Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies

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Abstract

Background: Epidemiological studies have clarified the potential associations between regular aspirin use and cancers. However, it remains controversial on whether aspirin use decreases the risk of cancers risks. Therefore, we conducted an updated meta-analysis to assess the associations between aspirin use and cancers.

Methods: The PubMed, Embase, and Web of Science databases were systematically searched up to March 2017 to identify relevant studies. Relative risks (RRs) with 95% confidence intervals (CIs) were used to assess the strength of associations.

Results: A total of 218 studies with 309 reports were eligible for this meta-analysis. Aspirin use was associated with a significant decrease in the risk of overall cancer (RR = 0.89, 95% CI: 0.87–0.91), and gastric (RR = 0.75, 95% CI: 0.65–0.86), esophageal (RR = 0.75, 95% CI: 0.62–0.89), colorectal (RR = 0.79, 95% CI: 0.74–0.85), pancreatic (RR = 0.80, 95% CI: 0.68–0.93), ovarian (RR = 0.89, 95% CI: 0.83–0.95), endometrial (RR = 0.92, 95% CI: 0.85–0.99), breast (RR = 0.92, 95% CI: 0.88–0.96), and prostate (RR = 0.94, 95% CI: 0.90–0.99) cancers, as well as small intestine neuroendocrine tumors (RR = 0.17, 95% CI: 0.05–0.58).

Conclusions: These findings suggest that aspirin use is associated with a reduced risk of gastric, esophageal, colorectal, pancreatic, ovarian, endometrial, breast, and prostate cancers, and small intestine neuroendocrine tumors.

Keywords: Aspirin, Cancers, Meta-analysis, Observational studies

Background

Aspirin has been used as an analgesic and in the prevention of cardiovascular diseases events in the past decades and is one of the most commonly used drugs worldwide [1, 2]. Clinical and epidemiological studies reported that the rates of aspirin usage in different populations across different countries ranging from 11% to 54% [3–5]. Since the 1970s, many researchers started to focus on the effects of aspirin on cancers [6, 7]. However, these original studies were not comprehensive, and the effects on some cancers were controversial [8, 9].

Although several meta-analyses have been conducted to assess the associations between aspirin use and the risk of cancers (e.g., gastric, esophageal, pancreatic, lung, squamous cell carcinoma, breast, ovarian, and prostate cancers) [10–18], most of these studies were restricted to certain types of cancers, and some types such as hepatobiliary and cervical cancer could not be investigated. In addition, 70 new studies have been published since 2012. Therefore, this comprehensive systematic review and updated meta-analysis was conducted to explore the reliability of risk estimates between aspirin usage and most types of cancers and provide a landscape of aspirin use and cancer incidence.

Methods

Search strategy

This systematic review was conducted in accordance with the checklist proposed by the Meta-analysis of Observational Studies in Epidemiology group [19]. We searched multiple electronic bibliographic databases to...
identify studies published from database inception till March 2017, including PubMed, Embase, and Web of Science databases, with the following search terms: (“cancer” OR “neoplasm” OR “carcinoma”) AND (“aspirin” OR “acetylsalicylic acid” OR “non-steroidal anti-inflammatory drugs” OR “NSAIDs”). We restricted our search to human studies and published in English. In addition, reference lists from relevant reviews and retrieved articles were searched for qualifying studies.

Inclusion criteria
The inclusion criteria were: 1) case-control or cohort studies; 2) studies that evaluated the relationships between the use of aspirin and the risk of cancers; 3) studies that reported risk estimates with 95% confidence interval (CI) or provided information that enabled us to calculate them. The exclusion criteria were: 1) studies that used other combinations of NSAIDs, which prevented the determination of the specific effect of aspirin, and 2) studies involving patients with specific diseases (e.g., Barrett’s esophagus, Crohn’s disease, or ulcerative colitis). Only the latest or the most informative study was included when multiple studies were published on the same study population.

Data extraction
The following information was obtained from each study: first author name, year of publication, study period, study location, study design, number of cases, number of participants, gender, definition of aspirin exposure, as curtained methods of exposure, odds ratios (ORs), hazard ratios (HRs) or relative risks (RRs) with their corresponding 95% CIs, and confounding factors adjusted in the analysis. The most fully-adjusted risk estimates with its corresponding 95% CIs (when available) were preferentially extracted. Data extraction was conducted independently by two authors (Y.Q. and T.T.Y.), and discrepancies were resolved by discussion with a third investigator (Z.X.L.).

Quality assessment
Quality assessment of eligible studies was performed independently by two reviewers (Y.Q. and T.T.Y.) according to the Newcastle-Ottawa Quality Assessment Scale [20]. This scale allocates a maximum of nine points based on the selection (0–4 points), comparability (0–2 points), and exposure/outcome of the study participants (0–3 points). Scores of 0–3, 4–6, and 7–9 were classified as low, moderate, and high-quality studies respectively.

Statistical analysis
RRs were used as the common measurement of the associations between aspirin use and the risk of cancer. Because cancer is a rare event in general, we could generally ignore the distinctions among the various measures of relative risk (e.g., odds ratios, rate ratios, and risk ratios) [21], and considered that ORs and HRs were similar to RRs. When risk estimates for different durations of aspirin use or different levels of aspirin utilization were available, the study-specific RRs were subsequently recalculated in the primary analysis by pooling the risk estimates compared with the reference group. A random effects model was selected to estimate the pooled RRs (95% CI) for the associations between aspirin use and the risk of cancer if the risk estimates for different subtypes of cancer were available. Summary estimates were derived from meta-analyses using random effects models. Studies involving different populations or different types of cancers were treated as independent studies.

To assess the heterogeneity in results of individual studies, $\hat{I}^2$ statistic (values of 25%, 50%, and 75% represented cutoff points for low, moderate, and high degrees of heterogeneity, respectively) were used [22]. Publication bias was assessed with Funnel plots, the Begg’s rank correlations and Egger’s regression model. Subgroup analyses for study design, study location, gender, exposure assessment, quality assessment, duration of aspirin use (years), and frequency of aspirin use (tablets/week) were conducted to explore the potential heterogeneity among studies. Subgroup analysis was not conducted for strata with less than five studies. Because time-related biases are common in observational studies of medications and are often responsible for apparent protective effects of drugs, we conducted analyses both including and excluding studies with immortal time bias (bias because of the inclusion of follow-up time during which events cannot occur) [23]. Statistical analyses were performed with Stata version 12.0. (College Station, TX, USA). All reported probabilities (P values) were two-tailed with a significance level of 0.05.

Results
Literature search and study characteristic
Figure 1 shows the process for the identification of eligible studies. A total of 28,683 studies were identified and 298 studies remained in the analysis after assessing the titles and abstracts according to the criteria mentioned above. In total, 307 potentially relevant articles were reviewed in their entirety. Among them, 89 articles were further excluded due to the following reasons: 26 articles were not observational design, 11 articles defined exposure combined with other NSAIDs, 8 articles evaluated cancer mortality, 39 articles were duplicate publications on the same subject population, and 5 articles (1 for Crohn’s disease [24], 1 for ulcerative colitis [25], 3 for Barrett’s esophagus [26–28]) included patients with specific diseases. Ultimately, 218 studies with 309 independent reports were included in the present meta-analysis.

The main characteristics of the 218 eligible articles published between 1985 and 2016 are summarized in Tables 1,
2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21. Results were presented according to study design. This study altogether included 161 cohort studies and 148 case-control studies. Among them, 135 studies were conducted in North America, 12 in Asia, 61 in Europe, 8 in Oceania, and 2 were multi-country studies. Overall, the summarized RR was 0.89 (95% CI: 0.87–0.91), indicating a decreased risk of cancer associated with the use of aspirin. The combined RRs were 0.82 (95% CI: 0.79–0.85) for the case-control studies and 0.94 (95% CI: 0.92–0.97) for the cohort studies. We also observed a apparent beneficial effect of aspirin use when excluding 41 studies deemed to be prone to immortal time bias (RR = 0.87, 95%CI:0.85–0.89) in the meta-analysis.

Aspirin use and the risk of cancers
Figures 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18 and Additional file 1: Table S1 shows the RRs for the 21 separate cancer sites that we assessed and that of the total cancers. The use of aspirin was associated with a reduced cancer risk for ten specific sites: gastric cancer (RR =0.75, 95%CI:0.65–0.86), esophageal cancer (RR = 0.75, 95%CI:0.62–0.89), colorectal cancer (RR = 0.79, 95%CI:0.74–0.85), pancreatic cancer (RR = 0.80, 95%CI:0.68–0.93), breast cancer (RR = 0.92, 95%CI:0.88–0.96), ovarian cancer (RR = 0.89, 95%CI:0.83–0.95), endometrial cancer (RR = 0.92, 95%CI:0.85–0.99), prostate cancer (RR = 0.94, 95%CI:0.90–0.99), and small intestine neuroendocrine tumors (RR = 0.17, 95%CI:0.05–0.58). However, there was no significant association between aspirin use and the risk of some cancers, including hepato-biliary, lung, cervical uterus, renal, renal pelvis and ureter, bladder, brain, head and neck, thyroid, and skin cancers, as well as lymphoma and leukemia.

Additional file 1: Tables S1–S18 shows the RRs for cancers at 17 sites, in subgroups of studies defined by their design, study location, gender, exposure assessment, quality assessment, duration of aspirin use, and frequency of aspirin use.

We conducted a subgroup analysis stratified by questionnaires and medical records, and found a lower risk in medical records with most cancers (gastric, esophageal, colorectal, hepato-biliary, and pancreatic cancers), however, significant heterogeneity of effects was noted for those subgroups (Additional file 1: Tables S2–S18). As we expected, the decreased risk of colorectal cancer
| Study source     | Sex | Study period       | Source of subjects                                      | No of case | No of control/cohort size | Cancer site   | Exposure assessment | Exposure Definition                                                                 | Adjustment for covariates | Study quality |
|------------------|-----|--------------------|----------------------------------------------------------|------------|----------------------------|---------------|---------------------|-----------------------------------------------------------------------------------|----------------------------|---------------|
| **Case-control studies** |     |                    |                                                          |            |                            |               |                     |                                                                                   |                            |               |
| Iqbal U [47], 2017, China | M/F | 2001–2011          | The Taiwan NHI database                                  | 22,574     | 90,296                     | Gastric cancer | Prescription        | Use at least for 2 months during the 3-year period before the initial cancer diagnosis | 1,2,13,14, 15,16,17         | 7             |
| Wang Y [48], 2015, China | M/F | 2005–2010          | Population from China                                     | 175        | 350                        | Gastric cancer | Structured questionnaire | Use at least once a week for one year (regular)                                  | 2,3,5,6,7, 10,18,19,20     | 7             |
| Gong EJ [49], 2014, Korea | M/F | 2000–2010          | Asian Medical Center                                      | 327        | 327                        | Gastric cancer | Self-administered questionnaire | Use of aspirin - not further defined                                             | 1,2,3,4,6,8,10,11, 12,18,21,22,23 | 6             |
| Bertuccio P [50], 2010, Italy | M/F | 1997–2007          | Population from Italy                                     | 229        | 543                        | Gastric cancer | Structured questionnaire | Use at least once a week for more than 6 months (regular)                          | 1,2,4,5,6,10,24             | 7             |
| Figueroa JD [51], 2009, US | M/F | 1993–1995          | Population from Connecticut, New Jersey, and western Washington state | 367        | 695                        | Gastric adenocarcinomas | Structured interviews | Use at least once per week for 6 months or more                                     | 1,2,3,10,25,26             | 7             |
| Duan L [52], 2008, US | M/F | 1992–1997          | Los Angeles County Cencer Surveillance Program           | 718        | 1356                       | Gastric adenocarcinomas | Structured questionnaire | Use of aspirin - not further defined                                             | 1,2,3,5,10, 20,25,27,28     | 7             |
| Fortuny J [53], 2007, US | M/F | 1980–2002 1993-2004 | GHC and HFHS                                                | 496        | 3996                       | Gastric cancer | Structured questionnaire | Use at least once a week for more than 6 months (regular)                          | 1,2,4,5,6,10,24             | 7             |
| Akre K [54], 2001, Sweden | M/F | 1989–1995          | Population from Swedish counties                          | 567        | 1165                       | Gastric cancer | Interviews           | Ever use of aspirin (ever users)                                                   | 1,2,3,10,25,26             | 7             |
| Coogan PF [55], 2000, US | M/F | 1977–1998          | Population from Baltimore, Boston, New York, and Philadelphia | 254        | 5952                       | Stomach cancer | Administered questionnaires | Use at least 4 days/week for at least 3 months (regular)                           | 1,2,3,4,5,6, 25,32,33,34    | 8             |
| Zaridze D [56], 1999, Russia | M/F | 1993–1997          | Moscow City Oncology Hospital and Cancer Research Center and were Moscow City residents | 448        | 610                        | Stomach cancer | Self-administered questionnaire | Use at least 2 days a week for 6 months or more (regular)                          | 1,5                        | 6             |
| **Cohort studies** |     |                    |                                                          |            |                            |               |                     |                                                                                   |                            |               |
| Kim YI [57], 2016, Korea* | M/F | 2004–2010          | KNHI database                                              | 117        | 11,598                     | Gastric cancer | Prescription database | Never make claims for aspirin prescription or less than 6 months of aspirin prescriptions (non-users) | 1,2,20, 35                 | 7             |
| Lee J [58], 2012, Korea | M/F | 1999–2008          | Samsung Medical Center                                     | 184        | 347                        | Gastric cancer | Prescription           | Have aspirin fill prescriptions for at least 6 months                                | 1,2,14                     | 6             |
| Abnet CC [59], 2009, US | M/F | 1995–2003          | AARP                                                       | 360        | 311,115                    | Gastric cancer | Questionnaire         | Any use in the past 12 months                                                   | 1,2,3,5,6, 10,34,36,37     | 7             |
| Study source                        | Sex | Study period     | Source of subjects                                      | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|------------------------------------|-----|------------------|---------------------------------------------------------|------------|---------------------------|-------------|----------------------|----------------------|------------------------|---------------|
| Epplein M [60], 2009, US           | M/F | 1993–2004        | Multiethnic Cohort (Hawaii and Los Angeles, California) | 643        | 169,292                   | Gastric cancer | Self-administered questionnaire | Use any aspirin at least 2 times a week (for 1 month or longer) | 1,2,3,6,10,25 | 7             |
| Lindblad M [61], 2005, UK          | M/F | 1994–2001        | General Practitioners Research Database                 | 1023       | 1000                      | Gastric cancer | Prescription database         | Any recorded use of aspirin (ever use)               | 1,2,3,6,10,28,31 | 8             |
| Friis S [62], 2003, Denmark        | M/F | 1989–1997        | Population from North Jutland County                   | 68         | 29,470                    | Stomach cancer | Prescription database         | 75–150 mg once daily (low-dose aspirin)             | 1,2          | 8             |
| Schreinemachers DM [63], 1994, US  | M/F | 1971–1987        | The National Health and Examination Survey I           | 39         | 12,668                    | Stomach cancer | Self-reported                  | Use aspirin during the 30-day period before the interview | 1,2          | 6             |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = marriage, 8 = fat distribution, 9 = social status, 10 = BMI, 11 = total cholesterol, 12 = triglyceride, 13 = charlson comorbidity index, 14 = statin, 15 = metformin, 16 = ACE inhibitors, 17 = angiotensin II receptor blockers, 18 = helicobacter pylori, 19 = history of diabetes, 20 = resident district, 21 = percent body fat, 22 = HDL cholesterol, 23 = LDL cholesterol, 24 = period of interview, 25 = race, 26 = gastro-esophageal reflux disease, 27 = antacid use, 28 = upper gastrointestinal tract history, 29 = health plan, 30 = duration of continuous, 31 = calendar year enrollment in the health plan at the date of diagnosis, 32 = interview year, 33 = center, 34 = religion, 35 = comorbidity, 36 = total calorie, fibre and calcium intake, 37 = fruit, vegetable and/or vitamin intake, 38 = physical activity, 39 = processed meat intake

AARP: AARP diet and health study, GHC: Group Health Cooperative, HFHS: Henry Ford health system’s health alliance plan, KNHI: Korean National Health Insurance database

