outcomes.

Table 1 – List of included systematic reviews

Publication (reference no.)	Search performed	Outcomes reported	Study types included
Algra 2012 (14)	Jan. 2011	Colorectal cancer - incidence Other cancers –incidence Cancer mortality	RCT, cohort, case-control
ATT coll. 2009 (15)	No date provided (Network and electronic databases)	Overall mortality Major extracranial bleeding	RCT
Baandrup 2013 (16)	Sept. 2012 (PubMed only)	Ovarian cancer- incidence	Case-control, cohort
Bosetti 2012 (17)	Sept. 2011 (PubMed/Medline)	12 selected cancer sites - incidence	Case-control,cohort
Choueiri 2013 (18)	June 2012	Kidney cancer - incidence	Case-control, cohort
Luo 2012 (19)	July 2011 (Medline only)	Breast cancer - incidence	RCT, case-control, cohort
Mills 2012 (low dose ASA) (20)	Dec. 2011	Cancer mortality All-cause mortality	RCT
Neill 2013 (21)	Dec 2011	Endometrial cancer - incidence	Cohort, case-control
Rothwell 2011 (22)	March 2010	Cancer mortality All-cause mortaltiy	RCT w/treatment ≥4years
Rothwell 2012 (23)	May 2011	Cancer mortality Overall mortality Cancer incidence Major bleeding	RCT w/treatment >90 days
Seshasai 2012 (24)	June 2011	Cancer mortality Nontrivial bleeding events All cause mortality Total bleeds	RCT
Wilson 2011 (25)	Dec. 2009	Risk of cancer - head and neck	Population-based prescribing database studies and case-control studies

Overall mortality in studies investigating ASA use

Overall mortality was reported in several systematic reviews (15;22-24). We present a short description of the included systematic reviews below and report the estimates of overall mortality associated with ASA use in table 2. Overall ASA use seemed to result in slightly lower overall mortality than no treatment; however this reduction was only statistically significant in one out of the four included systematic reviews. All studies were performed in patients needing primary or secondary prevention of vascular events.

Table 2 – All cause mortality associated with ASA use

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk ASA	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Overall mortality - primary prevention studies mostly low-dose ASA Follow-up: mean 6 years (24)	**38 per 1000**	**36 per 1000** (34 to 38)	**OR 0.94** (0.88 to 1)	102621 (9 studies)	⊕⊕⊕⊖ **moderate**[4]
Overall mortality - secondary prevention studies (15)	Events not reported by group[1]		**RR 0.90** (0.82 to 0.99)	17029 (16 studies)	⊕⊕⊕⊖ **moderate**[4]
Overall mortality - long term Follow-up: >5 years (22)	**111 per 1000**	**103 per 1000** (96 to 111)	**OR 0.92** (0.85 to 1)	25570 (8 studies)	⊕⊕⊕⊖ **moderate**[2,4]
Overall mortality - short term (prim.prev) Follow-up: >90 days (23)	**62 per 1000**	**57 per 1000** (53 to 62)	**OR 0.92** (0.85 to 1)	42356 (12 studies)	⊕⊕⊕⊖ **moderate**[3,4]

*The basis for the **assumed risk** is the calculated risk in the control group of the included studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the control group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

[1] Number of events by group not reported. However, number of overall events was 1856 out of 17029.
[2] Details of assessment of individual studies not provided. However, most studies were large RCTs and the authors of the systematic review had access to individual data.
[3] Details of assessment of individual studies not provided. However, most studies were large RCTs.
[4] Imprecision, chose to downgrade as one can argue that for such an outcome as overall mortality if either of the limits of the confidence interval were true, it could influence the decision to implement the intervention or not.

Overall mortality in primary prevention studies considering mostly low-dose ASA

Seshasai and colleagues aimed to assess the impact of ASA use on the primary prevention of vascular and non-vascular events (24). They included nine randomized placebo controlled trials with at least 1000 participants. Mean follow-up was 6.0 years. Three of the studies included only men, while in the remaining studies the percentage of men ranged from 28 to 55. The mean age was 57.3 years. Seven studies considered use of low doses of ASA, ranging from 100 mg every other day to 100 mg daily, accounting for approx. 75% of patients in the meta-analysis. The remaining two studies used 300-500 mg daily and 325 mg every other day. ASA seem to lower the overall mortality, the reported OR was 0.94 (0.88-1.00).

Overall mortality in secondary prevention studies

The Antithrombotic Trialists' (ATT) collaboration performed meta-analyses of individual patient data from randomized controlled trials published before 2009 (15). They included 6 primary prevention trials and 16 secondary prevention trials of vascular diseases. The secondary prevention trials were either post myocardial infarction (MI) or post transient ischemic attack (TIA) or stroke. The mean age was 56 and 62 years, respectively in the different subgroups of secondary prevention. A description of the dose of ASA or treatment duration was not included. ASA seem to lower the overall mortality, the reported RR based on the secondary prevention studies was 0.90 (0.82-0.99).

Overall mortality in studies examining ASA use for four years or longer

Rothwell and colleagues (2011) included in their systematic review randomized controlled trials of daily ASA use originally performed in both primary and secondary prevention of vascular events and with duration of trial treatment of ≥four years, and a range extending beyond five years (22). This led to inclusion of eight studies, four of which overlapped with those included by Seshasai and colleagues. In the other studies, ASA was used in 75 mg daily or in doses from 300-1200 mg daily. The mean percentage of men ranged from 52-100. ASA seem to lower the overall mortality, the reported OR was 0.92 (0.85-1.00) when total follow-up was 5 years or more.

Overall mortality in studies examining ASA use for 90 days or longer

In 2012, Rothwell and colleagues also published a systematic review with randomized controlled trials of daily ASA use for any dose, with duration of treatment of 90 days or more and compared to no ASA use (23). They used individual patient data if available, or extracted data from the publications. A total of 51 studies were identified, but not all studies were used for all outcomes. Overall mortality was reported based on 12 primary prevention studies. A description of included studies was not provided. ASA seem to lower the overall mortality, the reported OR was 0.92 (0.85-1.00).

Cancer related mortality in studies investigating ASA use

Cancer specific mortality was reported in several of the systematic reviews either as the main outcome of interest or as a subsidiary outcome (20;22;23). We present a short description of the included systematic reviews below and present the estimates of cancer mortality associated with ASA use in table 3. Overall, ASA use was associated with lower cancer mortality compared to no treatment. All the studies were performed in patients needing primary or secondary prevention of vascular events.