*Study deemed to be prone to immortal time bias
| Study source  | Sex | Study period | Source of subjects | No of case | No of control/cohorts | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|----------------------|-------------|---------------------|---------------------|----------------------|---------------|
| **Case-control studies**                       |     |              |                    |            |                      |             |                     |                     |                      |               |
| Figueroa JD [51], 2009, US                     | M/F | 1993–1995    | Population from Connecticut, New Jersey, and western Washington state | 282        | 695                  | Oesophageal cancer | Structured interviews | Use at least once per week for 6 months or more | 1, 2, 3, 10, 11, 12 | 7             |
| Sadeghi S [64], 2008, Australia                | M/F | 2001–2005    | Population from Australia | 1102       | 1580                 | Oesophageal cancer | Questionnaire         | Use at least once a week for duration of 6 months or more (regular) | 1, 2, 4, 6, 10, 16, 28, 29 | 6             |
| Duan L [52], 2008, US                          | M/F | 1992–1997    | Los Angeles County Cancer Surveillance Program | 220        | 1356                 | Esophageal adenocarcinoma | Structured questionnaire | Use of aspirin - not further defined | 1, 2, 3, 5, 10, 11, 14, 15, 16 | 7             |
| Fortuny J [53], 2007, US                       | M/F | 1980–2002    | GHC and HFHS        | 277        | 3996                 | Oesophageal cancer | Outpatient pharmacy records | No prescription for aspirin (never users) | 1, 2, 11, 17, 18 | 7             |
| Ranka S [65], 2006, UK                         | M/F | 1999–2004    | Population from Norfolk | 411        | 1644                 | Oesophageal cancer | Self-reported/medical admission notes and nursing records | Use of aspirin - not further defined | 3, 6         | 8             |
| Anderson LA [66], 2006, Ireland               | M/F | 2002–2004    | The FINBAR study    | 224        | 260                  | Esophageal adenocarcinoma | Interview | Use aspirin at least once weekly for ≥6 months | 1, 2, 3, 5, 6, 10, 30, 31 | 6             |
| Jayaprakash V [67], 2006, US                   | M/F | 1982–1998    | RPCI                | 163        | 482                  | Oesophageal cancer | Questionnaire         | Use at least once a week for 6 months (regular) | 1, 2, 3, 6, 10, 32 | 6             |
| Sharp L [68], 2001, UK                         | F   | 1993–1996    | Population in England and Scotland | 159        | 159                  | Oesophageal squamous cell carcinoma | Interview | Daily use of aspirin for at least a month | 1, 33        | 7             |
| **Cohort studies**                             |     |              |                    |            |                      |             |                     |                     |                      |               |
| Macfarlane TV [69], 2014, UKa                  | M/F | 1996–2010    | PCCIU database      | 1197       | 3585                 | Oesophageal cancer | Prescription database | Had at least one Prescription (users) | 1, 2, 13, 23, 24, 25, 26, 27 | 7             |
| Abnet CC [59], 2009, US                        | M/F | 1995–2003    | AARP                | 228        | 311,115              | Oesophageal adenocarcinoma | Questionnaire | Any use in the past 12 months | 1, 2, 3, 5, 6, 10, 20, 21, 22 | 7             |
| Lindblad M [61], 2005, UK                      | M/F | 1994–2001    | GPRD database       | 909        | 1000                 | Oesophageal cancer | Prescription database | Any recorded use of aspirin (ever use) | 1, 2, 3, 6, 10, 14, 19 | 8             |
| Friis S [62], 2003, Denmark                    | M/F | 1989–1997    | Population of North Jutland County | 26         | 29,470               | Oesophageal cancer | Prescription database | 75–150 mg once daily (low-dose aspirin) | 1, 2         | 8             |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = marriage, 8 = fat distribution, 9 = social status, 10 = BMI, 11 = race, 12 = gastroesophageal reflux disease, 13 = other NSAID, 14 = upper gastrointestinal tract history, 15 = antacid use, 16 = birthplace, 17 = health plan, 18 = duration of continuous enrollment in the health plan at the date of diagnosis, 19 = calendar year, 20 = total calorie, fibre and calcium intake, 21 = fruit, vegetable and/or vitamin intake, 22 = physical activity, 23 = CHD, 24 = stroke, 25 = COX-2 inhibitors, 26 = duration of observation in the database, 27 = deprivation, 28 = household income, 29 = cumulative and frequency of gastroesophageal reflux symptoms 10 y before diagnosis, 30 = location, 31 = job type, 32 = year of completing the questionnaire, 33 = general practice

AARP AARP diet and health study, FINBAR the factors influencing the Barrett's adenocarcinoma relationship study, GHC Group Health Cooperative, GPRD General Practitioners research database, HFHS Henry Ford health system's health alliance plan, PCCIU primary care clinical informatics unit database, RPCI the Roswell park cancer Institute

*aStudy deemed to be prone to immortal time bias*
| Study source | Sex | Study period | Source of subjects | No of case | No of control/cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|---------------------------|-------------|---------------------|---------------------|------------------------|---------------|
| Iqbal U [47], 2017, China | M/F | 2001–2011 | The Taiwan NHI database | 86,597 | 346,388 | Colorectal cancer | Prescription | Patients had aspirin prescribed at least for 2 months during the 3-year period before the initial cancer diagnosis | 1,2,13,14,15,16,17 | 7 |
| Friis S [70], 2015, Denmark | M/F | 1994–2011 | Danish Cancer Registry, Aarhus University Prescription Database, Danish National Patient Registry, Danish Civil Registration | 10,280 | 10,280 | Colorectal cancer | Prescription database | Have 2 or more prescriptions for aspirin(ever use) | 1,2,14,26,27,28,29, 30,31,32,33. | 8 |
| Rennert G [71], 2010, Israel | M/F | 1988–2006 | The MECC | 2648 | 2566 | Colorectal cancer | Interviewed | Daily aspirin use for at least 3 years | 1,2,7,26 | 5 |
| Din FV [72], 2010, UK | M/F | 2001–2008 | SCCS | 2279 | 2907 | Colorectal cancer | Questionnaire | Use > 4 tablets/week for > 1 month | 1,2,3,6,8,19, 34,35 | 4 |
| Harris RE [73], 2008, US | M/F | 2003–2004 | The CHRI | 326 | 652 | Colon cancer | Questionnaire | Use at least once per week for more than 1 year | 1,3,4,6,7,8,26,36 | 5 |
| Kim S [74], 2008, US | M/F | 2001–2006 | North Carolina Colon Cancer Study II | 1057 | 1019 | Colorectal cancer | Questionnaire | Any use of aspirin in the past 5 years (ever users) | 1,2,7,8,18,37, 38,39,40 | 6 |
| Hoffmeister M [75], 2007, Germany | M/F | 2003–2004 | The Rhine–Neckar–Odenwald region in the South-West of Germany | 477 | 517 | Colorectal cancer | Questionnaire | Use at least 2 times per week for at least 1 year(current regular use) | 1,2,3,4,5,6,8,22, 27,30,41,42,43 | 8 |
| Slattery ML [76], 2006, US | M/F | 1991–1994 | KPMCP | 2351 | 2972 | Colorectal cancer | Questionnaire | Use at least three times a week for 1 month(regular) | 1,2,7 | 7 |
| Macarthur M [77], 2005, UK | M/F | 1998–2000 | Grampian Health Board residents | 264 | 408 | Colorectal cancer | Questionnaire | Use aspirin every day for a month or more(regular) | 1,2 | 6 |
| Juarranz M [78], 2002, Spain | M/F | 1995–1996 | The Research Unit of the Council of Health and Social Services of the Community of Madrid | 196 | 228 | Colon cancer | Questionnaire | Consider aspirin use as a continuous numeric variable in milligrams/week - not further defined | 1,2 | 8 |
| Study source                          | Sex | Study period       | Source of subjects                                                                 | No of case | No of control/ cohort size | Cancer site                  | Exposure assessment        | Exposure Definition                    | Adjustment for covariates | Study quality |
|--------------------------------------|-----|--------------------|-------------------------------------------------------------------------------------|------------|---------------------------|------------------------------|----------------------------|---------------------------------------|--------------------------|----------------|
| Evans RC [79], 2002, UK              | M/F | –                  | Merseyside and Cheshire Cancer Registry                                            | 512        | 512                       | Colorectal cancer            | Questionnaire              | Use at least once per day(regular)    | 1,2,26,38                | 8              |
| Neugut AI [80], 1998, US             | M/F | 1989–1992          | Columbia–Presbyterian Medical Center                                                | 256        | 322                       | Colon cancer                 | Medical record              | Use aspirin-not further defined      | 1,4,5                    | 6              |
| Rosenberg L [81], 1998, US           | M/F | 1992–1994          | Hospital in Massachusetts                                                           | 942        | 935                       | Large bowel carcinoma        | Questionnaire              | Use at least 4 days a week for at least 3 months | 1,2                      | 9              |
| La VC [82], 1997, Italy              | M/F | 1992–1996          | Population from Italian areas                                                      | 1357       | 1891                      | Colorectal adenoma           | Questionnaire              | Use more than four times per week for > 6 months | 1,2,5,6,8,18,26,34, 43 | 7              |
| Reeves MJ [83], 1996, US             | F   | 1991–1992          | Wisconsin Cancer Reporting system                                                   | 21         | 22                        | Colorectal cancer            | Self-reported              | Use at least one tablet twice weekly or more than at least 12 months | 1,4,8,30                | 8              |
| Suh O [84], 1993, US                 | M/F | 1982–1991          | Roswell Park Tumor Registry and Diagnostic Index                                   | 830        | 1662                      | Colorectal adenoma           | Questionnaire              | Use aspirin for at least 1 year(users) | 1,2,5,26                | 9              |
| Kune GA [85], 1988, Australia        | M/F | 1980–1981          | Population in Melbourne                                                            | 715        | 727                       | Colorectal adenoma           | Questionnaire, hospital records, and interview | Use aspirin “daily” "weekly" or "don’t know" not further defined" | 1,2                     | 8              |
| **Cohort studies**                   |     |                    |                                                                                   |            |                           |                              |                           |                                       |                          |                |
| Park SY [86], 2017, US               | M/F | 1993–2012          | The MEC Study                                                                      | 3879       | 183,199                   | Colorectal cancer            | Questionnaire              | Had ever use of aspirin              | 1,3,46,8,18,19,27, 30,34,37,43, 48,49 | 8              |
| Kim C [87], 2016, US                 | M   | 1982–2000          | Physicians Health Study                                                            | 268        | 446                       | Colorectal cancer            | Questionnaire              | Use of aspirin-not further defined   | 10,2                     | 9              |
| Soriano LC [88], 2016, UK(STUDY 1)   | M/F | 2000–2011          | THIN                                                                                | 3033       | 10,000                    | Colorectal cancer            | Prescription               | No recorded use at any time(non user) | 1,2,3,8,21, 22,24,25 | 9              |
| Soriano LC [88], 2016, UK(STUDY 2)   | M/F | 2001–2012          | THIN                                                                                | 3174       | 10,000                    | Colorectal cancer            | Prescription               | No recorded use at any time(non user) | 1,2,3,8,21, 22,23 | 9              |
| Soriano LC [88], 2016, UK(STUDY 3)   | M/F | 2001–2012          | THIN                                                                                | 12,333     | 20,000                    | Colorectal cancer            | Prescription               | No recorded use at any time(non user) | 1,2,3,8,21, 22 | 9              |
| Vaughan LE [89], 2016, US            | F   | 2004–2011          | IWHS                                                                               | 218        | 14,386                    | Colon cancer                 | Questionnaire              | Never use aspirin (non-user)          | 1,3,8,22                 | 8              |
| Cao Y [8], 2016, US                  | M/F | 1980–2010          | NHS and HPFS                                                                       | 2895       | 135,965                   | Colorectal cancer            | Questionnaire              | Use at least 2 times per week(regular) | 3,4,6,7,8,18,19,27, 30,34,37,42,43,49, 50,51,52,53 | 9              |
| Study source | Sex | Study period | Source of subjects | No of case | No of control/cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|---------------------------|-------------|--------------------|---------------------|-----------------------|--------------|
| Lin CC [90], 2015, China | M/F | 2000–2009 | The Longitudinal Health Insurance Database | 467 | 60,828 | Colorectal cancer | Prescription database | Use any low-dose aspirin (75–165 mg) | 1,2,54,55 | 8 |
| Hollestein LM [91], 2014, Netherlands | M/F | 1998–2010 | PHARMO and the Eindhoven Cancer Registry | 972 | 109,276 | Colorectal cancer | Prescription database | Low dose aspirin (<100 mg daily) - not further defined | 1,2,56,72 | 8 |
| Brasky TM [92], 2014, US | F | 1998–2010 | WHI | 1397 | 140,933 | Colorectal cancer | Self-administered questionnaires | Use at both baseline and year 3 visits (consistent) | 1,3,4,5,6,7,8,37,18,19,22,26,27,33,43,50,57,58,59,60,61,62,63,64,65,66,67,68,69,70 | 9 |
| Brasky TM [93], 2012, US | M/F | 2002–2008 | The VITAL | 451 | 64,847 | Colorectal cancer | Questionnaire | Use ≥1 day/week for ≥1 year (regular) | 1,3,4,5,6,7,8,18,22,28,30,33,42,43,50,67,68,69,71 | 8 |
| Ruder EH [94], 2011, US | M/F | 1996–2006 | National Institutes of Health-AARP Diet and Health Study | 3894 | 301,240 | Colorectal cancer | Self-administered questionnaire | Use aspirin during the previous 12 months | 1,2,3,4,5,6,7,8,18,27 | 7 |
| Friis S [95], 2009, Denmark | M/F | 1995–2006 | Danish Diet, Cancer, and Health Study | 615 | 51,053 | Colorectal cancer | Questionnaire | Use fewer than 2 pills per month (nonuse) | 1,2,6,8,14,22,27,30,7,34,70,73,74 | 7 |
| Siemes C [96], 2008, Netherlands | M/F | 1992–2004 | The Rotterdam Study | 195 | 7621 | Colorectal cancer | Questionnaire and prescriptions | The absence of a prescription for any non-aspirin or aspirin NSAID (no use) | 1,2,3,8,18,27,34,70,71,73,74 | 8 |
| Vinogradova Y [97], 2007, UK | M/F | 1995–2005 | QRESEARCH database | 1226 | 5369 | Colorectal cancer | Prescription database | Receive ≥1 prescription for aspirin in the 13 to 48 months before index date | 3,8,22,41 | 8 |
| Jacobs EJ [98], 2007, US | M/F | 1992–2003 | Cancer Prevention Study II Nutrition Cohort | 1861 | 146,113 | Colorectal cancer | Questionnaire | Use at least 30 “times” per month (daily use of adult-strength) | 1,2,3,5,7,18,22,27,28,30,36,68,52,53 | 8 |
| Larsson SC [99], 2006, Sweden | M/F | 1998–2005 | Swedish Mammography Cohort and Cohort of Swedish Men | 705 | 74,250 | Colorectal cancer | Questionnaire | Aspirin use - not further defined | 1,2,3,4,5,6,7,18,22,27,28,30,36,68,52,53 | 8 |
| Muscat JE [100], 2005, US | M/F | 1983–1999 | The Framingham Heart study | 145 | 433 | Colorectal cancer | Questionnaire | Never <1/week, 1–3/week, >3/week | 1,2,3,4,5,6,7,18,22,27,28,30,36,68,52,53 | 8 |
| Rahme E [101], 2003, Canada | M/F | 1997–2001 | RAMQ | 179 | 2568 | Colorectal adenoma | Prescription | Use at least 1 year | 45,46,47 | 7 |
| Rodríguez LAG [102], 2001, UK | M/F | 1994–1997 | The GPRD | 2002 | 943,903 | Colorectal cancer | Prescription database | Never received a single prescription (non-user) | 1,2,4,5,6,7,8,18,22,27,28,30,36,68,52,53 | 8 |
| Study source | Sex | Study period | Source of subjects | No of case | No of control/cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|-----------|--------------------------|-------------|---------------------|---------------------|------------------------|---------------|
| Schreinemachers DM [63], 1994, US | M/F | 1971–1987 | The National Health and Examination Survey I | 169 | 12,668 | Colorectal cancer | Self reported | Use aspirin during the 30-day period before the interview | 1,2 | 6 |
| Paganini-Hill A [103], 1989, US | M/F | 1981–1988 | Population from Leisure World, Laguna Hills, US | 181 | 13,870 | Colon cancer | Questionnaire | Aspirin use: none, <daily, daily | 2 | 4 |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = BMI, 8 = marital status, 9 = self-rated health, 10 = C-reactive protein level, 12 = cholesterol, 13 = Charlson comorbidity index, 14 = statin, 15 = metformin, 16 = ACE inhibition, 17 = angiotensin II receptor blockers, 18 = physical activity, 19 = fruit, vegetable and/or vitamin intake, 20 = seafood and dairy foods intake, 21 = number of PCP visits in the year before the index date, 22 = other NSAIDs, 23 = paracetamol, 24 = insulin, 25 = oral steroids, 26 = area (county/region), 27 = hormone replacement therapy, 28 = history of diabetes mellitus, 29 = history of cholecystectomy, 30 = history of colonoscopy, 31 = chronic obstructive pulmonary disease or asthma, 32 = antidepressants, 33 = migraine, 34 = total energy intake, 35 = deprivation index, 36 = hypertension amplifying probability, 37 = ever use of calcium supplements in the past 5 years, 38 = primary care practitioner, 39 = dietary fat intake, 40 = sampling probability, 41 = morbidity (diabetes, ischemic heart disease, hypertension, stroke, colitis, rheumatoid arthritis, and osteoarthritis), 42 = former health checkup, 43 = red meat, 44 = Nitro-vasodilator use, 45 = number of drugs, 46 = number of physician encounters, 47 = all-cause hospitalization in prior year, 48 = dietary fiber, 49 = folate, 50 = height, 51 = Alternate Healthy Eating Index-2010, 52 = PSA test in past 2 years, 53 = mammogram in past 2 years, 54 = duration of diabetes, 55 = propensity score at baseline, 56 = unique number of hospitalizations in the year prior to start of follow up, 57 = observational study enrollment, 58 = diet modification trial enrollment, 59 = screening for cancer, 60 = age at menarche, 61 = age at menopause, 62 = gravidity, 63 = age at first birth, 64 = duration of estrogen therapy, 65 = duration of combined postmenopausal hormone therapy, 66 = hysterectomy status, 67 = use of antihypertensive medication, 68 = history of coronary heart disease, 69 = use of cholesterol-lowering medication, 70 = history of arthritis, 71 = history of Ulcer, 72 = unique number of dispensing

AARP: AARP diet and health study, CHRI: Cancer Hospital and Richard J. Solove Research Institute, GPDR: General Practitioners Research Database, HPFS: Health Professionals follow-up study, IWHS: Iowa Women’s Health Study, KPMCP: Kaiser Permanente Medical Care Program of Northern California, MECC: the molecular epidemiology of colorectal cancer, NHS: Nurses’ health study, RAMQ: Régie de l'Assurance Maladie du Québec, SCCS: study of colorectal cancer in Scotland, THIN: the health improvement Network, VITAL: the vitamins and lifestyle, WHI: women’s health initiative

aStudy deemed to be prone to immortal time bias
| Study source          | Sex | Study period | Source of subjects                  | No of case | No of control/ cohort size | Cancer site             | Exposure assessment                  | Exposure Definition          | Adjustment for covariates | Study quality |
|----------------------|-----|--------------|-------------------------------------|------------|---------------------------|-------------------------|--------------------------------------|--------------------------------|---------------------------|----------------|
| **Case-control studies** |
| Choi J [104], 2016, US | M/F | 2000–2014    | Patients seen at the Mayo Clinic    | 2395       | 4769                      | Cholangiocarcinoma      | Electronic medical record            | Use at least once per week at the index date | 1,2,3,11, 12,13,14,15 | 9              |
| Yang B [105], 2016, UK | M/F | 1988–2011    | CPRD                               | 814        | 3180                      | Primary liver cancer    | Medical records database             | Had two or more aspirin prescriptions recorded prior to the index date (ever use) | 3,6,10,15, 16,17,18 | 7              |
| Burr NE [106], 2014, UK | M/F | 2004–2010    | NNUH and LGH                        | 81         | 275                       | Cholangiocarcinoma      | Letters from general practitioners (GPs), hospital clerkings, surgical records, nursing notes and radiological reports | Drug was recorded in any of the data sources | 1,2,3,15 | 7              |
| **Cohort studies** |
| Kim G [107], 2017, Korea | M/F | 2003–2012    | NHIS-NSC                            | 229        | 1145                      | Hepatocellular carcinoma | Prescription                         | At least one prescription of aspirin between the cohort entry and the index date | 1,2,19,20, 21 | 6              |
| Petrick JL [108], 2015, US | M/F | from 1993    | AARP,AHS, USRT,BCDDP, PLCO,HPFS, CPSII, BWHS WH/NHS | 904       | 1,084,133                 | Hepatocellular carcinoma and intrahepatic cholangiocarcinoma | Questionnaire                      | Any reported aspirin use in the 12 months prior to baseline | 1,2,3,6, 10,11,15, 21 | 7              |
| Liu E [109], 2005, China | M/F | 1997–2001    | Population from Shanghai            | 368        | 1013                      | Gallbladder Cancer      | Questionnaire                       | Use at least twice a week for longer than a month 1 year before interview | 1,2,5, 22 | 6              |
| S Friis [62], 2003, Denmark | M/F | 1989–1997    | Population from North Jutland County | 21         | 29,470                    | Liver cancer            | Prescription database                | 75–150 mg once daily (low-dose aspirin) | 1,2          | 8              |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = marriage, 8 = Fat distribution, 9 = social status, 10 = BMI, 11 = age;12 = primary sclerosing cholangitis (PSC), 13 = non-PSC-related cirrhosis, 14 = biliary tract diseases, 15 = diabetes, 16 = hepatitis B or C virus infection, 17 = rare metabolic disorders, 18 = use of paracetamol, antidiabetic medications, and statins, 19 = follow-up duration, 20 = the date of the diabetes diagnosis, 21 = cohort (AARP, AHS, USRT, PLCO, HPFS, CPSII, BWHS, WH/NHS), 22 = biliary stone status

AARP: AARP diet and health study, AHS: Agriculture Health Study, BCDDP: the breast cancer detection demonstration project, BWHS: black women’s health study, CPRD: clinical practice research datalink, CPSII: cancer prevention study II, HPFS: Health Professionals follow-up study, IHWS: Iowa Women’s Health Study, LGH: Leicester General Hospital NHS Trust, NHIS-NSC: National Health Insurance Service National Sample Cohort, NHS: Nurses’ Health Study, NNUH: Norfolk and Norwich University Hospital, PLCO: prostate, lung, colorectal and ovarian cancer screening trial, USRT: United State Radiologic Technologist Study, WHI: women’s health initiative

*Study deemed to be prone to immortal time bias
| Study source | Sex | Study period | Source of subjects | No of case | No of control/cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|---------------|-----|--------------|--------------------|------------|--------------------------|-------------|---------------------|---------------------|------------------------|--------------|
| Risch HA [110], 2017, China | M/F | 2006–2011 | Our Shanghai study | 761 | 794 | Pancreatic cancer | In-person questionnaire interviews | Use at least one tablet per week for 3 months or longer(regular) | 1,2,3,5,7,10,50,51 | 7 |
| Kho PF [111], 2016, Australia | M/F | 2007–2011 | The QPCS | 522 | 652 | Pancreatic cancer | Questionnaire | Long-term use of aspirin (> 2 years) | 1,2,3,6,10 | 8 |
| Streicher SA [112], 2014, US | M/F | 2005–2009 | Population from Connecticut | 360 | 682 | Pancreatic cancer | Questionnaire | Use at least once a week on average for 3 months or more | 1,2,3,5,7,11,52 | 8 |
| Tan XL [113], 2011, US | M/F | 2004–2010 | Patients from the Mayo Clinic | 740 | 1043 | Pancreatic cancer | Questionnaire | Use aspirin ≥ 1 day per month | 1,2,3,7,10 | 6 |
| Pugh TFG [114], 2011, UK | M/F | 2004–2007 | Clinical management databases in Norfolk and Leicestershire | 206 | 251 | Pancreatic cancer | Medical records | Use of aspirin - not further defined | 1,2,3,7 | 6 |
| Boniﬁazi M [115], 2010, Italy | M/F | 1991–2008 | Patients in in the province of Pordenone and in the greater Milan area, northern Italy | 308 | 477 | Pancreatic cancer | Questionnaire | Use at least once a week for more than 6 months (regular) | 1,2,3,5,7,10,53,54 | 8 |
| Menezes RJ [116], 2002, US | M/F | 1982–1998 | The RPCI | 194 | 585 | Pancreatic cancer | Patient Epidemiology Data System (PEDS) and questionnaire | Use at least once a week for six consecutive months (regular) | 1,3,4 | 5 |
| Cohort studies |
| Cao Y [8], 2016, US | M/F | 1980–2010 | NHS and HPFS | 607 | 135,965 | Pancreatic cancer | Questionnaire | Use at least 2 times per week (regular) | 3,4,6,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24 | 9 |
| Brasky TM [92], 2014, US | F | 1998–2010 | WHI | 397 | 142,330 | Pancreatic cancer | Self-administered questionnaires | Use at both baseline and year 3 visits (consistent) | 1,3,4,5,6,10,11,17,18,19,21,22,23,24 | 9 |
| Bradley MC [117], 2010, UK | M/F | 1995–2006 | GPRD | 564 | 3984 | Pancreatic cancer | Prescription Database | Use 300 mg or more a day (high-dose) | 3,6,7,10,25,27,47,55 | 8 |
| Jacobs EJ [98], 2007, US | M/F | 1992–2003 | Cancer Prevention Study II Nutrition Cohort | 404 | 146,113 | Pancreatic cancer | Questionnaire | Use at least 30 “times” per month (daily use of adult-strength) | 1,2,3,5,7,10,11,15 | 8 |

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### Table 5 Characteristics of included studies- pancreatic cancer (Continued)

| Study source            | Sex | Study period | Source of subjects     | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition                  | Adjustment for covariates | Study quality |
|-------------------------|-----|--------------|------------------------|------------|---------------------------|-------------|---------------------|---------------------------------------|----------------------------|---------------|
| Friis S [62], 2003, Denmark\(^a\) | M/F | 1989–1997 | Population from North Jutland County | 62         | 29,470                    | Pancreatic cancer | Prescription Database | 75–150 mg once daily (low-dose aspirin) | 1,2                        | 8             |
| Anderson KE [118], 2002, US | F   | 1992–1999 | IWHS                   | 80         | 28,283                    | Pancreatic cancer | Questionnaire       | Never use any type of medication (never use) | 13,7,19                    | 7             |
| Schreinemachers DM [63], 1994, US | M/F | 1971–1987 | The National Health and Examination Survey I | 30         | 12,668                    | Pancreatic cancer | Self reported       | Use aspirin during the 30-day period before the interview | 1,2                        | 6             |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = diabetes, 8 = Fat distribution, 9 = social status, 10 = BMI, 11 = race, 12 = folate, 13 = height, 14 = Alternate Healthy Eating Index-2010, 15 = PSA test in past 2 y, 16 = mammogram in past 2 y, 17 = hormone replacement therapy, 18 = physical activity, 19 = fruit, vegetable and/or vitamin intake, 20 = history of colonoscopy, 21 = total energy intake, 22 = ever use of calcium supplements in the past 5 years, 23 = former health check-up, 24 = red meat, 25 = other NSAIDs, 26 = area (county/region), 27 = prior cancer, 28 = migraine, 29 = ever use of calcium supplements in the past 5 years, 30 = red meat, 31 = Nitro-vasodilator use, 32 = height, 33 = unique number of hospitalizations in the year prior to start of follow up, 34 = observational study enrollment, 35 = diet modification trial enrollment, 36 = screening for cancer, 37 = age at menarche, 38 = age at menopause, 39 = gravidity, 40 = age at first birth, 41 = duration of estrogen therapy, 42 = duration of combined postmenopausal hormone therapy, 43 = hysterectomy status, 44 = use of antihypertensive medication, 45 = history of coronary heart disease, 46 = use of cholesterol-lowering medication, 47 = history of arthritis, 48 = history of ulcer, 49 = hypertension, 50 = H. pylori CagA seropositivity, 51 = ABO blood group A vs. non-A, 52 = ABO blood group O vs. non-O, 53 = center, 54 = year of interview, 55 = history of chronic pancreatitis.

\(^a\)Study deemed to be prone to immortal time bias.

GPRD = General Practitioners Research Database, HPFS = Health Professionals follow-up study, IWHS = Iowa Women’s Health Study, NHS = nurses’ health study, QPCS = the Queensland Pancreatic Cancer Study, RPCI = the Roswell Park Cancer Institute, WHI = women’s health initiative.
### Table 6: Characteristics of included studies- lung cancer

| Study source              | Sex | Study period       | Source of subjects                      | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition                          | Adjustment for covariates | Study quality |
|---------------------------|-----|--------------------|-----------------------------------------|------------|---------------------------|-------------|---------------------|---------------------------------------------|--------------------------|---------------|
| Iqbal U [47], 2017, China | M/F | 2001–2011          | The Taiwan NHI database                 | 68,409     | 273,636                   | Lung cancer | Prescription        | Patients had aspirin prescribed at least for 2 months during the 3-year period before the initial cancer diagnosis | 1,2,13,14,15,16,17       | 7             |
| Lim WY [119], 2012, Singapore | F   | 2005–2008          | Population from Chinese                 | 252        | 556                       | Lung cancer | Questionnaire       | Use twice a week or more, for a month or more(regular) | 1,3,4,5,19,34             | 7             |
| McCormack VA [120], 2011, US | M/F | –                  | AHFTS                                   | 977        | 683                       | Lung cancer | Interview           | –                                           | 1,3,5,11                 | 7             |
| McCormack VA [120], 2011, US | M/F | –                  | Population from Boston                  | 768        | 123                       | Lung cancer | –                   | –                                           | 1,3,5,11                 | 7             |
| McCormack VA [120], 2011, US | M/F | –                  | Population from Florida                 | 467        | 889                       | Lung cancer | –                   | –                                           | 1,3,5,11                 | 7             |
| McCormack VA [120], 2011, US | M/F | –                  | Population from Hawaii                  | 629        | 588                       | Lung cancer | –                   | –                                           | 1,3,5,11                 | 7             |
| McCormack VA [120], 2011, US | M/F | –                  | MSKCC                                    | 102        | 101                       | Lung cancer | –                   | –                                           | 1,3,5,11                 | 7             |
| McCormack VA [120], 2011, US | M/F | –                  | NELCS                                    | 276        | 251                       | Lung cancer | –                   | –                                           | 1,3,5,11                 | 7             |
| McCormack VA [120], 2011, US | M/F | –                  | NICCC                                    | 280        | 270                       | Lung cancer | –                   | –                                           | 1,3,5,11                 | 7             |
| Kelly JP [121], 2008, US   | M/F | 1976–2007          | Patients in Boston Baltimore New York and Philadelphia | 1884       | 6251                      | Lung cancer | In-person interview | Use at least 4 days per week for at least three continuous months(regular) | 1,2,3,46,29,30,36         | 6             |
| Van Dyke Al [122], 2008, US | F   | 2001–2005          | Metropolitan Detroit Cancer Surveillance System, a participant in the National Cancer Institute’s Surveillance | 580        | 541                       | Lung Cancer | Questionnaire       | Had taken any aspirin                       | 1,3,4,5,10,11,3135,37    | 7             |
| Harris RE [123], 2007, US   | M/F | 2002–2004          | The Ohio State University Medical Center, Columbus, Ohio | 375        | 654                       | Lung Cancer | Interview           | Use no more than one pill per week for less than 1 year (nonuser) | 1,2,3,5,6,10,11,35         | 7             |
### Table 6 Characteristics of included studies- lung cancer (Continued)

| Study source                        | Sex | Study period          | Source of subjects                                      | No of case | No of control/cohort size | Cancer site | Exposure assessment | Exposure Definition                                                                 | Adjustment for covariates | Study quality |
|-------------------------------------|-----|-----------------------|----------------------------------------------------------|------------|---------------------------|-------------|---------------------|-------------------------------------------------------------------------------------|----------------------------|---------------|
| Muscat JE [124], 2003, US          | M/F | 1992–2000             | Hospitals in New York and Washington, D.C.               | 997        | 918                       | Lung Cancer | Questionnaire       | Use three tablets per week for 1 or more years (regular)                           | 1,2,3,4                    | 7             |
| Moysich KB [125], 2002, US         | M/F | 1982–1998             | RPCI                                                     | 868        | 935                       | Lung Cancer | Epidemiological questionnaire | Use at least once a week for one year (regular)                                    | 1,3,4                      | 8             |
| Cao Y [8], 2016, US                | M/F | 1980–2010             | NHS and HPFS                                            | 2430       | 135,965                   | Lung cancer | Questionnaire       | Use at least 2 times per week (regular)                                           | 3,5,6,7,8,9,10,11,12,18,19,20,21,22,23,24,25,28 | 9             |
| Baik CS [126], 2015, US            | F   | 1993–2010             | WHI                                                      | 1902       | 143,841                   | Lung cancer | Questionnaire       | Use at least twice a week in each of the two weeks preceding the interview (regular) | 13,5,6,10,11,19,25,31,50,51,52 | 8             |
| Hollestein LM [91], 2014, Netherlands a | M/F | 1998–2010             | PHARMO and the Eindhoven Cancer Registry                  | 915        | 109,276                   | Lung cancer | Prescription database | Low dose aspirin (≤ 100 mg daily)- not further defined                            | 1,2,26,27                  | 8             |
| Brasky TM [127], 2012, US          | M/F | 2000–2007             | The VITAL cohort                                         | 100        | 69,919                    | Lung cancer | The baseline questionnaire | Use aspirin ≥1 day/week for ≥1 year (regular)                                     | 1,2,3,4,5,10,11,29,35,46,53,54 | 8             |
| McCormack VA [130], 2011, US       | M/F | –                     | DDCHS                                                   | 812        | 55,396                    | Lung cancer | Questionnaire       | –                                                                                  | 1,3,5,11                   | 7             |
| Siemes C [96], 2008, Netherlands    | M/F | 1992–2004             | The Rotterdam Study                                      | 134        | 7621                      | Lung cancer | Questionnaire and prescriptions. | The absence of a prescription for any non-aspirin or aspirin NSAID(no use)          | 1,2,10,18,21,25,35,55,56,57 | 8             |
| Olse JH [128], 2008, Denmark        | M/F | 2002–2005             | Danish Diet, Cancer and Health prospective cohort study  | 282        | 390                       | Lung cancer | Questionnaire and prescription database | Any use of aspirin or 1 year or more before the index date                          | 1,2,3,4,38,39             | 7             |
| Hernández-Díaz S [129], 2007, UK a | M/F | 1995–2004             | THIN database                                            | 4336       | 10,000                    | Lung cancer | THIN database       | Had recorded prescription at any time before the index date                        | 1,2,3,6,10,14,33,35,40,41,42,43,44,45,46,47,48 | 8             |
| Jacobs EJ [98], 2007, US           | M/F | 1992–2003             | Cancer Prevention Study II Nutrition Cohort              | 1815       | 146,113                   | Lung cancer | Questionnaire       | Use at least 30 “times” per month (daily use of adult-strength)           | 1,2,3,4,9,10,11,18,25,28,29,31,32,33 | 8             |
| Hayes JH [130], 2006, US           | F   | 1992–2002             | WHS                                                     | 403        | 27,162                    | Lung cancer | Questionnaire       | Never, less than one weekly, once weekly, two to five times weekly, and six or more times weekly | 1,3,4,6,10,19,29,35,58 | 7             |
| Study source               | Sex | Study period | Source of subjects                          | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|---------------------------|-----|--------------|---------------------------------------------|------------|----------------------------|-------------|---------------------|----------------------|--------------------------|---------------|
| Akhmedkhanov A [131], 2002, US | F   | 1994–1996    | NYU and Women’s Health Study cohort.        | 81         | 808                        | Lung cancer | Questionnaire       | Use three or more times per week for a period of 6 months or longer | 1,3,4,49                 | 7             |
| Schreinemachers DM [63], 1994, US | M/F | 1971–1987    | The National Health and Examination Survey I | 163        | 12,668                     | Lung cancer | Self reported       | Use aspirin during the 30-day period before the interview | 1,2                      | 6             |
| Paganini-Hill A [103], 1989, US | M/F | 1981–1988    | Population in Leisure World, Laguna Hills, US | 111        | 13,870                     | Lung cancer | Questionnaire       | Aspirin use: none, <daily, daily | 2                        | 4             |

1 = age, 2 = sex, 3 = smoking, 4 = education level, 5 = family history, 6 = alcohol intake, 7 = height, 8 = Alternate Healthy Eating Index-2010, 9 = PSA test in past 2 y, 10 = BMI, 11 = race, 12 = folate, 13 = Charlson comorbidity index, 14 = statin, 15 = metformin, 16 = ACE inhibitors, 17 = Angiotensin II receptor blockers, 18 = physical activity, 19 = fruit, vegetable and/or vitamin intake, 20 = history of colonoscopy, 21 = total energy intake, 22 = ever use of calcium supplements in the past 5 years, 23 = former health checkup, 24 = red meat, 25 = hormone replacement therapy, 26 = unique number of dispensing, 27 = unique number of hospitalizations in the year prior to start of follow up, 28 = mammogram in past 2 y, 29 = other NSAIDs, 30 = area (county/region), 31 = history of coronary heart disease, 32 = diabetes, 33 = hypertension, 34 = housing type, 35 = history of arthritis, 36 = interview year, 37 = history of COLD, 38 = study, 39 = use of acetaminophen, 40 = smoking cessation advice by general practitioner, 41 = smoking cessation treatment, 42 = number of visits to general practitioner, 43 = number of referrals, 44 = use of oral corticosteroids, 45 = antihypertensives and other lipid-lowering drugs, 46 = chronic obstructive pulmonary disease, 47 = cerebrovascular disease, 48 = ischemic heart disease, 49 = menopausal status, 50 = age started and years since quitting smoking, 51 = emphysema, 52 = randomization arm of the DM trial, 53 = history of ulcer, migraine or chronic headache, osteoarthritis or chronic joint pain, 54 = coronary artery disease, 55 = C-reactive protein level, 56 = pack years of smoking, 57 = cholesterol, 58 = any heart disease/heart attack