Table 3 – Cancer mortality associated with ASA use

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk **Control**	Corresponding risk **ASA**			
Cancer mortality - low dose 75-325 mg Follow-up: mean 33.6 months (20)	**26 per 1000**	**20 per 1000** (16 to 25)	**RR 0.77** (0.63 to 0.95)	16066 (11 studies)	⊕⊕⊕⊕ **high**[1]
Cancer mortality - long term 75 -100 mg Follow-up: >5 years (22)	**37 per 1000**	**30 per 1000** (25 to 36)	**OR 0.81** (0.68 to 0.97)	14245 (5 studies)	⊕⊕⊕⊕ **high**[2]
Cancer mortality - long term Follow-up: >5 years (22)	**30 per 1000**	**24 per 1000** (21 to 28)	**OR 0.79** (0.68 to 0.92)	25570 (8 studies)	⊕⊕⊕⊕ **high**[2]
Cancer mortality – any duration Follow-up: >90 days (23)	**18 per 1000**	**16 per 1000** (14 to 17)	**OR 0.87** (0.78 to 0.98)	69224 (34 studies)	⊕⊕⊕⊕ **high**[3]

*The basis for the **assumed risk** is the calculated risk in the control group of the included studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the control group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

[1] Details of assessment of individual studies not provided. However, the overview of methodological issues shows low risk of bias.
[2] Details of assessment of individual studies not provided. However, most studies were large RCTs and authors of systematic review had access to individual data.
[3] Details of assessment of individual studies not provided. However, most studies were large RCTs.

Cancer mortality in studies investigating low dose ASA use

Mills and colleagues included any randomized clinical trial that evaluated the use of low-dose ASA alone on a daily basis in any population (20). In this publication, low-dose ASA was defined as 75 to 325 mg per day. They identified 24 trials reporting on non-cardiovascular deaths. Of these, 11 reported on cancer deaths and they were all trials in secondary prevention of cardiovascular disease. Mean follow-up was 33.6 months. The studies included between 48 and 100 % men and the mean age was between 56 and 74 years. ASA reduced cancer mortality, the reported RR was 0.77 (0.63-0.95). The authors also showed a cumulative effect plot of the 11 trials. They showed that the protective elements of ASA seem to start after approximately four years.

Cancer mortality in studies investigating ASA use for 4 years or longer

Rothwell and colleagues (2011) conducted a systematic review where they included randomized controlled trials of daily ASA use originally performed in both primary and secondary prevention of vascular events and with duration of trial treatment of ≥four years, and a range extending beyond five years (22). This led to inclusion of eight studies. ASA reduced cancer mortality, they reported cancer mortality across all doses of ASA (OR: 0.79 (0.68-0.92)) and provided an estimate based solely on the five studies using low-dose ASA (OR: 0.81 (0.68-0.97)). Here low-dose was defined as 75-100 mg ASA. All five studies were also included by Mills and colleagues.

Cancer mortality in studies investigating ASA use for 90 days or longer

In the systematic review by Rothwell and colleagues (2012) that included daily ASA use in any dose for a duration of 90 days or more compared to no ASA use, data on cancer mortality was available from 34 trials (23). A detailed description of the studies was not included. ASA reduced cancer mortality, they reported an OR of 0.87 (0.78-0.98).

Cancer incidence in studies investigating ASA use

In the included systematic reviews, cancer incidence was mostly reported as incidence of specific cancers, but one systematic review reported overall cancer incidence. To answer the question raised by the Health Directorate on the possible role for ASA in cancer prevention, as adequately as possible, we focused on estimates of overall cancer incidence. The data are presented in table 4. Overall, the results from one systematic review indicate that ASA use was associated with lower cancer incidence. This decrease seemed most evident among studies with longer follow-up. Studies presenting specific cancer sites were also considered and results are presented in appendix 4.

Table 4 – Total cancer incidence associated with ASA use

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	**ASA**			
Cancer incidence - low dose Follow-up: >90 days (23)	**22 per 1000**	**20 per 1000** (18 to 22)[1]	**HR 0.88** (0.8 to 0.98)	77386 (6 studies)	⊕⊕⊕⊕ **high**[2]

*The basis for the **assumed risk** is the calculated risk in the control group of the included studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the control group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **HR:** Hazard ratio;

[1] Number of events calculated by adding numbers of events presented separately for different follow-up period
[2] Details of assessment of individuals studies not provided. However, most studies were large RCTs.

Total cancer incidence in studies examining low dose ASA use

The 2012 publication by Rothwell and colleagues included randomized controlled trials of daily use of any dose of ASA for 90 days or more compared to no ASA use (23). Studies were designed to investigate ASA use in primary prevention of vascular events. For evaluation of cancer incidence, they considered incident cancer cases from five studies combined with fatal cancers from one study. They included six trials of low dose ASA (75-100 mg/daily) compared to no such treatment or placebo. They used individual patient data if available, or extracted data from the publications. Mean duration of scheduled treatment was 3.6 to 8.2 years and 28.5-100% of study participants were men. ASA lowered the cancer incidence, the authors reported an overall hazard ratio of 0.88 (0.80-0.98). In addition, they reported odds ratios stratified by trial follow-up, showing increasing effect with increasing treatment du-

ration. For 0-2.9 years of follow-up, the OR was 1.01 (0.88-1.15), for 3.0-4.9 years the OR was 0.81 (0.67-0.98) and for ≥5 years the OR was 0.70 (0.56-0.88).

Adverse events in studies investigating ASA use

We present a short description of the included systematic reviews below and present the estimates of different adverse events associated with ASA use in table 5 (15;24). The studies were performed in patients needing primary or secondary prevention of vascular events. They only reported serious adverse events. Overall ASA use resulted in an increased risk of bleeding events compared to no treatment. This applied to both total and serious bleeding events.

Table 5. Adverse events associated with ASA use

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk **Control**	Corresponding risk **ASA**			
Total bleeds Follow-up: mean 6 years (24)	**374 per 1000**	**504 per 1000** (412 to 595)	**OR 1.70** (1.17 to 2.46)	100076 (9 studies)	⊕⊕⊕⊖ **moderate**[1]
Nontrivial bleeds Follow-up: mean 6 years (24)	**96 per 1000**	**122 per 1000** (108 to 137)	**OR 1.31** (1.14 to 1.50)	100076 (9 studies)	⊕⊕⊕⊕ **high**
Nontrivial bleeds - low-dose (<100 mg/day) Follow-up: 3.6 - 10.1 years[2] (24)	Events not reported		**OR 1.40** (1.08 to 1.82)	0 (2 studies)	⊕⊕⊕⊕ **high**[3]
Major extracranial bleed - Primary prevention Follow-up: 3.7-10 years[2] (15)	Reported as % with events per year[5]		**RR 1.54** (1.30 to 1.82)	0 (6 studies)	⊕⊕⊕⊕ **high**[4]
Major extracranial bleed - Secondary prevention Follow-up: Not reported (15)	Reported as % with events per year[8]		**RR 2.69** (1.25 to 5.76)	0 (7 studies[6])	⊕⊕⊕⊖ **moderate**[4,7]
Haemorrhagic stroke - Primary prevention Follow-up: 3.7-10 years[2] (15)	Reported as % with events per year[9]		**RR 1.32** (1.00 to 1.75)	0 (6 studies)	⊕⊕⊕⊖ **moderate**[4,7]
Haemorrhagic stroke - Secondary prevention Follow-up: Not reported (15)	Reported as % with events per year[11]		**RR 1.67** (0.97 to 2.90)	0 (15 studies)	⊕⊕⊕⊖ **moderate**[4,7,10]

*The basis for the **assumed risk** is the calculated risk in the control group of the included studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the control group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

[1] Unexplained heterogeneity. Reported I^2=98%
[2] Mean or median follow-up range
[3] No information on inconsistency was reported
[4] Details of assessment of individual studies not provided. However, most studies were large RCTs.
[5] Number of events per year reported. In ASA group there is 335 events (0.10% / year), and 219 events (0.07% / year) in control group.
[6] Major bleeds were recorded for only 5 of the 16 studies on secondary prevention. The authors reported that the meta-analysis might be unreliable
[7] The total number of events is less than 300 (a threshold rule-of-thumb value) (based on: Mueller et al. Ann Intern Med. 2007;146:878-881)
[8] Number of events per year reported. In ASA group there is 23 events (0.25% / year), and 6 events (0.06% / year) in control group.
[9] Number of events per year reported. In ASA group there is 116 events (0.04% / year), and 89 events (0.03% / year) in control group.
[10] 95% confidence interval around the pooled estimate of effect includes both 1) no effect and 2) appreciable benefit

or appreciable harm. GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.
[11] Number of events per year reported. In ASA group there is 36 events (0.16% / year), and 19 events (0.08% / year) in control group.

Bleeding events in primary prevention studies considering mostly low-dose ASA

Seshasai and colleagues aimed to assess the impact of ASA use in primary prevention studies on vascular and nonvascular outcomes (24). They included nine randomized placebo controlled trials with at least 1000 participants. Mean follow-up was 6.0 years. Three of the studies included only men, otherwise 28-55% of trial participants were men. The mean age was 57.3 years. Seven studies used ASA in low doses, ranging from 100 mg every other day to 100 mg daily, accounting for approximately 75% of patients included in the meta-analysis. The remaining two studies used 300-500 mg daily or 325 mg every other day. The systematic review reported an increase in total bleeds (OR 1.70 (1.17-2.46)) and an outcome defined as nontrivial bleeding (OR 1.31 (1.14-1.50)). This outcome was created because definition of major bleeding varied across studies. Nontrivial bleeding is a composite endpoint including fatal bleeding from any site, cerebrovascular or retinal bleeding, bleeding from hollow viscus, bleeding requiring hospitalization and/or transfusion or study-defined major bleeding regardless of source. The authors of the systematic review included subgroup analysis based on average daily dose of ASA. For doses of 100 mg or above, the OR for nontrivial bleeds was 1.26 (0.99-1.61), while for doses less than 100 mg the OR was 1.40 (1.08-1.82).

Bleeding events in primary and secondary prevention studies

The ATT collaboration published meta-analyses of individual patient data from randomized controlled trials (15). The systematic review included six primary prevention trials and 16 secondary prevention trials. In the primary prevention studies four studies used ASA in 100 mg every other day to 100 mg daily; two studies used 325 mg or 500 mg daily. Three studies included only men and one study only women. Mean follow-up was 3.7-10 years. Mean age was 56 years. The studies in secondary prevention of vascular disease were described as post MI studies and post TIA/stroke studies. Mean age and percent men were 56 years with 90% men in post MI studies and 62 years with 70% men in post TIA/stroke studies. The dose of ASA and duration of follow up were not reported. Authors reported hemorrhagic strokes and major extra cranial bleedings, which were mainly gastrointestinal and usually defined as a bleed requiring transfusion or resulting in death. In studies performed in patients needing primary prevention the RR of major extra cranial bleeds was 1.54 (1.30-1.82) and for hemorrhagic stroke 1.32 (1.00-1.75), compared with persons not taking ASA. In studies performed in secondary prevention of vascular disease the RR for major extra cranial bleeds was 2.69 (1.25-5.76) and for hemorrhagic stroke the RR was 1.67 (0.97-2.90). All RR show a clear increase in bleeding events for those taking ASA.

Discussion

In this rapid review, we have systematically reviewed and summarized 12 systematic reviews of ASA use compared with no treatment or placebo in patients without prior cancer or increased risk of cancer. We examined ASA use with regard to its effect on overall mortality, cancer mortality, cancer incidence and adverse events/side effect.

Summary of results

Based on studies originally designed and performed to examine the role of ASA use in primary and secondary prevention of vascular events, the results indicated a lower overall mortality associated with ASA use. Results also showed that ASA use resulted in lower cancer mortality and cancer incidence. This benefit, however, came at a cost of a clear increase in risk of bleeding events.

To illustrate the different aspects of the results, we include one example based on results identified for low dose ASA in the included systematic reviews. If one assumes a group of 1000 persons the results show that treatment with low-dose ASA for more than five years could reduce the cancer mortality with 7 persons (from 37 to 30 cancer deaths) (22). When taking the confidence interval into account, it may be reduced with as much as 12 persons or only by 1 person. In comparison, serious bleeding events could increase by 26 events (from 96 bleeds per 1000 treated to 122 per 1000) with ASA use (24). Taking the confidence interval into account, it may increase to as few as 12 extra events or as many as 41 extra events. The risk estimates of serious bleeding events come from studies with mean treatment and follow-up of six years.

Further, subgroup analyses in the systematic reviews indicated that the beneficial effects of ASA increased with duration of use. When available we have presented analyses stratified by treatment follow-up. It appears that a potential benefit only seem to be apparent after some time. Rothwell and colleagues reported a reduced cancer incidence from three years onwards, and reduced cancer mortality from five years onwards (23). Similarly, Mills and colleagues reported that the protective elements of ASA seem to start after approximately four years (20). As cancer does not develop shortly after a certain exposure, it is expected that the reduction effect of ASA use would have a long latency period before it has a significant effect on cancer

risk. This raises questions about what would be an appropriate time to start treatment with ASA and for how long a period, if it were to be used in cancer prevention.

Prevention strategies are designed to reduce the risk of something happening in the future. The intervention would be delivered to a larger population to benefit some. However, possible risks of the intervention may be inherent for the entire population and for the entire duration of exposure. Hence, it is important to evaluate the possible risks and benefits, or possibly to identify populations with a high risk of cancer who would benefit the most from such an intervention. Different persons may balance this differently based on their own values and preferences.

This overview of systematic review has focused on the effects of ASA use as possible chemoprevention for cancer. While examining the effect of ASA on other clinical outcomes is out of the scope of the present report, a public health decision aiming at, for example, proposing ASA to the wider community would need to consider the possible effect on other clinical outcomes as well. Additionally, cost-effectiveness analyses for the Norwegian setting would have to be performed to assess whether all priority criteria were fulfilled before implementation in the health care.

Strengths and weaknesses of this review

Use of systematic reviews

This rapid review is based on a systematic search of published systematic reviews. This approach limits the duplication of work and overall use of resources. However, as we did not examine single studies included in the systematic reviews, results not brought forward by systematic review authors may have been missed.