AHFTS American Health Foundation Tobacco Study, DDCHS Danish Diet Cancer and Health Study, HPFS Health Professionals follow-up study, IWHS Iowa Women’s Health Study, MSKCC Memorial Sloan-Kettering Cancer Center, NELCS New England Lung Cancer Study, NHS nurses’ health study, NICCC National Israel Cancer Control Center, NYU New York University, RPCI the Roswell Park Cancer Institute, THIN the Health Improvement Network, VITAL the vitamins and lifestyle, WHI women’s health initiative

*Study deemed to be prone to immortal time bias
| Study source | Sex | Study period | Source of subjects | No of case | No of control/cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|-----------|--------------------------|-------------|---------------------|---------------------|------------------------|--------------|
| Iqbal U [47], 2017, China | F | 2001–2011 | The Taiwan NHI database | 65,491 | 435,364 | Breast cancer | Prescription | Patients had aspirin prescribed at least for 2 months during the 3-year period before the initial cancer diagnosis | 12,13,14, 15,16,17 | 7 |
| Dierßen-Sotos T [132], 2016, Spain | F | 2008–2013 | The MCC study | 1736 | 1909 | Breast cancer | Questionnaire | Use of aspirin - not further defined | 1,3,4,5,10,30,36,40,50,51 | 8 |
| Cui Y [133], 2014, US | F | 2001–2011 | Nashville Breast Health Study | 2154 | 1831 | Breast cancer | Telephone interview | Use aspirin three or more times a week for a minimum duration of 1 year (regular) | 13,4,5,6,11,18,25,40,50,51,52,53 | 7 |
| Brasky TM [134], 2010, US | F | 1996–2001 | WEB Study | 1057 | 2094 | Breast cancer | Self-reported | Use 0 days/month (non-users) | 1,4,5,11,25,29,36,37,38,53,61 | 6 |
| Cronin-Fenton DP [135], 2010, Denmark | F | 1991–2006 | Population from North Jutland and Aarhus counties, Denmark | 8195 | 81,950 | Breast cancer | Danish healthcare databases | Use at least 2 prescriptions within 2 years of diagnosis (recent use) | 1,4,5,11,29,36,37,38,53 | 8 |
| Slattery ML [136], 2007, US | F | 1999–2004 | Population from the southwestern United States (4-Corner’s Breast Cancer Study) | 2325 | 2525 | Breast cancer | Questionnaire | Use at least thrice weekly for at least 1 month (regular) | 1,10,18,38,54,55,56 | 7 |
| Harris RE [137], 2006, US | F | 2003–2004 | CHRI | 277 | 493 | Breast cancer | Questionnaire | Use at least two times per week for 2 years or more | 1,3,5,6,10,38,51 | 7 |
| Swede H [138], 2005, US | F | 1982–1998 | The Roswell Park Cancer Institute | 1478 | 3383 | Breast cancer | Questionnaire | Use aspirin at least once a week for at least 1 year (regular) | 1,4,5,6,10,11,36,37,38,40,53 | 6 |
| Zhang YQ [139], 2005, US | F | 1976–2002 | The Case-Control Surveillance Study Revisited | 2406 | 1554 | Breast cancer | Questionnaire | Use at least four times per week for 3 or more continuous months (regular) | 1,4,5,6,10,11,36,37,38,40,53 | 5 |
| Terry MB [140], 2004, US | F | 1996–1997 | The Long Island Breast Cancer Study Project | 1442 | 1420 | Breast cancer | Questionnaire | Use at least once a week for 6 months or longer (ever use) | 11,0,29,31 | 6 |
| Moorman PG [141], 2003, US | F | 1996–2000 | Phase II of the Carolina Breast Cancer and Carcinoma In Situ Study | 500 | 2631 | Breast cancer | Questionnaire | Use at least 8 days a month for three or more months (regular) | 1 | 6 |
| Cotterchio M [142], 2001, Canada | F | 1996–1998 | Population in Canada | 2696 | 2600 | Breast cancer | Questionnaire | Daily use for ≥ 2 months (any use) | 1,39,53 | 6 |
| Study source                  | Sex | Study period       | Source of subjects                     | No of case | No of control/cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|------------------------------|-----|--------------------|----------------------------------------|------------|---------------------------|-------------|---------------------|-----------------------|------------------------|---------------|
| Neugut Al [80], 1998, US     | F   | 1989–1992          | Columbia-Prebyterian Medical Center    | 252        | 176                       | Breast cancer | Medical record      | Use aspirin-not further defined | 14,5               | 6             |
| Cao Y [8], 2016, US          | F   | 1980–2010 1986–2012 | NHS and HPFS                          | 7424       | 135,965                   | Breast cancer | Questionnaire       | Use at least 2 times per week(regular) | 35,6,7,8,9,10,11,12,18,19,20,21,22,23,24,25,28 | 9             |
| Kim S [143], 2015, US        | F   | 2003–2013          | Sister Study                           | 2118       | 50,884                    | Breast cancer | Questionnaire       | Use at least once a week(current user) | 45,10,11,40,51,53,67 | 8             |
| Hollstein LM [91], 2014, Netherlands | F   | 1998–2010          | PHARMO and the Eindhoven Cancer Registry | 585        | 55,597                    | Breast cancer | Prescription database | Low dose aspirin (≤100 mg daily) not further defined | 12,26,27            | 8             |
| Brasky TM [92], 2014, US     | F   | 1998–2010          | WHI                                    | 5401       | 142,330                   | Breast cancer | Self-administered questionnaires | Use at both baseline and year 3 visits (consistent) | 13,4,5,6,7,10,11,18,20,21,22,23,24,25,26,27,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47 | 9             |
| Bardia A [144], 2011, US     | F   | 1986–2005          | The IHWS                               | 1581       | 26,580                    | Breast cancer | Questionnaire       | Ever use aspirin-not further defined | 13,4,5,6,10,18,25,36,37,38,39,40,68,69 | 8             |
| Bosco JL [145], 2011, US     | F   | 1995–2007          | BWHS                                   | 1275       | 59,000                    | Breast cancer | Questionnaire       | Use aspirin ≥ 3 days per week (regular) | 13,4,10,18,25,29,70 | 9             |
| Eliassen AH [146], 2009, US  | F   | 1989–2003          | NHS II                                 | 1229       | 112,292                   | Breast cancer | Questionnaire       | Use aspirin ≥ 2 times per week (regular) | 56,7,10,36,38,40,53,68,71 | 9             |
| Friisa S [147], 2008, Denmark| F   | 1993–2003          | The prospective Diet, Cancer and Health cohort study | 396        | 28,695                    | Breast cancer | Questionnaire       | Use more than one pill per month | 14,25,38,50,53    | 7             |
| Gierach GL [148], 2008, US   | F   | 1995–2003          | AARP                                   | 4451       | 126,124                   | Breast cancer | Questionnaire       | Ever use aspirin-not further defined | 15,6,11,25,29,40,49,72 | 7             |
| Ready A [149], 2008, US      | F   | 2000–2004          | VITAL cohort                           | 479        | 35,323                    | Breast cancer | Questionnaire       | Use at least once a week for a year during the last 10 years (any use) | 15,6,10,11,19,28,29,36,37,40,72,73,74 | 7             |
| Siemes C [96], 2008, Netherland | F   | 1992–2004          | The Rotterdam Study                    | 175        | 7621                      | Breast cancer | Questionnaire and prescriptions | The absence of a prescription for any non-aspirin or aspirin NSAID(no use) | 13,10,25,36,37,50,75 | 8             |
| Jacobs EJ [98], 2007, US     | F   | 1992–2003          | Cancer Prevention Study II Nutrition Cohort | 3121       | 76,303                    | Breast cancer | Questionnaire       | Use at least 30 “times” per month (daily use of adult-strength) | 13,4,10,11,18,20,25,28,29,45,48,49 | 8             |
| Gill JK [150], 2007, US      | F   | 1993–2002          | Multiethnic Cohort                     | 1457       | 98,920                    | Breast cancer | Questionnaire       | Use at least two times per week for 1 month or longer | 14,5,6,10,11,25,28,36,37,40,50,51,76 | 7             |
| Study source                          | Sex | Study period     | Source of subjects                  | No of case | No of control/cohort size | Cancer site | Exposure assessment | Exposure Definition                                      | Adjustment for covariates | Study quality |
|--------------------------------------|-----|------------------|-------------------------------------|------------|---------------------------|-------------|---------------------|-----------------------------------------------------------|---------------------------|--------------|
| Gallicchio L [151], 2007, US         | F   | 1989–2006        | CLUE II ("Give us a Clue to Cancer and Heart Disease") | 418        | 15,651                    | Breast cancer| Questionnaire      | Use aspirin in the last 48 h (current user)              | 1                         | 7            |
| Marshall SF [152], 2005, US          | F   | 1995–2001        | The California Teachers Study       | 2391       | 114,640                   | Breast cancer| Questionnaire      | Use at least once a Week (regular)                       | 13,5,6,10,11,18,25,28,31,33,59,77 | 9            |
| Rahme E [153], 2005, Canada¹         | F   | 1998–2202        | RAMQ                                | 664        | 23,573                    | Breast cancer| Prescription database | Ever use aspirin during the year prior to the index date | 12,5,28,33,57,58,60       | 7            |
| Rodríguez LA [154], 2004, UK²        | F   | 1995–2001        | GPRD                                | 3708       | 23,708                    | Breast cancer| Prescription database | No recorded use at any time before the index date (nonuser) | 13,6,10,25,29,53,62,63,66 | 8            |
| Harris RE [155], 1999, US            | F   | 1991–1996        | Population from The Ohio State University Comprehensive Cancer Center in Columbus, Ohio | 316        | 32,505                    | Breast cancer| Questionnaire      | Use aspirin ≥1 pill per week                             | 1                         | 5            |
| Schreinemachers DM [63], 1994, US     | F   | 1971–1987        | The National Health and Examination Survey 1 | 147        | 12,668                    | Breast cancer| Self reported      | Use aspirin during the 30-day period before the interview | 12                        | 6            |
| Paganini-Hill A [103], 1989, US       | F   | 1981–1988        | Population from Leisure World, Laguna Hills, US | 214        | 13,870                    | Breast cancer| Questionnaire      | Aspirin use: none, <daily, daily                         | 2                         | 4            |

¹Study deemed to be prone to immortal time bias
| Study source | Sex | Study period | Source of subjects | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|---------------------------|-------------|---------------------|---------------------|-----------------------|--------------|
| Peres LC [156], 2016, US | F | 2010–2015 | AACES | 541 | 731 | Epithelial ovarian cancer | Questionnaire | Use at least once a week or at least 5 days out of the month, at any point in their lifetime (regular) | 1,4,5,10,18, 29,48, 49,50,51,52,53,54, 55 | 7 |
| Brandrup L [157], 2015, Denmark | F | 2000–2011 | The Danish Cancer Registry | 4103 | 58,706 | Epithelial ovarian cancer | The Danish Prescription Registry | Use < 2 prescriptions (non-users) | 1,5,7,25,29,43,50, 52,55, 56,57,58, 8 | 8 |
| Lo-Ciganic WH [158], 2012, US | F | 2003–2008 | HOPE study | 625 | 1210 | Ovarian cancer | Questionnaire | Use at least 2 tablets per week for 6 months or more (regular) | 1,5,10,11,30,39, 42,49, 50,51,55, 60 | 7 |
| Ammundsen HB [159], 2012, Denmark | F | 1995–1999 | Danish MALOVA study | 756 | 1564 | Ovarian cancer | Questionnaire | Use two times or more per week for more than 1 month | 1,38,50,55, 61 | 6 |
| Pinheiro SP [160], 2010, US | F | 1992–2003 | New England Case-Control Study | 1120 | 1160 | Ovarian cancer | Questionnaire | Use at least twice a week (regular) | 1,54 | 7 |
| Wu AH [161], 2009, US | F | 1998–2002 | Population from Los Angeles County | 582 | 668 | Ovarian cancer | Questionnaire | Use aspirin medication 2 or more times a week for 1 month or longer | 1,4,5,11,49, 50,51, 55, 62 | 8 |
| Wernli KJ [162], 2008, US | F | 1998–2001 | Population from Wisconsin and Massachusetts | 400 | 2107 | Ovarian cancer | Telephone interview | Use aspirin for more than 6 months and more than twice per week (ever use) | 1,4,30,49,51, 65 | 7 |
| Merritt MA [163], 2008, Australia | F | 2002–2005 | Australian Ovarian Cancer Study | 1564 | 1502 | Ovarian cancer | Self-administered questionnaires | Ever use of aspirin—not further defined | 1,5,50,55 | 6 |
| Schildkraut JM [164], 2006, US | F | 1999–2003 | North carolina ovarian cancer study | 586 | 627 | Ovarian cancer | In-person questionnaires | Use at least 3 month of use during the 5-year period (regular) | 1,4,5,11,43,49, 50, 53,60,63,64 | 7 |
| Moysich KB [165], 2001, US | F | 1982–1998 | RPCI buffalo | 547 | 1094 | Ovarian cancer | Self-administered questionnaires | Use at least once a week for 6 consecutive months (regular) | 1,4,40,49,55, 65 | 6 |
| Rosenberg L [166], 2000, US | F | 1976–1998 | Patients from hospital in Baltimore, Boston, New York, and Philadelphia | 780 | 4623 | Ovarian cancer | Questionnaire | Use at least 1 day per week for at least 6 months (regular) | 1,30,59 | 7 |
| Tavani A [167], 2000, US | F | 1992–1999 | Population from Italy | 749 | 898 | Ovarian cancer | Questionnaires | Use at least once a week for more than six consecutive months (regular) | 1,5,10,37,50,54, 55,59 | 6 |
| Cramer DW [168], 1998, US | F | 1992–1997 | Patients from hospital in eastern Massachusetts and all of New Hampshire | 563 | 523 | Ovarian cancer | In-person interviews | Use at least once a week for at least 6 months | 1,5,9,46,54,55,66, 67,68 | 8 |
| Study source          | Sex | Study period | Source of subjects | No of case | No of control/cohort size | Cancer site               | Exposure assessment | Exposure Definition                                                                 | Adjustment for covariates | Study quality |
|-----------------------|-----|--------------|--------------------|------------|--------------------------|---------------------------|---------------------|---------------------------------------------------------------------|-----------------------------|---------------|
| Brasky TM [92], 2014, US | F   | 1998–2010    | WHI                | 445        | 116,248                  | Ovarian cancer            | Questionnaire        | Use at both baseline and year 3 visits (consistent) | 1, 3, 4, 5, 6, 10, 11, 18, 19, 22, 24, 25, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 | 9              |
| Setiawan VW [169], 2012, Multinational | F   | 1993–2008    | MEC                | 275        | 64,000                   | Ovarian cancer            | Questionnaire        | Use at least 2 times a week for 1 month or longer               | 1, 11, 23, 36, 50, 55      | 7              |
| Murphy MA [170], 2012, US | F   | 1995–2006    | AARP               | 438        | 96,710                   | Ovarian cancer            | Mailed questionnaires | Use one or more pills per week (regular)                         | 1, 4, 11, 23, 36, 37, 43, 50, 55 | 7              |
| Prizment AE [171], 2010, US | F   | 1992–2006    | IWHS               | 157        | 21,694                   | Ovarian cancer            | Questionnaire        | Had ever taken aspirin-not further defined                       | 1, 4, 11, 23, 36, 37, 43, 50, 55 | 9              |
| Pinheiro SP [160], 2010, US | F   | 1992–2003    | NHS and NHS-II cohorts | 217     | 628                      | Ovarian cancer            | Questionnaire        | Use at least twice a week (regular)                              | 1, 11, 23, 36, 50, 55      | 7              |
| Lacey JV [172], 2004, US | F   | 1979–1998    | BCDDP              | 116        | 31,364                   | Ovarian cancer            | Telephone interview and mailed questionnaires | Use at least once a week for 1 year (regular)                        | 1, 4, 11, 23, 36, 50, 55 | 7              |
| Friis S [62], 2003, Denmarka | F   | 1989–1997    | Population from North Jutland County | 34      | 29,470                   | Ovarian cancer            | Prescription database | 75–150 mg once daily (low-dose aspirin)                           | 1, 4, 11, 23, 36, 50, 55 | 8              |
| Akhmedkhanov A [173], 2001, US | F   | 1994–1996    | The NYU Women's Health Study | 68      | 680                      | Epithelial ovarian cancer | Self-administered questionnaires | Use three or more times per week for at least 6 months | 1, 4, 11, 23, 36, 50, 55 | 8              |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = chronic obstructive pulmonary disease or asthma, 8 = Fat distribution, 9 = religion, 10 = BMI, 11 = race, 12 = folate, 13 = Charlson comorbidity index, 14 = statin, 15 = metformin, 16 = ACE inhibitors, 17 = Angiotensin II receptor blockers, 18 = physical activity, 19 = fruit, vegetable and/or vitamin intake, 20 = history of colonoscopy, 21 = total energy intake, 22 = ever use of calcium supplements in the past 5 years, 23 = former health checkup, 24 = red meat, 25 = hormone replacement therapy, 26 = unique number of dispensing, 27 = unique number of hospitalizations in the year prior to start of follow up, 28 = mammogram in past 2 y, 29 = other NSAIDs, 30 = area (county/region), 31 = migraine, 32 = Nitro-vasodilator use, 33 = observational study enrollment, 34 = diet modification trial enrollment, 35 = screening for cancer, 36 = age at menarche, 37 = age at menopause, 38 = gravidity, 39 = history of arthritis, 40 = age at first birth, 41 = duration of estrogen therapy, 42 = duration of combined postmenopausal hormone therapy, 43 = hysterectomy status, 44 = use of antihypertensive medication, 45 = history of coronary heart disease, 46 = use of cholesterol-lowering medication, 47 = history of ulcer, 48 = income, 49 = tubal ligation, 50 = oral contraceptive use, 51 = menopausal status, 52 = endometriosis, 53 = pelvic inflammatory disease, 54 = study site, 55 = parity, 56 = infertility, 57 = diabetes mellitus, 58 = tubal sterilization, 59 = interview year, 60 = breastfeeding, 61 = duration of oral contraceptive use, 62 = tac use, 63 = months of pregnancy, 64 = severe menstrual cramping, 65 = presence of irregular menses, 66 = menstural, headache, or arthritic pain, 67 = ibuprofen, 68 = paracetamol, 69 = partial oophorectomy, 70 = African American Cancer Epidemiology Study, 71 = AARP AARP. Diet and Health Study, BCDDP the Breast Cancer Detection Demonstration Project, HOPE hormones and Ovarian cancer prediction study, Iowa Women's Health Study, MALOVA Danish MALignant Ovarian cancer study, MEC multiethnic cohort study, NHS nurses' health study, NYU New York University, RPCI Roswell Park Cancer Institute, WHI women's health initiative.
Table 9 Characteristics of included studies - endometrial cancer