When reviewing articles for inclusion in this report, we noticed that authors made slightly different choices of which articles to include, and in which study design the articles were classified. However, there was substantial overlap in the included studies and estimates of effect and safety endpoints were mostly in the same direction. We have presented results from the most updated systematic reviews to increase the likelihood that the most recent data were included.

Quality assessments and quality of the documentation

To be classified as a systematic review, a clear description of the objectives and method used to select studies included for analyses had to be provided. We did not exclude systematic reviews on the basis of limited, or lack of, evaluation of quality or risk of bias of the included studies. This is, however, a debatable approach. Most authors did present some sort of description of the included studies and/or tables with study characteristics to an extent that made it possible for us to use GRADE to assess our confidence in the estimates presented.

Most of the studies used to estimate the association between ASA use and cancer in our rapid review of systematic reviews are based on randomized controlled trials. This design is usually considered as the gold standard, or best choice, when examining the effect of interventions. However, several authors summarized observational studies in the quest to estimate incidence of specific cancer types. Even with adjustment for known confounders, results from such studies are less robust, and we generally have less confidence in the effect estimates from non-randomized trials. We included the results for information, but did not prioritize making individual assessments of the quality of the documentation for each cancer type.

Evidence base originally designed for other objectives

Although the possible role of ASA in cancer prevention has been discussed for several years, none of the included systematic reviews identified any long-term randomized controlled studies designed purposely to investigate ASA use for cancer prevention. The published estimates of the association between ASA use and the risk of cancer or cancer mortality resulted from analyses of patients included in randomized controlled trials examining ASA use for primary or secondary prevention of vascular disease. Trials included in the systematic reviews were mostly conducted in the 1970s and 1980s. However, before a decision regarding ASA use to prevent cancer can be made, one may want to perform a well-designed randomized controlled trial in the intended population with the intended dose of ASA and report on both effect on cancer and on adverse events simultaneous.

An extrapolation of results in one population to another, or to a more general population, should only be done after careful consideration. The results presented here are from studies performed in a setting of primary or secondary prevention of cardiovascular diseases, while a possible cancer prevention program may include a much wider population. Different background risks could influence the absolute effects even if the relative effects remained. But different populations may also show different relative effects.

Some review authors have included studies with ASA use given only every other day, while others have excluded them because they state that dosing every other day may not be adequate to maintain the inhibition of COX enzymes in the plausible biological mechanism of preventing cancer. However, meta-analyses of the association of ASA use on cancer mortality performed with and without studies of alternate day ASA use showed similar estimates (24). Furthermore, the doses used in the studies ranged from low- to high doses of ASA and varied in the duration of use. As far as possible, we have presented data by separate categories of dose, treatment duration and follow-up period after the study. The risk is usually calculated on an intention-to-treat principle, leaving the possibility that high drop-out rates in the treatment arms in the studies could lead to an underestimation of potential effects and adverse

events; similarly if the control group start using ASA after the trial end, this can also influence the results.

In observational studies, exposure ascertainment, such as ASA use, is often based on self-report and the accuracy of such reports' may be a problem. It may therefore be more difficult to measure specific aspects of ASA use such as dose, frequency and duration of use. However, the results are mainly in the same direction across all study designs, showing a possible protective effect of ASA use on cancer risk.

Effect of an exposure on cancer prevention is best measured by assessing the effect of that exposure on cancer risk (incidence). However, some studies that have examined the association between ASA use and cancer incidence have considered cancer mortality and incidence together as an outcome. The systematic review we identified reported on cancer incidence based on data from four studies reporting cancer incidence and from one study reporting only fatal cancers. This approach could also underestimate the incidence of cancer, as non-fatal cancers are not part of the evidence. From such an analysis, one cannot disentangle the possible effect of ASA use on the risk of getting cancer, an effect on the biology and aggressiveness of the cancer or from a possible treatment effect on the cancer.

Conclusion

In this rapid review, we investigated the potential use of ASA in cancer prevention.

Based on studies originally designed and performed to examine the role of ASA use in primary and secondary prevention of vascular events, the results indicated a lower overall mortality associated with ASA use. Results also showed that ASA use resulted in lower cancer mortality and cancer incidence. This benefit, however, came at a cost of a clear increase in bleeding events.

Need for further research

The current evidence for ASA in cancer prevention originates from randomized controlled trials examining ASA use in primary or secondary prevention of vascular disease and from observational studies. In order to arrive at a better evidence base regarding the effect of ASA in prevention of cancer, well designed randomized controlled trials in the intended populations with the intended doses of ASA and report simultaneously on both effects on cancer and adverse events associated with ASA use might be useful.

References

1. Vainio H, Morgan G. Aspirin for the second hundred years: new uses for an old drug. Pharmacol Toxicol 1997;81(4):151-2.

2. Vainio H, Morgan G, Elwood P. The public health potential of aspirin. Pharmacol Toxicol 2002;91(2):49-50.

3. Baron JA, Sandler RS. Nonsteroidal anti-inflammatory drugs and cancer prevention. Annu Rev Med 2000;51:511-23.

4. Vainio H, Morgan G, Kleihues P. An international evaluation of the cancer-preventive potential of nonsteroidal anti-inflammatory drugs. Cancer Epidemiol Biomarkers Prev 1997;6(9):749-53.

5. Helsedirektoratet. Nasjonale retningslinjer for primærforebygging av hjerte- og karsykdommer. 2009.

6. Bennett A, Tacca MD, Stamford IF, Zebro T. Prostaglandins from tumours of human large bowel. Br J Cancer 1977;35(6):881-4.

7. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 1971;231(25):232-5.

8. Kune GA, Kune S, Watson LF. Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer Study. Cancer Res 1988;48(15):4399-404.

9. WHO Ask the expert. [Oppdatert 2008; Lest 16.8.2013]. Tilgjengelig fra: http://www.who.int/features/qa/15/en/index.html

10. Cancer Registry of Norway. Cancer in Norway 2010 – Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway; 2012.

11. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. BMJ 2000;321(7270):1183-7.

12. Rostom A, Dube C, Lewin G. Use of aspirin and NSAIDs to prevent colorectal cancer; an evidence synthesis. 2007.

13. Hailey D, Harstall C. Aspirin in the primary prevention of cardiovascular disease and colon cancer. 1997.

14. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: A systematic comparison of evidence from observational studies versus randomised trials. The Lancet Oncology 2012;13(5):May.

15. Antithrombotic Trialists' A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. The Lancet 2009;373(9678):20090530-0605.

16. Baandrup L, Faber MT, Christensen J, Jensen A, Andersen KK, Friis S, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. Acta Obstet Gynecol Scand 2013;92(3):245-55.

17. Bosetti C, Rosato V, Gallus S, Cuzick J, La VC. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol 2012;23(6):1403-15.

18. Choueiri TK, Je Y, Cho E. Analgesic use and the risk of kidney cancer: A meta-analysis of epidemiologic studies. International journal of cancer Journal international du cancer 2013;

19. Luo T, Yan HM, He P, Luo Y, Yang YF, Zheng H. Aspirin use and breast cancer risk: a meta-analysis. Breast Cancer Res Treat 2012;131(2):581-7.