| Study source | Sex | Study period | Source of subjects | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|----------------------------|-------------|---------------------|---------------------|------------------------|--------------|
| Borss N [174], 2015, Denmark | F | 2000–2009 | Patients from Civil Registration System | 5382 | 72,127 | Endometrial cancer | Prescription | Use ≥2 prescriptions on separate dates over the entire study period (ever users) | 1,5,25,29,48,49,50,51 | 8 |
| Neill AS [175], 2013, Australia | F | 2005–2007 | ANECS | 1360 | 712 | Endometrial cancer | Telephone interview | Had ever taken aspirin - not further defined | 13,10,25,36,48,50,52 | 7 |
| Bosetti C [176], 2010, Italy | F | 1992–2006 | Population from Italy | 442 | 676 | Endometrial Cancer | Questionnaire | Use at least once a week for more than 6 months (regular) | 1,5,10,25,36,48,52,53,54,55 | 5 |
| Fortuny J [177], 2009, US | F | 2001–2005 | The EDGE Study | 469 | 467 | Endometrial cancer | Interview | Use aspirin for 6 months or longer | 1,10 | 7 |
| Bodelon C [178], 2009, US | F | 2003–2005 | Population from King, Pierce, and Snohomish counties | 330 | 286 | Endometrial Cancer | In-person interview | Use for more than 5 days per month for at least 6 months | 1,7,10,25,30 | 6 |
| Moysich KB [179], 2005, US | F | 1982–1998 | RPCI Institute | 427 | 427 | Endometrial Cancer | Questionnaire | Use at least once a week for 6 months (regular) | 1,5,10,36,37,48 | 6 |
| Brasky TM [92], 2014, US | F | 1998–2010 | WHI | 865 | 85,351 | Endometrial cancer | Questionnaire | Use at both baseline and year 3 visits (consistent) | 1,3,4,5,6,10,11,18,19,22,24,25,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47 | 9 |
| Brasky TM [180], 2013, US | F | 2000–2010 | VITAL Cohort | 248 | 22,268 | Endometrial Cancer | Mailed baseline questionnaire | Use ≥4 days/week and ≥4 years (high use) | 1,3,4,5,6,10,11,18,25,29,31,36,37,39,40,41,42,43,44,45,46,47 | 7 |
| Setiawan VW [169], 2012, Multinational | F | 1993–2008 | MEC | 620 | 64,000 | Endometrial cancer | Questionnaire | Use at least 2 times a week for 1 month or longer | 1,3,10,11,18,25,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47 | 7 |
| Prizment AE [171], 2010, US | F | 1992–2006 | IWHS | 311 | 21,694 | Endometrial cancer | Questionnaire | Had ever taken aspirin - not further defined | 1,6,10,25,36,37,50,52,56 | 9 |
| Danforth KN [181], 2009, US | F | 1995–2003 | AARP | 576 | 72,524 | Endometrial cancer | Mailed questionnaire | Had ever taken aspirin - not further defined | 3,4,10,11,18,36,37,45,48,50,52,56 | 7 |
| Viswanathan AN [182], 2008, US | F | 1980–2004 | The NHS | 436 | 82,971 | Endometrial cancer | Medical record | Use at least 1 tablet per week or 1 day per week (current user) | 4,10,18,25,37,40,60,61,62 | 6 |
Table 9: Characteristics of included studies- endometrial cancer (Continued)

| Study source | Sex | Study period | Source of subjects | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|---------------|--------------------|------------|---------------------------|-------------|---------------------|---------------------|------------------------|--------------|
| Friis S [62], Denmarka | F | 1989–1997 | Population of North Jutland County | 45 | 29,470 | Endometrial cancer | Prescription database | 75–150 mg once daily (low-dose aspirin) | 1,2 8 | 8 |
| Schreinemachers DM [63], 1994, US | F | 1971–1987 | The National Health and Examination Survey 1 | 26 | 12,668 | Endometrial cancer | Self reported | Use aspirin during the 30-day period before the interview | 1,2 6 | 6 |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = calendar year, 8 = Fat distribution, 9 = social status, 10 = BMI, 11 = race, 12 = folate, 13 = Charlson comorbidity index, 14 = statin, 15 = metformin, 16 = ACE inhibitors, 17 = Angiotensin II receptor blockers, 18 = physical activity, 19 = fruit, vegetable and/or vitamin intake, 20 = history of colonoscopy, 21 = total energy intake, 22 = ever use of calcium supplements in the past 5 years, 23 = former health checkup, 24 = red meat, 25 = hormone replacement therapy, 26 = unique number of dispensing, 27 = unique number of hospitalizations in the year prior to start of follow up, 28 = mammogram in past 2 y, 29 = other NSAIDs, 30 = area (county/region), 31 = migraine, 32 = Nitro-vasodilator use, 33 = observational study enrollment, 34 = diet modification trial enrollment, 35 = screening for cancer, 36 = age at menarche, 37 = age at menopause, 38 = gravidity, 39 = history of arthritis, 40 = age at first birth, 41 = duration of estrogen therapy, 42 = duration of combined postmenopausal hormone therapy, 43 = hysterectomy status, 44 = use of antihypertensive medication, 45 = history of coronary heart disease, 46 = use of cholesterol-lowering medication, 47 = history of ulcer, 48 = parity, 49 = obesity, 50 = diabetes, 51 = chronic obstructive pulmonary disease, 52 = oral contraceptive use, 53 = study center, 54 = period of interview, 55 = menopausal status, 56 = hypertension, 57 = years of oral contraceptive use, 58 = oophoerectomy, 59 = history of stroke, 60 = waist-hip ratio, 61 = intrauterine device use, 62 = height

AARP AARP diet and health study, ANECS Australian National Endometrial Cancer Study, EDGE Study estrogen, diet, genetics, and endometrial cancer, IWHS Iowa Women’s Health Study, MEC multiethnic cohort study, NHS nurses’ health study, RPCI the Roswell Park Cancer Institute, VITAL the vitamins and lifestyle, WHI women’s health initiative

*Study deemed to be prone to immortal time bias.
| Study source                  | Sex | Study period     | Source of subjects | No of case/cohort size | Cancer site       | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|------------------------------|-----|------------------|-------------------|------------------------|-------------------|--------------------|---------------------|------------------------|---------------|
| **Case-control studies**     |     |                  |                    |                        |                   |                    |                     |                        |               |
| Friel G [183], 2015, US F    | 1982–1998 RPCI | 272               | 1072               | Cervical Cancer        | Questionnaire     | Use at least once a week for 6 months (regular) | 1,3,4,5, 6,7,8,9,10, 11,12,13 | 7            |
| Wilson JC [184], 2013, UKa F  | 1995–2010 CPRD | 724               | 3479               | Cervical Cancer        | Prescription database | Use of aspirin - not further defined | 3,14,15,16,17,18, 19,20,21 | 7            |
| Friis S [62], 2003, Denmarka F | 1989–1997 Population from North Jutland County | 15               | 29,470             | Cervix uterus cancer   | Prescription database | 75–150 mg once daily (low-dose aspirin) | 1,2          |
| Schreinemachers DM [63], 1994, US F | 1971–1987 The National Health and Examination Survey I | 29               | 12,668             | Cervix uterus cancer   | Self reported | Use aspirin during the 30 day period before the interview | 1,2          |

1 = age, 2 = sex, 3 = smoking, 4 = spermicide contraceptive use, 5 = circulatory system disease, 6 = education, 7 = age at first pregnancy, 8 = menopausal status, 9 = genital tract disease, 10 = year survey completed, 11 = blood and blood-forming organs disease, 12 = oral, 13 = barrier, 14 = HRT use, 15 = hormone contraceptive use, 16 = systemic steroids, 17 = DMARD use, 18 = history of cancer, 19 = years of follow-up, 20 = sexually transmitted infections, 21 = use of antiviral drugs

CPRD clinical practice research data link, RPCI the Roswell Park Cancer Institute

aStudy deemed to be prone to immortal time bias
| Study source                      | Sex | Study period | Source of subjects                                                  | No of case | No of control/ cohort size | Cancer site       | Exposure assessment | Exposure Definition                                                                 | Adjustment for covariates | Study quality |
|----------------------------------|-----|--------------|---------------------------------------------------------------------|------------|---------------------------|-------------------|---------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------|---------------|
| Iqbal U [47], 2017, China        | M   | 2001–2011    | The Taiwan NHI database                                            | 32,419     | 129,676                   | Prostate cancer   | Prescription        | Patients had aspirin prescribed at least for 2 months during the 3-year period before the initial cancer diagnosis               | 1,2,13,14, 15,16,17        | 7             |
| Skriver C [185], 2016, Denmark   | M   | 2000–2012    | Danish nationwide registries                                       | 35,600     | 177,992                   | Prostate cancer   | Prescription        | Use aspirin ≥ 2 prescriptions redeemed on separate dates (ever use)                                                            | 1, 4,14,28,30,36,37, 38,40, | 8             |
| Veitonmäki T [186], 2013, Finland | M   | 1995–2002    | Finnish Cancer Registry                                            | 13,478     | 24,657                    | Prostate cancer   | Prescription database | Ever use aspirin- not further defined                                                                                           | 1,32                       | 8             |
| Murad AS [187], 2011, UK         | M   | 2001–2008    | ProtecT                                                             | 1016       | 5043                      | Prostate cancer   | Questionnaire       | Ever use aspirin- not further defined                                                                                           | 1,28,33,35                 | 8             |
| Salinas CA [188], 2010, US       | M   | 2002–2005    | SEER cancer registry                                               | 1000       | 942                       | Prostate cancer   | Questionnaire       | Use at least once per week for 3 months (ever use)                                                                                | 1,11,42                    | 7             |
| Harris RE [189], 2007, US        | M   | 1999–2005    | CHRI                                                                | 24         | 39                        | Prostate cancer   | Medical-record      | At least two times per week for 2 years or more                                                                               | 1,35,6,10                  | 5             |
| Bosetti C [190], 2006, Italy     | M   | 1991–2002    | Population from the greater Milan area, the provinces of Pordenone, Gorizia, Latina and the urban area of Naples | 1261       | 1131                      | Prostate cancer   | Standard questionnaire | Use at least once a week for more than 6 months (regular)                                                                        | 1,45,34                    | 5             |
| Dasgupta K [191], 2006, Canada   | M   | 1999–2002    | RAMQ                                                                | 2025       | 2150                      | Prostate cancer   | Prescription database | Did not receive any prescription for aspirin (nonuser)                                                                         | 1,43                       | 6             |
| Liu X [192], 2006, US            | M   | 2001–2004    | Population from Cleveland, Ohio                                     | 471        | 468                       | Prostate cancer   | Personal interview  | Use at least twice a week for more than a month (any use)                                                                        | 1,11,44                    | 5             |
| Menezes RJ [193], 2006, US       | M   | 1982–1998    | RPCI                                                                | 1029       | 1029                      | Prostate cancer   | Questionnaire       | Use at least once a week for at least 6 months (regular)                                                                        | 1,5,10                     | 5             |
| Perron L [194], 2003, Canada     | M   | 1993–1995    | RAMQ                                                                | 2221       | 11,105                    | Prostate cancer   | Prescription database | Ever use aspirin- not further defined                                                                                           | 1,50                       | 6             |
| Norrish AE [195], 1998, New Zealand | M | 1996–1997 | Auckland Prostate Study | 317    | 480   | Prostate cancer | Questionnaire | At least once per week (regular)                                                                                               | 1,50,51,52,53              | 7             |
Table 11 Characteristics of included studies- prostate cancer (Continued)

| Study source                  | Sex | Study period          | Source of subjects                                      | No of case | No of control/cohort size | Cancer site     | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|-------------------------------|-----|-----------------------|---------------------------------------------------------|------------|---------------------------|-----------------|---------------------|-----------------------|-------------------------|---------------|
| Neugut AI [80], 1998, US      | M   | 1989–1992             | Columbia-Prebyterian Medical Center                    | 319        | 189                       | Prostate cancer | Medical record       | Use aspirin-not further defined | 1,45                    | 6             |
| Cohort studies               |     |                       |                                                         |            |                           |                 |                     |                       |                         |               |
| Cao Y [8], 2016, US           | M   | 1980–2010 1986–2012   | NHS and HPFS                                           | 1019       | 135,965                   | Prostate cancer | Questionnaire        | Use at least 2 times per week(regular) | 3,5,6,7,8,9,10,11,12,18,19,20,21,22,23,24,25,70 | 9             |
| Lapi F [196], 2016, Italya    | M   | 2002–2013             | HSD                                                    | 187        | 13,453                    | Prostate Cancer | Prescription database | Use low-dose aspirin-not further defined | 1,3,6,9,13,14,16,28,38,54,55,5657 | 8             |
| Nordström T [197], 2015, Swedena | M   | 2007–2012             | Population from Stockholm County, Sweden               | 8430       | 204,241                   | Prostate cancer | Swedish Prescribed Drug Register | Any dispensed prescription of the drug within 2 years before biopsy | 1,4,13,14,58,59,60 | 5             |
| Hollestein LM [91], 2014, Netherlandsa | M   | 1998–2010             | PHARMO and the Eindhoven Cancer Registry              | 882        | 53,679                    | Prostate cancer | Prescription database | Low dose aspirin (≤100 mg daily)- not further defined | 1,2,26,27               | 8             |
| Shebl FM [198], 2012, US      | M   | 1993–2001             | PLCO                                                   | 3573       | 29,450                    | Prostate cancer | Questionnaire        | Regular use aspirin-not further defined | 5,11,34,42,62            | 7             |
| Mahmud SM [199], 2011, Canadaa | M   | 1985–2000             | Saskatchewan Ministry of Health (SH) databases and the Saskatchewan Cancer Registry (SCR). | 9007       | 35,891                    | Prostate cancer | Prescription database | Had a participant ever filled a prescription of aspirin in the index class at any time during his exposure history | 28,41,42               | 6             |
| Brasky TM [200], 2010, US      | M   | 2000–2007             | VITAL Cohort                                          | 1547       | 34,132                    | Prostate cancer | Questionnaire        | Use aspirin ≥1 day/week for ≥1 year (regular) | 1,4,5,9,10,11,19,30,55,65,66,67 | 5             |
| Siemes C [96], 2008, Netherland | M   | 1992–2004             | The Rotterdam Study                                   | 216        | 7621                      | Prostate cancer | Questionnaire and prescriptions | The absence of a prescription for any non-aspirin or aspirin NSAID(no use) | 1,3,10,61              | 8             |
| Jacobs EJ [98], 2007, US       | M   | 1992–2003             | Cancer Prevention Study II Nutrition Cohort           | 5539       | 69,810                    | Prostate cancer | Questionnaire        | Use at least 30 "times" per month(daily use of adult-strength) | 1,3,4,9,10,11,18,20,28,29,30,31 | 8             |
| Platz EA [201], 2005, US       | M   | 1980–2004             | BLSA                                                   | 141        | 9748                      | Prostate cancer | Self-reported        | Had ever taken aspirin-not further defined | 1,2,84,65                | 7             |
| Garcia Rodriguez LA [44], 2004, UKa | M   | 1995–2001             | GPRD                                                   | 2096       | 9579                      | Prostate cancer | Prescription database | No use of aspirin at any time before the index date(nonuser) | 1,45,46,47,48,49        | 8             |
| Friis S [52], 2003, Denmarka   | M   | 1989–1997             | Population of North Jutland County                    | 196        | 29,470                    | Prostate cancer | Prescription database | 75–150 mg once daily (low-dose aspirin) | 1,2                    | 8             |
| Study source            | Sex | Study period | Source of subjects                                                                 | No of case | No of control/cohort size | Cancer site            | Exposure assessment | Exposure Definition                        | Adjustment for covariates | Study quality |
|------------------------|-----|--------------|------------------------------------------------------------------------------------|------------|---------------------------|------------------------|---------------------|-------------------------------------------------|--------------------------|---------------|
| Habel LA [202], 2002, US | M   | 1964–1973    | The Kaiser Permanente Medical Care Program in Northern California                  | 2574       | 90,100                    | Prostate cancer        | Questionnaire        | Use more than six aspirin per days              | 1,4,11,69               | 6             |
| Schreinemachers DM [63], 1994, US | M   | 1971–1987    | The National Health and Examination Survey I                                      | 123        | 12,668                    | Prostate cancer        | Self reported        | Use aspirin during the 30-day period before the interview | 1,2                      | 6             |
| Paganini-Hill A [103], 1989, US | M   | 1981–1988    | Population from Leisure World, Laguna Hills, US                                    | 149        | 13,870                    | Prostate cancer        | Questionnaire        | Aspirin use none, <daily, daily                  | 2                        | 4             |