20. Mills EJ, Wu P, Alberton M, Kanters S, Lanas A, Lester R. Low-dose aspirin and cancer mortality: a meta-analysis of randomized trials. Am J Med 2012;125(6):560-7.

21. Neill AS, Nagle CM, Protani MM, Obermair A, Spurdle AB, Webb PM. Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: A case-control study, systematic review and meta-analysis. Int J Cancer 2013;132(5):01.

22. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377(9759):31-41.

23. Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 2012;doi.

24. Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med 2012;172(3):209-16.

25. Wilson JC, Anderson LA, Murray LJ, Hughes CM. Non-steroidal anti-inflammatory drug and aspirin use and the risk of head and neck cancer: A systematic review. Cancer Causes Control 2011;22(5):May.

Appendix

Appendix 1 - Literature search

Databases: Embase, Ovid Medline, Cohrane Database of Systematic Reviews (CDSR), Centre for Reviews and Disseminations) (CRD)
Date : 26.02.2013
Study design: Systematic reviews. Ovids filter"reviews (maximizes specificity)" + textword: systematic* review*
Result: 308 (384 including duplicates)
Performed by: Ingrid Harboe, research librarian

Ovid databases – Embase and MEDLINE

Embase 1980 to 2013 Week 07. Ovid MEDLINE(R) In-Process & Other Non Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Date: 26.02.2013
Result: 272

1	acetylsalicylic acid/ use emez
2	salicylic acid derivative/ use emez
3	exp Salicylic Acids/ use prmz
4	(acetylsalicy*lic acid? or asa or aspirin* or salicy*lic acid? or "albyl e" or disp*ril or acetysal).tw.
5	or/1-4
6	exp neoplasm/ use emez
7	exp neoplasms/ use prmz
8	(cancer* or neoplasm* or neoplasia or tumo*r?).tw.
9	or/6-8
10	5 and 9
11	10 and systematic* review*.tw.
12	limit 10 to "reviews (maximizes specificity)"
13	or/11-12
14	limit 13 to yr="1992 -Current"
15	remove duplicates from 13

Cochrane database of systematic reviews (CDSR)

Date: 25.02.2013
Result: 38 (6 CDSR, 26 Other Reviews, 6 Technology Assessments)

1 MeSH descriptor: [Salicylic Acids] explode all trees
2 (acetylsalicy*lic acid* or asa or aspirin* or salicy*lic acid* or "albyl e" or disp*ril or acetysal):ti,ab,kw
3 #1 or #2
4 MeSH descriptor: [Neoplasms] explode all trees
5 (cancer* or neoplasm* or neoplasia or tumor* or tumour*):ti,ab,kw
6 #4 or #5
7 #3 and #6 from 1992 to 2013ASA and cancer

Database: Centre for Reviews And Disssemination: DARE and HTA

Date: 25.02.2013
Result: 72 ASA neoplasms

1 MeSH DESCRIPTOR Salicylic Acids EXPLODE ALL TREES
2 ("acetylsalicylic acid*" or asa or aspirin* or "salicylic acid*" or "albyl e" or dispril or acetysal)
3 #1 OR #2
4 MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES
5 (cancer* or neoplasm* or neoplasia or tumor* or tumour*)
6 #4 OR #5
7 #3 AND #6
8 (#11) IN DARE, HTA

PubMed

Date: 26.02.2013
Result: 2

5 Search ((#3) AND #4) 4 Filters: Systematic Reviews; Publication date from 2012/01/01 to 2013/12/31
4 Search ((#1) AND #2) AND #3 Schema: all Filters: Meta-Analysis
3 Search pubstatusaheadofprint
2 Search (cancer*[Title/Abstract]) OR neoplasm*[Title/Abstract]
1 Search (acetylsalicylic acid[Title/Abstract]) OR aspirin[Title/Abstract]

Appendix 2 - List of publications reviewed in full text

If no exclusion reason is stated and presented in italics, the systematic review is included.

Reason for exclusion:

1. Not a systematic review (clear aim, description of search procedures, defined inclusion criteria, methods to ensure studies were not missed). Not enough information.
2. ASA not used as intervention or comparator, not our outcomes of interest
3. The patient group or outcomes are covered in a more recent publication
4. Other

	Publication	1	2	3	4
1.	Abnet CC, Freedman ND, Kamangar F, Leitzmann MF, Hollenbeck AR, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: Results from a cohort study and a meta-analysis. Br J Cancer 2009;100(3):10.			X	
2.	*Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: A systematic comparison of evidence from observational studies versus randomised trials. The Lancet Oncology 2012;13(5):May.*				
3.	Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. JAMA 1999;282(21):2058-67.			X	
4.	Antiplatelet TC. Collaborative overview of randomised trials of antiplatelet therapy - II: maintenance of vascular graft or arterial patency by antiplatelet therapy. BMJ 1994;308:159-68.			X	
5.	Antiplatelet TC. Collaborative overview of randomised trials of antiplatelet therapy - III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. BMJ 1994;308:235-46.		X		
6.	*Antithrombotic Trialists' A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. The Lancet 2009;373(9678):20090530-0605.*				
7.	Asano TK, McLeod RS. Non steroidal anti-inflammatory drugs (NSAID) and aspirin for preventing colorectal adenomas and carcinomas. cochrane database of systematic reviews 2004;(1):CD004079.		X		
8.	*Baandrup L, Faber MT, Christensen J, Jensen A, Andersen KK, Friis S, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. Acta Obstet Gynecol Scand 2013;92(3):245-55.*				
9.	Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer: a meta-analysis. Br J Clin Pharmacol 2005;60(2):194-203.			X	
10.	*Bosetti C, Rosato V, Gallus S, Cuzick J, La VC. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol 2012;23(6):1403-15.*				
11.	Bretthauer M, Hoff G. [Prevention and early diagnosis of colorectal cancer]. [Review] [35 refs] [Norwegian]. Tidsskr Nor Laegeforen 2007;127(20):2688-91.	X			
12.	Capurso G, Schunemann HJ, Terrenato I, Moretti A, Koch M, Muti P, et al. Meta-analysis: the use of non-steroidal anti-inflammatory drugs and pancreatic cancer risk for different exposure categories. Aliment Pharmacol Ther 2007;26(8):1089-99.			X	
13.	Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: A systematic review. J Pain Symptom Manage 2003;26(5):November.		X		
14.	*Choueiri TK, Je Y, Cho E. Analgesic use and the risk of kidney cancer: A meta-analysis of epidemiologic studies. International journal of cancer Journal international du cancer 2013;*				
15.	Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. J Natl Cancer Inst 2009;101(4):256-66.			X	