1 = age, 2 = sex, 3 = smoking, 4 = education level, 5 = family history, 6 = alcohol intake, 7 = height, 8 = Alternate Healthy Eating Index-2010, 9 = PSA test in past 2 y, 10 = BMI, 11 = race, 12 = folate, 13 = Charlson comorbidity index, 14 = statin, 15 = metformin, 16 = ACE inhibitors, 17 = Angiotensin II receptor blockers, 18 = physical activity, 19 = fruit, vegetable and/or vitamin intake, 20 = history of colonoscopy, 21 = total energy intake, 22 = ever use of calcium supplements in the past 5 years, 23 = former health checkup, 24 = mammogram in past 2 y, 25 = hormone replacement therapy, 26 = unique number of dispensing, 27 = unique number of hospitalizations in the year prior to start of follow up, 28 = other NSAIDs, 29 = history of heart attack, 30 = diabetes, 31 = hypertension, 32 = simultaneous use of other medications (cholesterol lowering drugs, anti-diabetic drugs, antihypertensive drugs and benign prostatic hyperplasia medication), 33 = the primary care centers from which they were recruited, 34 = study center, 35 = any paracetamol use, 36 = residence (by design), 37 = use of high-dose aspirin, 38 = 5-alpha reductase inhibitors, 39 = income, 40 = selected cardiovascular drugs, and antidepressants or neuroleptics, 41 = ever visited a urologist 1–11 years prior, 42 = SCREENED and volume of family physician visits in the 5 years prior to the index date, 43 = finasteride, 44 = medical institution, 45 = calendar year, 46 = prior BPH history, 47 = number of visits to general practitioners, 48 = referrals, 49 = hospitalizations, 50 = recent medical contacts, 51 = socio-economic status, 52 = total polyunsaturated fat consumption, 53 = a-linolenic acid and ratio of dietary n-6long-chain n-3 polyunsaturated fatty acids, 54 = presence of obesity, 55 = benign prostatic hypertrophy, 56 = alpha-adrenerceptor antagonists, 57 = immunosuppressive drugs, 58 = natural log-transformed prostate specific antigen (PSA) concentration, 59 = PSA quotient, 60 = use of antidiabetic medication, 61 = C-reactive protein level, 62 = ibuprofen use, 63 = osteoarthritis, 64 = rheumatoid arthritis, 65 = enlarged prostate, 66 = coronary artery disease, 67 = chronic joint pain, chronic headaches, and migraines, 68 = acetaminophen, 69 = and number of health checkups, 70 = red meat, 71 = Baltimore Longitudinal study of Aging, 72 = Cancer Hospital and Richard J. Solove Research Institute, 73 = general practitioners research database, 74 = Health Professionals follow-up study, 75 = health search IMS health longitudinal patient database, 76 = NHS nurses’ health study, 77 = PLCO prostate, lung, colorectal and ovarian cancer screening trial, 78 = Prostate Testing for Cancer and Treatment, 79 = Re’seau du Quebec, 80 = the Roswell Park Cancer Institute, 81 = SEER surveillance, epidemiology and end results, 82 = VITAL the vitamins and lifestyle

Study deemed to be prone to immortal time bias
| Study source         | Sex | Study period | Source of subjects                | No of case | No of control/cohort size | Cancer site          | Exposure assessment | Exposure Definition                                                                 | Adjustment for covariates | Study quality |
|---------------------|-----|--------------|----------------------------------|------------|---------------------------|----------------------|--------------------|--------------------------------------------------------------------------------------|---------------------------|---------------|
|                      |     |              |                                   |            |                           |                      |                    |                                                                         |                           |               |
| **Case-control studies** |     |              |                                   |            |                           |                      |                    |                                                                         |                           |               |
| Karami S [203], 2016, US | M/F | 2002–2007    | US Kidney Cancer Study            | 1187       | 1204                      | Renal-cell cancer    | Questionnaires     | Use at least once a week for 3 months or longer, at least 2 years prior to the interview | 1,2,3,4,5,10,11,27,51,52  | 8             |
| Tavani A [204], 2010, Italy | M/F | 1992–2004    | Population from Italian areas     | 755        | 1297                      | Renal-cell cancer    | Questionnaires     | Use at least once a week for more than 6 months (regular)                       | 1,2,3,5,6,7,27,55,56      | 7             |
| Gago-Dominguez M [205], 1999, US | M/F | 1986–1994    | Patients from Los Angeles County  | 1204       | 1204                      | Renal-cell cancer    | Questionnaires     | Had ever taken the drug 20 or more times                                        | 3,5,10,27,57              | 6             |
| Chow WH [206], 1994, US | M/F | 1988–1990    | Population from Minnesota         | 440        | 691                       | Renal-cell cancer    | Interviewer        | Use at least 2 or more times per week for 1 month or longer (regular)           | 1,3,10                    | 6             |
| McCredie M [207], 1993, Australia | M/F | 1989–1990    | The NSW Central Cancer Registry   | 489        | 523                       | Renal-cell cancer    | Questionnaires     | Had ever taken the drug 20 or more times                                        | 1,2,3,5,58                | 7             |
| McCredie M [208], 1988, Australia | M/F | 1977–1982    | New South Wales Central Cancer Registry | 360    | 985                       | Kidney cancer        | Questionnaires     | Had taken a total of more than 0.1 kg                                           | 1,2,3,4,5,60,61           | 6             |
| **Cohort studies**   |     |              |                                   |            |                           |                      |                    |                                                                         |                           |               |
| Karami S [203], 2016, US | M/F | 2002–2007    | Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial | 135       | 98,807                    | Renal cell carcinoma | Questionnaires     | Use at least once per week                                                      | 1,3,5,10,11,27,51         | 7             |
| Brasky TM [92], 2014, US | F   | 1998–2010    | WHI                               | 329        | 141,880                   | Kidney cancer        | Questionnaires     | Use at both baseline and year 3 visits (consistent)                            | 1,3,4,5,6,10,11,17,18,19,25,26,28,29,30,31,32,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48 | 7             |
| Liu W [209], 2013, US | M/F | 1996–2006    | AARP                              | 884        | 298,468                   | Renal cell carcinoma | Questionnaires     | Any use of aspirin                                                            | 1,2,3,4,5,6,7,10,11,18,19,25,26,28,29,30,31,32,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48 | 9             |
| Cho E [210], 2011, US | F   | 1986–2006    | NHS                               | 153        | 77,525                    | Renal cell carcinoma | Questionnaires     | Use aspirin ≥ 2 times/week (regular)                                           | 1,3,6,10,18,19,27,39       | 7             |
|                      | M   | 1990–2006    | HPFS                              | 180        | 49,403                    | Renal cell carcinoma | Questionnaires     | Use aspirin ≥ 2 times/week (regular)                                           | 1,3,6,10,18,19,27          | 9             |
| Jacobs EJ [98], 2007, US | M/F | 1992–2003    | Cancer Prevention Study II Nutrition Cohort | 365       | 146,113                   | Kidney cancer        | Questionnaires     | Use at least 30 “times” per month (daily use of adult-strength)                | 1,2,3,5,7,10,11,15,16,17,18,20,25,27,45 | 8             |
Table 12 Characteristics of included studies - renal cancer (Continued)

| Study source | Sex | Study period | Source of subjects | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|-----------|---------------------------|-------------|---------------------|---------------------|----------------------|--------------|
| Friis S [62], 2003, Denmarka | M/F | 1989–1997 | Population from North Jutland County | 67 | 294/70 | Kidney cancer | Prescription database | 75–150 mg once daily (low-dose aspirin) | 1, 2 | 8 |
| Schreinemachers DM [63], 1994, US | M/F | 1971–1987 | The National Health and Examination Survey | 32 | 12,668 | Kidney cancer | Self reported | Use aspirin during the 30-day period before the interview | 1, 2 | 6 |
| Paganini-Hill A [103], 1989, US | M/F | 1981–1988 | Population from Leisure World, Laguna Hills, US | 25 | 13,870 | Kidney cancer | Questionnaires | Aspirin use: none, <daily, daily | 2 | 4 |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = diabetes, 8 = fat distribution, 9 = social status, 10 = BMI, 11 = race, 12 = folate, 13 = height, 14 = Alternate Healthy Eating Index-2010, 15 = PSA test in past 2 y, 16 = mammogram in past 2 y, 17 = hormone replacement therapy, 18 = physical activity, 19 = fruit, vegetable and/or vitamin intake, 20 = history of colonoscopy, 21 = total energy intake, 22 = ever use of calcium supplements in the past 5 years, 23 = former health checkup, 24 = red meat, 25 = other NSAIDs, 26 = area (county/region), 27 = hypertension, 28 = migraine, 29 = ever use of calcium supplements in the past 5 years, 30 = red meat, 31 = Nitro-vasodilator use, 32 = height, 33 = unique number of hospitalizations in the year prior to start of follow up, 34 = observational study enrollment, 35 = diet modification trial enrollment, 36 = screening for cancer, 37 = age at menarche, 38 = age at menopause, 39 = gravidity, 40 = age at first birth, 41 = duration of estrogen therapy, 42 = duration of combined postmenopausal hormone therapy, 43 = hysterectomy status, 44 = use of antihypertensive medication, 45 = history of coronary heart disease, 46 = use of cholesterol-lowering medication, 47 = history of arthritis, 48 = history of ulcer, 49 = method of interview, 50 = obesity, 51 = center, 52 = dialysis treatment, 53 = marital status, 54 = total dietary fiber, 55 = study center, 56 = year of interview, 57 = regular use of amphetamines, 58 = method of interview, 59 = phenacetin, 60 = paracetamol, 61 = urological disease AARP AARP diet and health study, HPFS Health Professionals follow-up study, NHS nurses’ health study, WHI women’s health initiative

a Study deemed to be prone to immortal time bias
Table 13 Characteristics of included studies- renal pelvis and ureter

| Study source | Sex | Study period | Source of subjects | No of case | No of control/cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|--------------------------|-------------|---------------------|----------------------|------------------------|--------------|
| Linet MS [211], 1995, US | M/F | 1983–1986 | Cancer registries in New Jersey, Iowa and Los Angeles | 418 | 405 | Renal pelvis and ureter cancer | Questionnaire | Use 2 or more doses per week for at least 1 month or longer (regular) | 1,2,3,7 | 8 |
| Mccredie M [207], 1993, Australia | M/F | 1989–1990 | The NSW Central Cancer Registry | 147 | 523 | Renal pelvis cancer | Questionnaire | Had ever taken the drug 20 or more times | 1,2,3,5,8 | 7 |
| Ross RK [212], 1989, US | M/F | 1978–1982 | The Cancer Surveillance Program in Los Angeles County | 187 | 187 | Renal pelvis and ureter cancer | Telephone interviews | Use aspirin for more than 30 days in a single year | 1,2,6 | 8 |
| Jensen OM [213], 1989, Denmark | M/F | 1979–1982 | Patients in hospitals of Copenhagen | 90 | 251 | Renal pelvis and ureter cancer | Face-to-face interviews | Use of aspirin - not further defined | 1,2,4 | 7 |

1 = age, 2 = sex, 3 = smoking, 4 = hospital, 5 = educational level, 6 = race, 7 = geographic site, 8 = method of interview
| Study source           | Sex | Study period | Source of subjects                                                                 | No of case | No of control/ cohort size | Cancer site       | No of reference | Exposure assessment | Exposure Definition                          | Adjustment for covariates | Study quality |
|-----------------------|-----|--------------|------------------------------------------------------------------------------------|------------|---------------------------|------------------|------------------|---------------------|---------------------------------------------|---------------------------|---------------|
| **Case-control studies** |     |              |                                                                                    |            |                           |                  |                  |                     |                                             |                           |               |
| Baris D [214], 2013, US | M/F | 2001–2004    | Population from Maine, Vermont and New Hampshire                                   | 783        | 890                       | Bladder cancer   | Self-reported    | Use at least 20 times (any)               | 1,2,3,11,26,51             | 6              |
| Fortuny J [215], 2007, US | M/F | 1998–2001    | The New Hampshire State Department of Health and Human Services’ rapid reporting Cancer Registry | 456        | 369                       | Bladder cancer   | Interview        | Use at least four times a week for 1 month or longer prior to the reference date | 1,2,3,25                  | 7              |
| Fortuny J [216], 2006, Spain | M/F | 1997–2000    | Patients from five regions in Spain (Barcelona, Valles/Bages, Alacant, Tenerife, and Asturias) | 907        | 965                       | Bladder cancer   | Self-reported    | Use twice or more weekly for ≥ 1 month (regular) | 1,2,3,25,26,52,53          | 8              |
| Castelao JE [217], 2000, US | M/F | 1987–1996    | SEER cancer registry                                                               | 1514       | 1514                      | Bladder cancer   | Questionnaire    | Use at least 20 times (any)               | 3,5,53,54,55,56, 57,58,59,60 | 7              |
| Steineck G [218], 1995, Sweden | M/F | 1985–1987    | Population from the County of Stockholm                                            | 325        | 393                       | Bladder cancer   | Questionnaire    | Had ever taken aspirin-not further defined | 1,2,3,55,56,61,62, 63        | 5              |
| **Cohort studies**     |     |              |                                                                                    |            |                           |                  |                  |                     |                                             |                           |               |
| Brasky TM [92], 2014, US | F   | 1998–2010    | WHI                                                                                | 175        | 142,330                  | Bladder cancer   | Questionnaire    | Use at both baseline and year 3 visits (consistent) | 1,3,4,5,6,10,11,17, 18,19,25,26, 28, 29,30,31,32,34,35, 36,37,38,39,40,41, 42,43,44,45,46,47, 48 | 9              |
| Shih C [219], 2013, US | M/F | 2000–2010    | The VITAL cohort                                                                  | 344        | 77,048                   | Bladder cancer   | Questionnaire    | Use at least once per week, for at least 1 year | 1,2,3,4,5,11,49             | 8              |
| Daugherty SE [220], 2011, US | M/F | 1995–1996    | AARP                                                                               | 1660       | 334,908                  | Bladder cancer   | Questionnaire    | Use aspirin ≥ 2times/week (regular)         | 3,10,11,25,27             | 7              |
|                         |     | 1993–2001    | PLCO Cancer Screening                                                             | 704        | 154,952                  | Bladder cancer   | Questionnaire    | Use aspirin ≥ 2times/week (regular)         | 3,10,11,25,27             | 7              |
|                         |     | 1994–1998    | The USRT Study                                                                    | 97         | 90,972                   | Bladder cancer   | Questionnaire    | Use aspirin ≥ 2times/week (regular)         | 3,10,11,25,27             | 7              |
| Genkinger JM [221], 2007, US | M   | 1986–2004    | HPFS                                                                               | 392        | 49,448                   | Bladder cancer   | Questionnaire    | Use 2 or more times per week (regular)       | 1,3,26,50                 | 9              |
| Jacobs EJ [98], 2007, US | M   | 1992–2003    | Cancer Prevention Study II Nutrition Cohort                                        | 867        | 146,113                  | Bladder cancer   | Questionnaire    | Use at least 30 “times” per month (daily use of adult-strength) | 1,2,3,5,7,10,11, 15,16,17,18,22, 23, 25, 45, 63 | 8              |
| Friis S [62], 2003, Denmark | M/F | 1989–1997    | Population of North Jutland County                                                | 161        | 29,470                   | Bladder cancer   | Prescription database | 75–150 mg once daily (low-dose aspirin) | 1,2                | 8              |
Table 14 Characteristics of included studies- bladder cancer (Continued)

| Study source                        | Sex | Study period   | Source of subjects     | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|-------------------------------------|-----|----------------|------------------------|------------|----------------------------|-------------|---------------------|----------------------|--------------------------|---------------|
| Schreinemachers DM [63], 1994, US   | M/F | 1971–1987      | The National Health and Examination Survey I | 35         | 12,668                     | Bladder cancer | Self reported       | Use aspirin during the 30-day period before the interview | 1, 2, 6       | 6             |
| Paganini-Hill A [103], 1989, US     | M/F | 1981–1988      | Population from Leisure World, Laguna Hills, US | 96         | 13,870                     | Bladder cancer | Questionnaire       | Aspirin use: none, <daily, daily | 2            | 4             |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = history of colorectal endoscopy, 8 = Fat distribution, 9 = social status, 10 = BMI, 11 = race, 12 = education, 13 = height, 14 = Alternate Healthy Eating Index 2010, 15 = PSA test in past 2 y, 16 = mammogram in past 2 y, 17 = hormone replacement therapy, 18 = physical activity, 19 = fruit, vegetable and/or vitamin intake, 20 = history of colonoscopy, 21 = total energy intake, 22 = diabetes, 23 = former health checkup, 24 = red meat, 25 = other NSAIDs, 26 = area (county/region), 27 = study, 28 = migraine, 29 = smoking history of calcium supplements in the past 5 years, 30 = red meat, 31 = Nitro-vasodilator use, 32 = height, 33 = number of hospitalizations in the year prior to start of follow up, 34 = observational study enrollment, 35 = diet modification trial enrollment, 36 = screening for cancer, 37 = age at menarche, 38 = age at menopause, 39 = gravidity, 40 = age at first birth, 41 = duration of estrogen therapy, 42 = duration of combined postmenopausal hormone therapy, 43 = hysterectomy status, 44 = use of antihypertensive medication, 45 = history of coronary heart disease, 46 = use of cholesterol-lowering medication, 47 = history of arthritis, 48 = history of ulcer, 49 = indications for NSAID use, 50 = fluid intake, 51 = hispanic status, 52 = Metamizol, 53 = Acetic acids, 54 = number of years employed as hairdresser/barber, 55 = use of phenacetin, 56 = acetaminophen, 57 = Other salicylic acids, 58 = Propionic acids, 59 = Oxicam, 60 = Pyrazolon derivatives, 61 = Dextropropoxyphene, 62 = Phenazon, 63 = Other analgesics (codeine, chlorphenamine, caffeine), 64 = hypertension AARP AARP diet and health study, HPFS Health Professionals follow-up study, PLCO prostate, lung, colorectal and ovarian cancer screening trial, SEER surveillance, epidemiology and end results, USRT United State Radiologic Technologist Study, VITAL the vitamins and lifestyle, WHI women’s health initiative