16.	Cooper K, Squires H, Carroll C, Papaioannou D, Booth A, Logan RF, et al. Chemoprevention of colorectal cancer: systematic review and economic evaluation. Health Technol Assess 2010;14(32):1-205.			X	
17.	Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. Gastroenterology 2003;124(1):47-56.			X	
18.	Daugherty SE, Pfeiffer RM, Sigurdson AJ, Hayes RB, Leitzmann M, Schatzkin A, et al. Nonsteroidal antiinflammatory drugs and bladder cancer: a pooled analysis. [Review]. Am J Epidemiol 2011;173(7):721-30.	X			
19.	Davies RA, Maher CG, Hancock MJ. A systematic review of paracetamol for non-specific low back pain. Eur Spine J 2008;17(11):1423-30.		X		
20.	De BG, Sacco M, Strippoli GFM, Pellegrini F, Graziano G, Tognoni G, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: Meta-analysis of randomised controlled trials. BMJ 2009;339(7732):2009.			X	
21.	Deffieux X, Touboul C, Uzan C, Faivre E, Frydman R, Fernandez H, et al. [Chemoprevention and prophylactic surgery in ovarian carcinoma]. [Review] [58 refs] [French]. J Gynecol Obstet Biol Reprod (Paris) 2007;36(8):756-63.	X			
22.	Dube C, Rostom A, Lewin G, Tsertsvadze A, Barrowman N, Code C, et al. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med 2007;146(5):365-75.			X	
23.	Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 2007;369(9573):12.			X	
24.	Garcia Rodriguez LA, Hernandez-Diaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. Br J Clin Pharmacol 2001;52(5):563-71.			X	
25.	Girolami B, Bernardi E, Prins MH, ten Cate JW, Prandoni P, Simioni P, et al. Antiplatelet therapy and other interventions after revascularisation procedures in patients with peripheral arterial disease: a meta-analysis. Eur J Vasc Endovasc Surg 2000;19(4):370-80.			X	
26.	Gonzalez-Perez A, Garcia Rodriguez LA, Lopez-Ridaura R. Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: A metal-analysis. BMC Cancer 2003;3			X	
27.	Hailey D, Harstall C. Aspirin in the primary prevention of cardiovascular disease and colon cancer. 1997.				X
28.	Hart AR, Kennedy H, Harvey I. Pancreatic cancer: a review of the evidence on causation. [Review] [124 refs]. Clinical Gastroenterology & Hepatology 2008;6(3):275-82.	X			
29.	Herendeen JM, Lindley C. Use of NSAIDs for the chemoprevention of colorectal cancer. [Review] [123 refs]. Ann Pharmacother 2003;37(11):1664-74.	X			
30.	Hoffmeister M, Chang-Claude J, Brenner H. Do older adults using NSAIDs have a reduced risk of colorectal cancer? Drugs Aging 2006;23(6):513-23.			X	
31.	Jolly K, Cheng KK, Langman MJS. NSAIDs and gastrointestinal cancer prevention. Drugs 2002;62(6):2002.			X	
32.	Jones R, Rubin G, Berenbaum F, Scheiman J. Gastrointestinal and Cardiovascular Risks of Nonsteroidal Anti-inflammatory Drugs. Am J Med	X			

	2008;121(6):June.				
33.	Kanik EA, Canbaz H, Colak T, Aydin S. Chemopreventive effect of nonsteroidal anti-inflammatory drugs on the development of a new colorectal polyp or adenoma in a high-risk population: A meta-analysis. Current Therapeutic Research - Clinical and Experimental 2004;65(4):July/August.		X		
34.	Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis: meta-analysis of randomised trials. BMJ 2006;332:1302.	X			
35.	Kelley MJ, McCrory DC. Prevention of lung cancer: summary of published evidence. Chest 2003;123(1 Supplement):50S-9S.			X	
36.	Khuder SA, Mutgi AB. Breast cancer and NSAID use: A meta-analysis. Br J Cancer 2001;84(9):04.			X	
37.	Kwok CS, Loke YK. Critical overview on the benefits and harms of aspirin. Pharmaceuticals 2010;3(5):2010.			X	
38.	Larsson SC, Giovannucci E, Bergkvist L, Wolk A. Aspirin and nonsteroidal anti-inflammatory drug use and risk of pancreatic cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15(12):2561-4.			X	
39.	Liao LM, Vaughan TL, Corley DA, Cook MB, Casson AG, Kamangar F, et al. Nonsteroidal anti-inflammatory drug use reduces risk of adenocarcinomas of the esophagus and esophagogastric junction in a pooled analysis. Gastroenterology 2012;142(3):March.	X			
40.	*Luo T, Yan HM, He P, Luo Y, Yang YF, Zheng H. Aspirin use and breast cancer risk: a meta-analysis. Breast Cancer Res Treat 2012;131(2):581-7.*				
41.	Mahmud S, Franco E, Aprikian A. Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis. Br J Cancer 2004;90(1):93-9.			X	
42.	Mahmud SM, Franco EL, Aprikian AG. Use of nonsteroidal anti-inflammatory drugs and prostate cancer risk: a meta-analysis. Int J Cancer 2010;127(7):1680-91.			X	
43.	Mangiapane S, Blettner M, Schlattmann P. Aspirin use and breast cancer risk: a meta-analysis and meta-regression of observational studies from 2001 to 2005. Pharmacoepidemiology and Drug Safety 2008;17(2):115-24.			X	
44.	Mc Menamin UC, Murray LJ, Higgins C, Hughes CM, Cardwell CCR, Cantwell MM. Non-steroidal anti-inflammatory drugs and colorectal cancer progression and survival: A systematic review. Pharmacoepidemiology and Drug Safety Conference: 28th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, ICPE 2012 Barcelona Spain Conference Start: 20120823 Conference End: 20120826 Conference Publication: (var pagings) 2012;21(pp 407-408):August.	X			
45.	McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Medicine 2011;8(9):e1001098.		X		
46.	Meade T. Primary prevention of ischaemic cardiovascular disorders with antiplatelet agents. Antiplatelet Agents Handbook of Experimental Pharmacology 2012;210(pp 565-605):2012.	X			
47.	*Mills EJ, Wu P, Alberton M, Kanters S, Lanas A, Lester R. Low-dose aspirin and cancer mortality: a meta-analysis of randomized trials. Am J Med*				

	2012;125(6):560-7.				
48.	Murphy MA, Trabert B, Yang HP, Park Y, Brinton LA, Hartge P, et al. Non-steroidal anti-inflammatory drug use and ovarian cancer risk: Findings from the NIH-AARP Diet and Health Study and systematic review. Cancer Causes Control 2012;23(11):November.			X	
49.	*Neill AS, Nagle CM, Protani MM, Obermair A, Spurdle AB, Webb PM. Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: A case-control study, systematic review and meta-analysis. Int J Cancer 2013;132(5):01.*				
50.	Ni X, Ma J, Zhao Y, Wang Y, Wang S. Meta-analysis on the association between non-steroidal anti-inflammatory drug use and ovarian cancer. Br J Clin Pharmacol 2013;75(1):January.			X	
51.	Oh S-W, Myung S-K, Park JY, Lee CM, Kwon HT. Aspirin use and risk for lung cancer: A meta-analysis. Ann Oncol 2011;22(11):November.			X	
52.	Paganini-Hill A. Aspirin and the prevention of colorectal cancer: a review of the evidence. Semin Surg Oncol 1994;10(3):158-64.	X			
53.	Peters CJ, Fitzgerald RC. Systematic review: The application of molecular pathogenesis to prevention and treatment of oesophageal adenocarcinoma. Aliment Pharmacol Ther 2007;25(11):June.		X		
54.	Rostom A, Dube C, Lewin G, Tsertsvadze A, Barrowman N, Code C, et al. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med 2007;146(5):376-89.		X		
55.	Rostom A, Dube C, Lewin G. Use of aspirin and NSAIDs to prevent colorectal cancer; an evidence synthesis. 2007.				X
56.	*Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377(9759):31-41.*				
57.	Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet 2012;doi.		X		
58.	Rothwell PM. Meta-analysis: Aspirin reduces risk for colon cancer and related mortality at 20 years, particularly when taken for >= 5 years. Ann Intern Med 2011;154(6):March.	X			
59.	*Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 2012;doi.*				
60.	Salvo F, Fourrier-Reglat A, Bazin F, Robinson P, Riera-Guardia N, Haag M, et al. Cardiovascular and gastrointestinal safety of NSAIDs: A systematic review of meta-analyses of randomized clinical trials. Clin Pharmacol Ther 2011;89(6):June.			X	
61.	Schnitzer TJ, Ferraro A, Hunsche E, Kong SX. A comprehensive review of clinical trials on the efficacy and safety of drugs for the treatment of low back pain. J Pain Symptom Manage 2004;28(1):July.	X			
62.	Seshasai S. Review: Aspirin does not reduce CHD or cancer mortality but increases bleeding. Ann Intern Med 2012;156(12):19.	X			

63.	*Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med 2012;172(3):209-16.*				
64.	Silva MT, Galvao TF, Zimmerman IR, Pereira MG, Lopes LC. Non-aspirin non-steroidal anti-inflammatory drugs for the primary chemoprevention of non-gastrointestinal cancer: Summary of evidence. Curr Pharm Des 2012;18(26):2012.		X		
65.	Singh S, Singh A, Paul SP, Murad MH, Iyer P. Statins and the risk of esophageal cancer: A systematic review and meta-analysis acg/astrazeneca fellow award. American Journal of Gastroenterology Conference: 77th Annual Scientific Meeting of the American College of Gastroenterology Las Vegas, NV United States Conference Start: 20121019 Conference End: 20121024 Conference Publication: (var pagings) 2012;107(pp S11-S12):October.	X			
66.	Sommer IE, De WL, Begemann M, Kahn RS. Nonsteroidal anti-inflammatory drugs in schizophrenia: Ready for practice or a good start? A meta-analysis. J Clin Psychiatry 2012;73(4):April.	X			
67.	Sun L, Yu S. Meta-analysis: Non-steroidal anti-inflammatory drug use and the risk of esophageal squamous cell carcinoma. Dis Esophagus 2011;24(8):November.			X	
68.	Takkouche B, Regueira-Mendez C, Etminan M. Breast cancer and use of non-steroidal anti-inflammatory drugs: a meta-analysis. J Natl Cancer Inst 2008;100(20):15.			X	
69.	Tang CL. Chemoprevention of colorectal cancer--experimental approach and clinical applications. [Review] [70 refs]. Ann Acad Med Singapore 2003;32(2):169-75.	X			
70.	Tian W, Zhao Y, Liu S, Li X. Meta-analysis on the relationship between non-steroidal anti-inflammatory drug use and gastric cancer. Eur J Cancer Prev 2010;19(4):288-98.			X	
71.	Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086.		X		
72.	Tsoi KK, Ng SC, Hirai HW, Chan FK, Sung JJ. Low-dose aspirin cannot prevent colorectal cancer: A meta-analysis of randomized controlled trials. Journal of Gastroenterology and Hepatology Conference: Asia Pacific Digestive Week Kuala Lumpur Malaysia Conference Start: 20100919 Conference End: 20100922 Conference Publication: (var pagings) 2010;25(pp A16-A17):September.	X			
73.	Wang F, Lv ZS, Fu YK. Nonsteroidal anti-inflammatory drugs and esophageal inflammation - Barrett's esophagus - adenocarcinoma sequence: a meta-analysis. Dis Esophagus 2011;24(5):318-24.			X	
74.	Wang W-H, Liu F-X, Wang J, Hu F-L. Use of non-steroidal anti-inflammatory drug and colorectal polyps: A systematic review and Meta-analysis. [Chinese]. World Chinese Journal of Digestology 2008;16(24):August.				X
75.	Wang WH, Huang JQ, Zheng GF, Lam SK, Karlberg J, Wong BCY. Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: A systematic review and meta-analysis. J Natl Cancer Inst 2003;95(23):03.			X	
76.	Wang Y-P, Pan T, Yang J-L, Wang Q, Gan T. Nonsteroidal anti-inflammatory drugs for prevention of colorectal neoplasms: A systematic review. Chinese Journal of Evidence-Based Medicine 2005;5(6):1672-2531.			X	

77.	Wang YP, Wang Q, Gan T, Pan T, Yang JL. Non-steroidal anti-inflammatory agents for chemoprevention of colorectal polyps: a meta-analysis. [Chinese]. Zhonghua nei ke za zhi [Chinese journal of internal medicine] 2004;43(1):Jan.			X	
78.	Watson HG, Chee YL. Aspirin and other antiplatelet drugs in the prevention of venous thromboembolism. Blood Rev 2008;22(2):March.	X			
79.	Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. Arch Intern Med 2002;162(19):2197-202.			X	
80.	*Wilson JC, Anderson LA, Murray LJ, Hughes CM. Non-steroidal anti-inflammatory drug and aspirin use and the risk of head and neck cancer: A systematic review. Cancer Causes Control 2011;22(5):May.*				
81.	Wilson JC, Murray LJ, Hughes CM, Anderson LA. Non-steroidal anti-inflammatory drug and aspirin use and the risk of malignant melanoma - A systematic review and meta-analysis. Pharmacoepidemiology and Drug Safety Conference: 28th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, ICPE 2012 Barcelona Spain Conference Start: 20120823 Conference End: 20120826 Conference Publication: (var pagings) 2012;21(pp 419):August.	X			
82.	Winberg H, Lindblad M, Lagergren J, Dahlstrand H. Risk factors and chemoprevention in Barrett's esophagus - An update. Scand J Gastroenterol 2012;47(4):April.	X			
83.	Xu J, Yin Z, Gao W, Liu L, Wang R, Huang P, et al. Meta-analysis on the association between nonsteroidal anti-inflammatory drug use and lung cancer risk. Clinical Lung Cancer 2012;13(1):44-51.			X	
84.	Yang P, Zhou Y, Chen B, Wan HW, Jia GQ, Bai HL, et al. Aspirin use and the risk of gastric cancer: a meta-analysis. Dig Dis Sci 2010;55(6):1533-9.			X	
85.	Yiannakopoulou E. Modulation of lymphangiogenesis: A new target for aspirin and other nonsteroidal anti-inflammatory agents? A systematic review. J Clin Pharmacol 2012;52(11):November.		X		
86.	Zhao YS, Zhu S, Li XW, Wang F, Hu FL, Li DD, et al. Association between NSAIDs use and breast cancer risk: a systematic review and meta-analysis. Breast Cancer Res Treat 2009;117(1):141-50.			X	