*Study deemed to be prone to immortal time bias
| Study source | Sex | Study period | Source of subjects | No of case | No of control/cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|--------------------------|-------------|----------------------|---------------------|------------------------|----------------|
| Egan KM [41], 2016, US | M/F | 2004–2012 | Population in Southeastern US | 1433 | 1296 | Brain tumor | Interview | Use at least twice a week for 12 consecutive months (regular) | 1,2,5,7,8 | 6 |
| Gaist D [222], 2013, Denmark | M/F | 2000–2009 | Danish Cancer Registry, Civil Registration System, National Prescription Registry, Danish National Registry of Patients, and Danisheducation and fertility registries within Statistics Denmark | 2688 | 18,848 | Glioma | National Prescription Registry | Use aspirin as a ‘low’ (≤100 mg) or ‘high’ (150 mg) daily dose of low-dose aspirin | 5,10,13,14,15,16,17,18 | 7 |
| Ferris J [223], 2012, US | M/F | 2007–2010 | CUMC | 236 | 230 | Glioma | Questionnaire | Use at least twice a week for 6 months or longer (ever use) | 1,2,7,9,11,12,13 | 7 |
| | | | The UCSF | 281 | 170 | Glioma | Questionnaire | Use at least twice a week for 6 months or longer (ever use) | 1,2,7,9,11,12,13 | 7 |
| Bannon FJ [224], 2013, UK | M/F | 1987–2009 | UK Clinical Practice Research Datalink(CPRD) | 5052 | 42,678 | Brain tumor | Prescription database | Had ever taken aspirin- not further defined | 1,2,8 | 7 |
| Daugherty SE [225], 2011, US | M/F | 1996–2006 | AARP | 605 | 302,767 | Glioma | Questionnaire | Use aspirin ≥ 2 times/wk. (regular) | 1,2,7,19 | 7 |
| Friis S [62], 2003, Denmark | M/F | 1989–1997 | Population from North Jutland County | 70 | 29,470 | Brain tumor | Prescription database | 75–150 mg once daily (low-dose aspirin) | 1,2 | 8 |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = race, 8 = state of residence, 9 = center, 10 = anti-asthma medications, 11 = individual NSAIDs, 12 = acetaminophen, 13 = statins, 14 = diabetes, 15 = stroke, 16 = allergy, 17 = asthma, 18 = antihistamines, 19 = history of heart disease using age as time metric
AARP AARP diet and health study, CPRD clinical practice research dataalink, CUMC Columbia University Medical Center, UCSF University of California San Francisco
aStudy deemed to be prone to immortal time bias
### Table 16: Characteristics of included studies- head and neck cancers

| Study source | Sex | Study period | Source of subjects | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|---------------------------|-------------|--------------------|---------------------|------------------------|---------------|
| **Case-control studies** |     |              |                    |            |                           |             |                    |                     |                        |               |
| Di Maso M [226], 2015, Italy | M/F | 1992–2008 | Population from Aviano, Pordenone and the greater Milan area in northern Italy | 198 | 596 | Nasopharyngeal cancer | Questionnaire | Use at least one aspirin a week for at least 6 months (regular) | 1,2,3,5,11,12,13 | 6 |               |
| Becker C [227], 2015, UK | M/F | 1995–2013 | CPRD | 2745 | 16,470 | Head and neck cancer | Prescription database | Use aspirin ≥1 Prescription | 3,6,8,10 | 7 |               |
| Macfarlane TV [228], 2012, Europe | M/F | | ARCAGE | 1779 | 1993 | Head and neck cancer | Questionnaire | Use at least once a week for a year (regular) | 1,2,3,5,6,10,18 | 7 |               |
| Ahmadi N [229], 2010, US | M/F | 2003–2007 | Patients from the Lombardi Comprehensive Cancer Center, at GUMC | 25 | 25 | Head and neck cancer | Questionnaire | Daily use of aspirin | 5,19 | 5 |               |
| Jayaprakash V [230], 2006, US | M/F | 1982–1998 | RPCI | 529 | 529 | Head and neck cancer | Questionnaire | Had ever taken aspirin before the onset of the present illness | 1,2,3,6 | 7 |               |
| Rosenquist K [231], 2000, Sweden | M/F | 2000–2004 | Population from the Southern healthcare region of Sweden | 132 | 320 | Oral and oropharyngeal squamous cell carcinoma | Interview | Had ever taken aspirin-not further defined | 36 | 6 |               |
| Bosetti C [232], 2003, Italy | M/F | 1992–2000 | Population from Italy | 740 | 1779 | Oral and pharyngeal, laryngeal cancer | Questionnaire | Use at least once a week for more than 6 months | 1,2,3,5,6,11 | 6 |               |
| **Cohort studies** |     |              |                    |            |                           |             |                    |                     |                        |               |
| Macfarlane TV [69], 2014, UK | M/F | 1996–2010 | PCCIU database | 1195 | 3580 | Head and neck cancer | Prescription database | Had at least one Prescription (users) | 1,2,8,14,15,16,17 | 7 |               |
| Wilson JC [233], 2013, US | M/F | 1993–2001 | PLCO | 316 | 142,034 | Head and neck cancer | Questionnaire | Use aspirin regularly-not further defined | 12,3,10 | 7 |               |
| Friis S [62], 2003, Denmark | M/F | 1989–1997 | Population from North Jutland County | 68 | 29,470 | Head and neck cancer | Prescription database | 75–150 mg once daily (low-dose aspirin) | 1,2 | 8 |               |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = race, 8 = other NSAIDs, 9 = social status, 10 = BMI, 11 = area of residence, 12 = period of interview, 13 = occupation, 14 = deprivation, 15 = CHD, 16 = stroke, 17 = COX-2 inhibitors, 18 = fruit consumption, 19 = marital status

ARCAGE the alcohol-related cancers and genetic susceptibility, CPRD clinical practice research datalink, GUMC Georgetown University Medical School, PCCIU primary care clinical informatics unit database, PLCO prostate, lung, colorectal and ovarian cancer screening trial, RPCI the Roswell Park Cancer Institute

Study deemed to be prone to immortal time bias
| Study source | Sex | Study period | Source of subjects | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|----------------------------|-------------|--------------------|---------------------|----------------------|--------------|
| Patel D [234], 2015, US | M/F | 1993–2001 | AARP | 292 | 269,553 | Thyroid cancer | Questionnaires | Use aspirin ≤ 2 times/Week (no regular use) | 2,3,6,8,11 | 7 |
| | | | PLCO | 56 | 58,433 | Thyroid cancer | Questionnaires | Use aspirin ≤ 2 times/Week (no regular use) | 2,3,6,8,11 | 6 |
| | | | U.S. Radiologic Technologists Study | 133 | 60,591 | Thyroid cancer | Questionnaires | Use aspirin ≤ 2 times/Week (no regular use) | 2,3,6,8,11 | 6 |
| Brasky TM [92], 2014, US | F | 1998–2010 | WHI | 229 | 142,330 | Thyroid cancer | Questionnaires | Use at both baseline and year 3 visits (consistent) | 1,3,4,5,6,7,9,10,11,12,13,14,15,16,17,18,19,22,24,25,26,27,28,29,30,31,32,33,34,35,36,37 | 9 |

1 = age, 2 = sex, 3 = smoking, 4 = education level, 5 = family history, 6 = alcohol intake, 7 = height, 8 = weight, 9 = history of ulcer, 10 = BMI, 11 = race, 12 = duration of estrogen therapy, 13 = duration of combined postmenopausal hormone therapy, 14 = hysterectomy status, 15 = use of antihypertensive medication, 16 = history of coronary heart disease, 17 = use of cholesterol-lowering medication, 18 = physical activity, 19 = fruit, vegetable and/or vitamin intake, 20 = history of colonoscopy, 21 = total energy intake, 22 = ever use of calcium supplements in the past 5 years, 23 = former health checkup, 24 = red meat, 25 = hormone replacement therapy, 26 = gravidity, 27 = history of arthritis, 28 = age at first birth, 29 = other NSAIDs, 30 = area (county/region), 31 = migraine, 32 = Nitro-vasodilator use, 33 = observational study enrollment, 34 = diet modification trial enrollment, 35 = screening for cancer, 36 = age at menarche, 37 = age at menopause

AARP: AARP diet and health study, PLCO: prostate, lung, colorectal and ovarian cancer screening trial, WHI: women’s health initiative
Table 18 Characteristics of included studies- skin cancer

| Study source | Sex | Study period | Source of subjects | No of case | No of control/cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|--------------------------|-------------|---------------------|---------------------|-----------------------|--------------|
| Case-control studies |     |              |                    |            |                          |             |                     |                     |                       |              |
| Reinau D [235], 2015, UK | M/F | 1995–2013 | GPRD               | 73,262     | 96,854                   | Skin cancer | Prescription database | Last prescription ≤ 1 year before the index date (current user) | 36,10, 2943,47, 4849,50,51,52 | 8            |
| Johannesdottir SA [236], 2012, Denmark | M/F | 1991–2009 | Population from northern Denmark | 18,532     | 178,655                  | Skin cancer | Prescription records | Redeemed > 2 prescriptions during the entire study period | 1,2,20,44,45,46 | 8            |
| Torti DC [237], 2011, US | M/F | 1997–2000 | Population from New Hampshire and bordering regions | 1022       | 1484                     | Skin cancer | Interview            | Use at least four times a week for at least 1 month | 1,2,3,53,54,55 | 8            |
| Curiel-Lewandrowski C [238], 2011, US | M/F | 2004–2007 | Dana Farber Harvard Cancer Center Institutions and Dermatology Associates of Concord, Boston(USA) | 400        | 600                      | Cutaneous melanoma | Telephone interview | Use at least once weekly within a year preceding the interview (current user) | 56 | 8            |
| Jeter JM [239], 2011, US | M/F | 2000–2003 | The GEM study      | 327        | 119                      | Melanoma     | Self-reported         | Daily basis for at least 3 months | 1,2,453,57 | 6            |
| Asgari MM [240], 2010, US | M/F | 1994–2004 | KPNC               | 415        | 415                      | Cutaneous squamous cell carcinoma | Questionnaire | Use at least once a week for at least 1 year (regular) | 3,4,5,30,53,56,58,59,60,61,62,63,64,65,66,67,68 | 8            |
| Cohort studies |     |              |                    |            |                          |             |                     |                     |                       |              |
| Hollestein LM [91], 2014, Netherlands | M/F | 1998–2010 | PHARMO and the Eindhoven Cancer Registry | 2363       | 109,276                  | Skin cancer | Prescription database | Low dose aspirin ≤ 100 mg daily- not further defined | 1,2,11,12 | 8            |
| Wysong A [241], 2014, US | F   | 1993–1998 | WHI                | 7652       | 54,728                   | Non-melanoma skin cancer | Questionnaire | Use ≥ 2 times/week for at least 2 weeks (regular) | 1,3,4,5,10,14,15,19,21,29,43,69,70,71,72,73,74 | 6            |
| Brasky TM [92], 2014, US | F   | 1998–2010 | WHI                | 585        | 142,330                  | Melanoma     | Self-administered questionnaires | Use at both baseline and year 3 visits (consistent) | 1,3,4,5,6,10,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37 | 9            |
| Jeter JM [242], 2012, US | F   | 1980–2008 | NHS                | 17,074     | 92,125                   | Skin cancer | Questionnaire         | Use at least 1–2 tablets/week or 1 day/week of regular use at any lifetime (current user) | 13,47,10,14,15,54,57,75,76,77,78,79 | 7            |
| Cahoon EK [243], 2012, US | M/F | 1994–1998, 2003–2005 | United States Radiologic Technologists study | 2215       | 58,213                   | Basal cell carcinoma | Questionnaire | Use at least 1 days per month in the past year | 1,2,80 | 8            |
Table 18 Characteristics of included studies- skin cancer (Continued)

| Study source | Sex | Study period | Source of subjects | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|----------------------------|-------------|---------------------|---------------------|--------------------------|-------------|
| Asgari MM [244], 2008, US | M/F | 2000–2005 | The VITAL cohort | 216 | 39,909 | Melanoma | Questionnaire | Use at least once a week for a year in the 10-year period before baseline (ever use) | 1,2,4,5,15,29, 30,56,59,69,73, 81,82,83 | 8 |
| Jacobs EJ [98], 2007, US | M/F | 1992–2003 | Cancer Prevention Study II Nutrition Cohort | 1049 | 146,113 | Melanoma | Questionnaire | Use at least 30 “times” per month(daily use of adult-strength) | 1,2,3,5,10,13, 14,18,19, 36,38,39,40,41,42 | 8 |
| Schreinemachers DM [63], 1994, US | M/F | 1971–1987 | The National Health and Examination Survey I | 69 | 12,668 | Melanoma | Self reported | Use aspirin during the 30-day period before the interview | 1,2 | 6 |

1 = age, 2 = sex, 3 = smoking, 4 = family history, 5 = educational level, 6 = alcohol intake, 7 = skin reaction to the sun, 8 = Fat distribution, 9 = social status, 10 = BMI, 11 = unique number of dispensing, 12 = unique number of hospitalizations in the year prior to start of follow up, 13 = race, 14 = physical activity, 15 = fruit, vegetable and/or vitamin intake, 16 = ever use of calcium supplements in the past 5 years, 17 = red meat, 18 = hormone replacement therapy, 19 = other NSAIDs, 20 = area (county/region), 21 = migraine, 22 = Nitro-vasodilator use, 23 = observational study enrollment, 24 = diet modification trial enrollment, 25 = screening for cancer, 26 = age at menarche, 27 = age at menopause, 28 = gravidity, 29 = history of arthritis, 30 = history of ulcer, 31 = age at first birth, 32 = duration of estrogen therapy, 33 = duration of combined postmenopausal hormone therapy, 34 = hysterectomy status, 35 = use of antihypertensive medication, 36 = history of coronary heart disease, 37 = use of cholesterol-lowering medication, 38 = mammography, 39 = history of colorectal endoscopy, 40 = history of PSA testing, 41 = diabetes, 42 = hypertension, 43 = the number of general practitioner visits in the year before the index date, 44 = use of systemic glucocorticoids, cytostatic or immunosuppressive medication, 45 = drugs with pigmenting adverse effects, 46 = Charlson comorbidity index, 47 = photosensitising or phototoxic drugs, 48 = inflammatory bowel disease, 49 = ischemic stroke/ transient ischemic attack, 50 = ischemic heart disease, 51 = psoriasis, 52 = systemic glucocorticoids and other immunosuppressants, 53 = skin type, 54 = lifelong number of painful sunburns, 55 = lifelong cumulative number of hours of sun exposure, 56 = number of sunburns of children, 57 = number of moles, 58 = eye color, 59 = natural hair color, 60 = exposure to industrial chemicals, 61 = history of freckling, 62 = outdoor sun exposure, 63 = occupational sun exposure, 64 = tanning bed use, 65 = history of high-risk exposures such as UV light, 66 = burn scar, 67 = radiation treatment, 68 = arsenic exposure, 69 = personal history of nonmelanoma skin cancer, 70 = personal history of melanoma, 71 = current and childhood summer sun exposure, 72 = sunscreen use, 73 = history of cardiovascular disease, 74 = regional solar radiation (Langley), 75 = menopausal status and use of postmenopausal hormones, 76 = questionnaire cycle, 77 = ability to tan, 78 = UV-B availability at state of residence, 79 = height, 80 = solar UV exposure quartile calculated from summer erythemal UV weighted by time outdoors, 81 = ever had moles removed, 82 = chronic pain in last year, 83 = kidney disease or ulcer

GEM the genes, environment, and melanoma study, GPRD general practitioners research database, KPNC Kaiser Permanente Northern California population, NHS nurses' health study, VITAL the vitamins and lifestyle, WHI women's health initiative

*aStudy deemed to be prone to immortal time bias*
| Study source               | Sex  | Study period | Source of subjects                                                                 | No of case | No of control/ cohort size | Cancer site               | Exposure assessment         | Exposure Definition                                      | Adjustment for covariates | Study quality |
|----------------------------|------|--------------|------------------------------------------------------------------------------------|------------|---------------------------|---------------------------|----------------------------|----------------------------------------------------------|---------------------------|---------------|
| Case-control studies       |      |              |                                                                                    |            |                           |                           |                            |                                                          |                           |               |
| Baecklund E [245], 2006, Swedish | M/F  | 196–1995     | From the Swedish Inpatient Register                                               | 269        | 225                       | Lymphoma                  | Hospital records           | Use aspirin for 4 consecutive weeks                      | 15,16                     | 5             |
| Zhang YQ [246], 2006, US   | M/F  | 197–2002     | Subjects were recruited from patients admitted to hospitals in New York, Philadelphia, Boston and Baltimore | 412        | 1524                      | Non-Hodgkin lymphoma       | Nurse-interviewers administered standard questionnaires | Use at least four times per week for at least three or more continuous months(regular) | 1,2,7,8                | 7             |
| Flick ED [247], 2006, US+  | M/F  | 200–2004     | Population from the California counties of San Francisco, Alameda, Marin, Contra Costa, San Mateo, and Santa Clara | 604        | 638                       | Non-Hodgkin lymphoma       | Interview                  | Use at least 2 days per week for 3 months or longer during the past 20 years | 1,2,17                    | 7             |
| Baker JA [248], 2005, US   | M/F  | 198–1998     | RPCI                                                                               | 628        | 2512                      | Non-Hodgkin lymphoma       | Questionnaire              | Use at least once per week for 6 months                 | 1                         | 5             |
| Chang ET [249], 2004, US   | M/F  | 1997–2000    | Population from the greater Boston, Massachusetts, metropolitan area and in the state of Connecticut | 565        | 679                       | Hodgkin’s lymphoma         | Telephone interview        | Use two or more tablets per Week(regular)               | 1,2,3,9,17               | 6             |
| Zhang YW [250], 2004, US   | M/F  | 1996–2000    | Patients in Yale Cancer Center’s Rapid Case Ascertainment Shared Resource(RCA)   | 601        | 717                       | Non-Hodgkin lymphoma       | Interview                  | Use at least once a day for a period of 6 months or longer previous to 1 year ago | 1,4,10,18               | 7             |
| Cohort studies             |      |              |                                                                                    |            |                           |                           |                            |                                                          |                           |               |
| Hollestein LM [91], 2014, Netherlands | M/F  | 1998–2010    | PHARMO and the Eindhoven Cancer Registry                                            | 256        | 109,276                   | Lymphoma                  | Prescription database      | Low dose aspirin (≤100 mg daily)- not further defined   | 1,2,11,12                | 8             |
| Birmann BM [251], 2014, US  | F    | 1976–2008    | NHS                                                                                | 196        | 85,942                    | Multiple myeloma           | Questionnaire              | 81-mg “baby” and 325-mg “adult” strength                | 1,10                     | 8             |
|                             | M    | 1986–2008    | HPFS                                                                               | 132        | 47,029                    | Multiple myeloma           | Questionnaire              | 81-mg “baby” and 325-mg “adult” strength                | 1,10                     | 8             |
| Teras LR [252], 2013, US   | M/F  | 1992–2007    | The CPS-II Nutrition Cohort Cancer Prevention Study-II (CPS-II) Nutrition Cohort | 1709       | 149,570                   | Lymphoma                  | Questionnaire              | Use aspirin ≥30 aspirin pills/Month(regular)            | 1,3,4,5,6,10,19,20, 21,22,23,24,25 | 7             |
| Study source                          | Sex | Study period | Source of subjects                  | No of case | No of control/ cohort size | Cancer site       | Exposure assessment     | Exposure Definition                          | Adjustment for covariates | Study quality |
|--------------------------------------|-----|--------------|-------------------------------------|------------|---------------------------|------------------|-------------------------|-----------------------------------------------|---------------------------|---------------|
| Chang ET [233], 2011, Denmark         | M/F | 1995–2008    | Population from Denmark             | 1659       | 8089                      | Hodgkin lymphoma | Prescription database  | Use aspirin ≥ 2 times per week                | 1,2,13,14                 | 8             |
| Walter RB [254], 2011, US             | M/F | 2000–2002    | VITAL Study                         | 224        | 64,839                    | Lymphoma         | Questionnaire           | Had ever taken low dose aspirin (81 mg)       | 4,21,23,26,27,28, 29,33 | 6             |
| Erber E [255], 2009, US               | M/F | 199–1996     | MEC Study                           | 896        | 193,050                   | Non-Hodgkin Lymphoma | Self-completed questionnaire | Use at least two times per week for 1 month or longer | 5,6,10                    | 8             |
| Cerhan JR [256], 2003, US             | M/F | 199–1999     | IWHS                                | 130        | 27,290                    | Non-Hodgkin Lymphoma | Self-completed questionnaire | Had ever taken aspirin- not further defined | 1,3,6,17,21,25, 29, 30,31,32 | 7             |
| Friis S [62], 2003, Denmark           | M/F | 1989–1997    | Population from North Jutland County | 57         | 29,470                    | Non-Hodgkin's lymphoma | Prescription database  | 75–150 mg once daily (low-dose aspirin)       | 1,2                       | 8             |
| Schreinemachers DM [63], 1994, US     | M/F | 1971–1987    | The National Health and Examination Survey | 48         | 12,668                    | Lymphoma         | Self reported           | Use aspirin during the 30-day period before the interview | 1,2                       | 6             |

1=age, 2=sex, 3=smoking, 4=family history, 5=educational level, 6=alcohol intake, 7=year of interview, 8=study center, 9=use of other analgesics, 10=BMI, 11=unique number of dispensing, 12=unique number of hospitalizations in the year prior to start of follow up, 13=Charlson comorbidity index, 14=history of connective tissue disorder, 15=auranofin, chlorambucil, cyclophosphamide, cyclosporine, D-penicillamine, and podophyllotoxin, 16=disease activity, 17=guidance, 18=menopausal status, 19=race, 20=sitting time, 21=diabetes status, 22=heumatoid arthritis status, 23=cholesterol-lowering drug use, 24=acetaminophen use, 25=postmenopausal hormone use, 26=self-reported health, 27=history of coronary artery disease, 28=stroke, 29=marital status, 30=transfusion history, 31=red meat and fruit intake, 32=replacement therapy, 33=history of fatigue/lack of energy.

*HPFS* Health Professionals follow-up study, *IWHS* Iowa Women's Health Study, *MEC* multiethnic cohort study, *NHS* nurses’ health study, *RPCI* the Roswell Park Cancer Institute, *VITAL* the vitamins and lifestyle study

*Study deemed to be prone to immortal time bias*
| Study source | Sex | Study period | Source of subjects | No of case | No of control/ cohort size | Cancer site | Exposure assessment | Exposure Definition | Adjustment for covariates | Study quality |
|--------------|-----|--------------|--------------------|------------|---------------------------|-------------|---------------------|---------------------|--------------------------|--------------|
| Case-control studies | | | | | | | | | | |
| Ross JA [257], 2011, US | M/F | 2005–2009 | The MCSS | 734 | 697 | Leukemia | Questionnaire | Use at least once per week for at least 1 year | 1,7,10 | 9 |
| Weiss JR [258], 2006, US | M/F | 1981–1998 | RPCI | 169 | 676 | Leukemia | Questionnaire | Use at least once per week for 6 months (regular) | 1,2 | 6 |
| Oleske D [7], 1985, US | M/F | 1975–1981 | Hairy Cell Tumor Registry and Treatment Center | 45 | 134 | Leukemia | Questionnaire | Use three times a week or more for more than 2 months | 1,2,6,11 | 6 |
| Cohort studies | | | | | | | | | | |
| Jacobs EJ [98], 2007, US | M/F | 1992–2003 | Cancer Prevention Study II Nutrition Cohort | 465 | 146,113 | Leukemia | Questionnaire | Use at least 30 “times” per month (daily use of adult-strength) | 1,2,3,5,10,11,12, 13,14,15,16,17, 18,19 | 8 |
| Kasum CM [259], 2003, US | F | 1992–2000 | IWHS | 81 | 28,224 | Leukemia | Questionnaire | Had ever taken aspirin, not further defined | 1,3,5 | 8 |
| Friis S [62], 2003, Denmark* | M/F | 1989–1997 | Population from North Jutland County | 69 | 29,470 | Leukemia | Prescription database | 75–150 mg once daily (low-dose aspirin) | 1,2 | 8 |
| Schreinemachers DM [63], 1994, US | M/F | 1971–1987 | The National Health and Examination Survey I | 39 | 12,668 | Leukemia | Self reported | Use aspirin during the 30-day period before the interview | 1,2 | 6 |

1=age, 2=sex, 3=smoking, 4=family history, 5=educational level, 6=residence, 7=other analgesic use, 8=fat distribution, 9=social status, 10=BMI, 11=race, 12=physical activity level, 13=use of hormone replacement therapy, 14=history of mammography, 15=history of colorectal endoscopy, 16=use of non-aspirin NSAIDs, 17=history of heart attack, 18=diabetes, 19=hypertension

IWHS Iowa Women’s Health Study, MCSS the Minnesota Cancer Surveillance System, RPCI the Roswell Park Cancer Institute

*Study deemed to be prone to immortal time bias
(RRs = 0.76, 95%CI: 0.66–0.87 for ≥5 years), pancreatic cancer (RRs = 0.75, 95%CI: 0.57–0.99 for ≥5 years), ovarian cancer (RRs = 0.77, 95%CI: 0.63–0.93 for ≥5 years), and brain cancer (RRs = 0.65, 95%CI: 0.43–0.97 for ≥5 years) were more pronounced with longer duration of aspirin use. However, the aspirin-associated RR for 21 specific cancers did not vary significantly by other characteristics (gender, quality assessment and frequency of aspirin use).

Publication bias
The funnel plot showed asymmetry (Fig. 19). In addition, the Begg’s test and Egger’s test provided evidence of publication bias among the included studies (Begg’s test Z = 4.34, P < 0.001; Egger’s test Z = −5.27, P < 0.001).

Discussion
The results of our meta-analysis supported the presence of inverse associations between aspirin use and the risk of overall cancer, gastric, esophageal, colorectal, pancreatic, breast, ovarian, endometrial, and prostate cancers, as well as small intestine neuroendocrine tumors. However, no significant associations were observed between the use of aspirin and the risk of other cancers, including hepatobiliary, lung, cervical uterus, renal, renal pelvis and ureter, bladder, brain, head and neck, thyroid, and skin cancers, as well as lymphoma, and leukemia.

There are several potential biological mechanisms through which aspirin could reduce the risk of cancer. First, aspirin and other NSAIDs have been proven to inhibit the activity of the enzyme cyclooxygenase 2 (COX-2), which is responsible for the synthesis of prostaglandins [29]. COX-2 has been reported to be overexpressed in many cancers and participates in key cellular activities, including cell proliferation, apoptosis, angiogenesis, and metastasis [30–32]. Second, aspirin could activate the NF-kappa B (NF-κB) signaling pathway,
Fig. 3 Forest plot of aspirin use and the risk of esophageal cancer

Fig. 4 Forest plot of aspirin use and the risk of colorectal cancer
which triggers apoptosis in neoplasia \[33, 34\]. In addition, some studies showed that aspirin might induce gene selection and modulate mitochondrial voltage dependent anion channels (VDACs) to reduce the risk of cancer progression and metastasis \[35, 36\].

The results of this meta-analysis indicated that utilization of aspirin had different protective effects on the development of cancer. This difference may be attributed to the different expression levels of COX in various cancers \[37\]. Furthermore, Zumwalt et al. \[38\] reported that the effectiveness of aspirin was primarily determined by specific genetic variants. Aspirin inhibited cell growth in all cancer cell lines regardless of mutational background, however, the effects were exacerbated...
Fig. 7 Forest plot of aspirin use and the risk of lung cancer

Fig. 8 Forest plot of aspirin use and the risk of breast cancer
in cells with PIK3CA mutations, which might explain the different effects of aspirin on cancers.

The decreased risk of gastric, esophageal, pancreatic, lung, breast, and ovarian cancers was observed in the case-control studies but not in the cohort studies. One possible explanation for the difference might be that cases in the case-control studies might have a recall bias and tended to overestimate the risk of cancer by aspirin use. Another possible explanation is that misclassification or measurement errors for aspirin use in the cohort studies might have distorted the association because most of our analyses were based on baseline data, and there might be a discrepancy between initial recruitment and subsequent aspirin consumption.

The longer those who had used aspirin, the lower their risk of cancer was, with longer duration of use associated with an RR of 0.90 (95% CI 0.89–0.94), based on 118 studies that reported associations with longer (≥5 years) duration of aspirin use and 105 studies that reported associations with shorter (<5 years) duration of use.

![Fig. 9 Forest plot of aspirin use and the risk of ovarian cancer](image)

![Fig. 10 Forest plot of aspirin use and the risk of endometrial cancer](image)
aspirin use. For most cancers (colorectal, pancreatic, ovarian, and brain cancers), risk reductions were more pronounced with longer duration of use, and these results agree with those of previous studies [39–41]. In addition, the United States Preventive Services Task Force (USPSTF) indicated that cancer prevention was a significant aspect in the overall health benefit of aspirin, but this benefit was not apparent until several years after the initiation of aspirin therapy [42, 43]. It is of note that a significant inverse association with prostate cancer was observed in the patients who took aspirin for less than 5 years. Indeed, after the study that relied on the
General Practice Research Database [44] was excluded, the discrepancy disappeared. Considering that aspirin use was off-prescription in the United Kingdom, misclassification was likely to occur in this study because many commonly used aspirins do not require a prescription. Therefore, it can be deduced that the patients who used aspirin for at least 5 years were more likely to realize the potential cancer prevention benefit.

There was no statistically significant difference between the pooled RRs for the frequency of aspirin in most studies. Given that a few studies were included in the subgroup analysis on the basis of the frequency of aspirin use.
aspirin use and most studies lacked information on this variable, the results on the risks associated with the frequency of aspirin use should be interpreted with caution. Further studies that explore the associations between the frequency of aspirin use and cancer risk are necessary to elucidate the effects of aspirin.

In addition, our results indicated that the strongest reduction in the risk of most cancers associated with aspirin was found in North American countries. However, two-thirds of the included studies were performed in North America and a few studies were performed in Asian and European countries, which might distort the

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**Fig. 15** Forest plot of aspirin use and the risk of head and neck cancers

| Study          | RR (95% CI) | Weight |
|----------------|-------------|--------|
| Di Masso M(2016) | 0.24 (0.07, 0.87) | 1.44   |
| Becker C(2015)  | 1.09 (0.96, 1.20) | 18.13  |
| Macfarlane TV(2012) | 0.91 (0.72, 1.15) | 13.65  |
| Ahmadi H(2010)   | 0.15 (0.02, 1.30) | 0.56   |
| Jayaprakash V(2005) | 0.77 (0.62, 0.95) | 14.32  |
| Rosenquist H(2005) | 1.00 (0.60, 1.70) | 6.22   |
| Booeti C(2003)   | 0.86 (0.46, 1.61) | 4.76   |
| Macfarlane TV(2014) | 0.93 (0.76, 1.15) | 14.64  |
| Wilson JC(2013)  | 0.78 (0.62, 0.98) | 13.66  |
| Frie S(2003)     | 1.36 (1.04, 1.77) | 12.54  |
| Overall (I-squared = 66.6%, p = 0.001) | 0.92 (0.79, 1.08) | 100.00 |

**NOTE:** Weights are from random effects analysis

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**Fig. 16** Forest plot of aspirin use and the risk of skin cancer

| Study          | RR (95% CI) | Weight |
|----------------|-------------|--------|
| Reinau D(2015)  | 0.98 (0.93, 1.02) | 16.30  |
| Johannesdottir SA(2012) | 0.94 (0.90, 0.99) | 16.02  |
| Torti DC(2011)  | 0.79 (0.62, 0.97) | 3.13   |
| Curiel-Lewandrowski C(2011) | 0.72 (0.55, 0.94) | 2.27   |
| Jeter JM(2011)  | 1.45 (1.44, 4.74) | 0.13   |
| Asgari MM(2010) | 1.38 (0.96, 1.97) | 1.33   |
| Hollestein LM(2014) | 1.12 (0.91, 1.36) | 3.69   |
| Wyssong A(2014) | 0.98 (0.93, 1.02) | 16.39  |
| Brasky TM(2014) | 0.69 (0.65, 0.67) | 3.03   |
| Jeter JM(2012)  | 1.01 (0.96, 1.07) | 14.61  |
| Cahoon EL(2012) | 0.97 (0.90, 1.04) | 12.84  |
| Asgari MM(2008) | 0.97 (0.73, 1.38) | 1.99   |
| Jacobs EJ(2007) | 1.04 (0.92, 1.18) | 7.57   |
| Schweinenschmacher DM(1984) | 0.91 (0.56, 1.49) | 0.74   |
| Overall (I-squared = 53.2%, p = 0.010) | 0.96 (0.92, 1.01) | 100.00 |
accuracy of the results. Therefore, more studies are necessary to examine the discrepancies among the different countries and regions.

**Comparison with other studies**

Bosetti et al. (2011) [45] conducted a meta-analysis on aspirin and 12 selected cancer sites based on 139 observational studies and 187,167 cases. Our study included 218 studies involving 737,409 cases and examined the correlation between aspirin use and the risk of skin, head and neck, hepatobiliary, thyroid, cervical uterus, renal pelvis, ureter, and brain cancers, lymphoma, small intestine neuroendocrine tumors, and leukemia, thereby providing more comprehensive and reliable evidence for this correlation. More importantly, this study was the first meta-analysis to evaluate the association between aspirin use and the risk of hepatobiliary cancer and we found a non-significant effect of aspirin on the risk of hepatobiliary cancer (OR = 0.64, 95% CI: 0.40–1.02).
Algra and Rothwell (2012) [46] conducted a meta-analysis on the association between aspirin use and the risk of cancer based on 195 studies and 215,211 cases. Compared with their review, our meta-analysis have added approximately 70 new articles published since 2012, with a total of 737,409 cases, which significantly enhanced the statistical power to determine this potential association. In addition, the exposure in the previous review was inconsistent, which may mislead the estimation. Many studies defined aspirin as the exposure but only a few studies defined NSAIDs as the exposure, and thus the specific effect of aspirin on cancers was not defined. The exposure to aspirin in our meta-analysis was consistent and ensured the reliability of the findings.

Strengths and limitations
This study is the most up-to-date comprehensive review of the effect of aspirin use on the risk of all types of cancers, and the large sample size provides reliable results with greater precision and power. The potential limitations of this study should be noted. First, there was substantial heterogeneity across the included studies, which was likely due to differences in the definitions of exposure, units, assessment methods, and the adjusted variables across different studies. Second, misclassification or measurement errors for aspirin use might distort the association because our analyses were based on baseline data, and changes in the exposure to aspirin were not updated during the follow-up period. Third, the visual inspection of a funnel plot showed asymmetry, and the Begg’s test and Egger’s test also identified evidence of publication bias among the studies included in our meta-analysis.

Our meta-analysis indicated a beneficial role for aspirin for overall cancers; however, the results should be interpreted with caution. Considering that most evaluated studies were based on secondary prevention rather than on primary prevention, the totality of evidence for the high-risk population was incomplete, and it is appropriate to let the beneficial role remain uncertain. At present, we should accept the uncertainties, and future chemoprevention trials should clarify the extent to which aspirin decreases cancers incidence.

Conclusions and implications
Evidence from observational studies indicates that utilization of aspirin is associated with reduced risk of gastric, colorectal, esophageal, pancreatic, ovarian, endometrial, breast, and prostate cancers, in addition to small intestine neuroendocrine tumors. A stronger protective effect was observed in the North American populations and patients who used aspirin for at least 5 years. It is important to address immortal time bias not only to ensure the integrity of the meta-analysis, but also to ensure the integrity of pharmacoepidemiological studies. Moreover, given the confidence limits of the evaluated studies, adequately powered mechanistic studies should help elucidate the mechanisms underlying this correlation.

Additional file

**Additional file 1:** Table S1. Summary table. Table S2. Subgroup analysis of relative risk of gastric cancer. Table S3. Subgroup analysis of relative risk of esophageal cancer. Table S4. Subgroup analysis of relative risk of colorectal cancer. Table S5. Subgroup analysis of relative risk of hepatobiliary cancer. Table S6. Subgroup analysis of relative risk of pancreatic cancer. Table S7. Subgroup analysis of relative risk of lung cancer. Table S8. Subgroup analysis of relative risk of breast cancer. Table S9. Subgroup analysis of relative risk of ovarian cancer. Table S10. Subgroup analysis of relative risk of endometrial cancer. Table S11. Subgroup analysis of relative risk of prostate cancer. Table S12. Subgroup analysis of relative risk of renal cancer. Table S13. Subgroup analysis of relative risk of bladder cancer. Table S14. Subgroup analysis of relative risk of brain cancer.
of relative risk of head and neck cancers. Table S16. Subgroup analysis of relative risk of skin cancer. Table S17. Subgroup analysis of relative risk of lymphoma. Table S18. Subgroup analysis of relative risk of leukemia. (DOC 549 kb)

Abbreviations
CI: Confidence interval; COX-2: Cyclooxygenase 2; HRs: Hazard ratios; NF-kB: NFKappa B; NSAIDs: Non-steroidal anti-inflammatory drugs; ORs: Odds ratios; RR: Relative risk; USPSTF: United States Preventive Services Task Force; VDACs: Voltage dependent anion channels

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Availability of data and materials
All data generated or analysed during this study are included in this published article.

Authors’ contributions
YQ, YT, and ZL designed the study and were responsible for writing, analysis, and interpretation of data and the review and revision of the manuscript. YQ, YT, and CW performed the statistical analyses. YQ, YT, and ZL drafted the manuscript. YQ, YT, and ZL designed the study and were responsible for writing, analysis, and interpretation of data and the review and revision of the manuscript. All authors read and approved the final manuscript.

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