Appendix 3 - Checklist for systematic reviews and individual evaluations

Sjekkliste for systematiske oversikter*		Ja	Uklart	Nei
1	Beskriver forfatterne klart hvilke metoder de brukte for å finne primærstudiene?			
Kommentar				
2	Ble det utført et tilfredsstillende litteratursøk? (bruk hjelpespørsmål på neste side for å besvare dette spørsmålet)			
Kommentar				
3	Beskriver forfatterne hvilke kriterier som ble brukt for å bestemme hvilke studier som skulle inkluderes (studiedesign, deltakere, tiltak, ev. endepunkter)?			
Kommentar				
4	Ble det sikret mot systematiske skjevheter (bias) ved seleksjon av studier (eksplisitte seleksjonskriterier brukt, vurdering gjort av flere personer uavhengig av hverandre)?			
Kommentar				
5	Er det klart beskrevet et sett av kriterier for å vurdere intern validitet?			
Kommentar				
6	Er validiteten til studiene vurdert (enten ved inklusjon av primærstudier eller i analysen av primærstudier) ved bruk av relevante kriterier?			
Kommentar				
7	Er metodene som ble brukt da resultatene ble sammenfattet, klart beskrevet?			
Kommentar				
8	Ble resultatene fra studiene sammenfattet på forsvarlig måte?			
Kommentar				
9	Er forfatternes konklusjoner støttet av data og/eller analysen som er rapportert i oversikten?			
Kommentar				
10	Hvordan vil du rangere den vitenskapelige kvaliteten i denne oversikten?			
Kommentar				

*Basert på EPOC Checklist for Refereeing Protocols for Reviews. EPOC, Effective Practice and Organisation of Care group, Guide for review authors. www.epoc.cochrane.org

Study/Checklist item	1 Method	2 Search	3 Criteria	4 Selection	5 Q.assessement	6 Q assessment	7 Method (re-	8 Method (poo-	9 Conclusions	10 Quality
Algra (14)	Y	Y	Y	Y	N	N	Y	Y	Y	M
ATT coll(15)	Y	U	Y	Y	N	N	Y	Y	Y	M
Baandrup (16)	Y	Y	Y	Y	N	N	Y	Y	Y	M
Bosetti (17)	Y	Y	Y	Y	N	N	Y	Y	Y	M
Choueiri (18)	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
Luo (19)	Y	Y	Y	Y	N	N	Y	Y	Y	M
Mills (20)	Y	Y	Y	Y	U	N	Y	Y	Y	M
Neill (21)	Y	Y	Y	U	N	N	U	U	Y	M
Rothwell (long term) (22)	Y	Y	Y	Y	N	N	Y	Y	Y	M
Rothwell (short term) (23)	Y	Y	Y	Y	N	N	Y	Y	Y	M
Seshasai (24)	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
Wilson (25)	Y	Y	Y	Y	N	N	NA	NA	Y	M

Y: yes, N: no; U: unclear; NA: not applicable
Overall quality assessment: High, Moderate, Low

Appendix 4 – Cancer incidence according to specific cancer sites

Cancer specific sites incidence associated with ASA use

We present a table with results for incidence of different cancer specific sites associated with ASA use. These estimates are based on systematic reviews containing observational case-control or cohort studies. Unless otherwise specified, the estimates were adjusted for confounders and reported for any use/dose of ASA. The type and number of confounders varied, but most systematic reviews stated that they included the estimates adjusted for most variables in each publication. The systematic reviews often only use the term risk of cancer; this could include both incident cancers and cancer mortality. We report risks from the most recent systematic review that included the most studies for a specific cancer site and/or for the most specific cancer site.

Table – Cancer specific incidences

Cancer type	case-control (No. studies)	cohort (No. studies)	All studies
Head and neck (25)	(3) not pooled. 1 favor ASA, 2 NS	(2) not pooled. NS	NR
Lung (17)	(5) RR 0.73(0.55-0.98)	(15) RR 0.98(0.92-1.05)	(20) RR 0.91(0.84-0.99)
Ovarian (16)	(14) RR 0.89(0.77-1.03)	(6) RR 1.00(0.90-1.12)	(20) RR 0.93(0.84-1.02)
Endometrial Neill(21)	(5) RR 0.82(0.71-0.96)	(4) RR 0.91(0.80-1.03)	(9) RR 0.87(0.79-0.96)
Breast (19)	(8 pop.based) OR 0.79(0.68-0.90); (5 hospital.based) OR 9.75(0.65-0.84)	(19) OR 0.91(0.84-0.98)	(33) OR 0.86(0.81-0.92)*
Kidney (18)	(8) RR 1.10(0.91-1.32)	(5) RR 1.12(0.84-1.49)	(13) RR 1.10(0.95-1.28)
Bladder (17)	(3) RR 0.81(0.63-1.05)	(6) RR 1.02(0.94-1.11)	(9) RR 0.95(0.83-1.07)
Prostate (17)	(9) RR 0.87(0.74-1.02)	(15) RR 0.91(0.85-0.97)	(24) RR 0.90(0.85-0.96)
Esophageal (SCC/NOS) (17)	(7) RR 0.54(0.44-0.67)	(4) RR 0.73(0.51-1.07)	(11) RR 0.61(0.50-0.76)
Esophageal and gastric cardia adenocarcinoma (17)	(9) RR 0.60(0.48-0.75)	(2) RR 0.88(0.68-1.15)	(11) RR 0.64(0.52-0.78)
Gastric (14)	(11) OR 0.71(0.53-0.83)	(4) RR 0.66(0.57-0.77)	NR
Pancreatic (17)	(3) RR 0.82(0.68-1.00)	(7) RR 0.95 (0.85-1.05)	(10) RR 0.91(0.83-1.01)
Hepato-biliary (14)	(3) OR 0.95(0.83-1.07)	NR	NR
Colorectal (14)	(32) OR 0.70(0.64-0.77)	(11) RR 0.89(0.84-0.95)	NR

* include data from 1 RCT, OR 0.98(0.87-1.09), NR-Not reported, NS-Not significant

Norwegian Knowledge Centre for the Health Services (Kunnskapssenteret)
PO Box 7004, St. Olavs plass
N-0130 Oslo
(+47) 23 25 50 00
www.kunnskapssenteret.no
Report: ISBN 978-82-8121-639-6 ISSN 1890-1298

no 18–2013

kunnskapssenteret