

Non-aspirin Non-steroidal Anti-inflammatory Drugs for the Primary Chemoprevention of Non-gastrointestinal Cancer: Summary of Evidence

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Abstract: *Background:* There is evidence that aspirin is effective for the chemoprevention of colorectal cancer. Due to their similar pharmacodynamics, the use of other non-steroidal anti-inflammatory drugs (NSAIDs) has been suggested for other cancer sites. Although this possibility has been discussed in the literature, uncertainty remains about the actual effects of NSAIDs other than aspirin in non-gastrointestinal cancer.

Objective: To summarize the best available evidence of the primary chemopreventive effects of non-aspirin NSAIDs for non-gastrointestinal cancer.

Methods: Our inclusion criteria were narrative or systematic reviews, clinical guidelines and, if they had not been previously included, primary controlled studies that evaluated the effectiveness of non-aspirin NSAIDs in preventing non-gastrointestinal cancer in healthy individuals. Studies were retrieved from the following databases: Guidelines.gov, BMJ Clinical Evidence, TRIP database, UpToDate, MEDLINE, CANCELIT, Embase, CINAHL, ISI Web of Science and Scopus. Two independent reviewers selected eligible studies. Data were extracted by one reviewer and crosschecked by two others.

Results: We found 9,984 non-duplicated articles and included 56 eligible studies. Most of these studies were observational. The studies reported conflicting results or no statistically significant associations between the use of non-aspirin NSAIDs and risk of lung, ovary, bladder, prostate, skin, and head and neck cancers. In contrast, an increased risk of renal cell carcinoma and a reduced risk of breast cancer were found to be statistically significant. The included studies had methodological limitations, which reduces our confidence in their results.

Conclusions: We did not find sufficient evidence to support the use of the non-aspirin NSAIDs for the primary chemoprevention of a wide variety of non-gastrointestinal cancers. This scenario suggests caution when considering the routine use of non-aspirin NSAIDs. Additional well-conducted controlled studies may provide more conclusive evidence on this issue, but there are concerns about the risks of such exposure.

Keywords: Non-steroidal anti-inflammatory agents, chemoprevention, primary prevention, neoplasms, non-gastrointestinal, non-aspirin.

BACKGROUND

Cancer is a leading cause of death in the developed world [1]. Globally, an estimated 12.7 million cases of cancer and 7.6 million cancer deaths occurred in 2008. Successful cancer prevention in high-risk populations suggests that chemoprevention with anti-inflammatory agents is a rational and appealing strategy [2]. Overall, cancer chemoprevention has earned serious consideration as a potential means of controlling the incidence of cancer.

Evidence from epidemiological studies has shown a consistent inverse association between the use of non-steroidal anti-inflammatory drugs (NSAIDs), mainly aspirin, and the incidence of cancer and cancer-related death [3-5]. The NSAIDs have demonstrated a protective effect on gastrointestinal cancer morbidity and mortality [4, 5]. The effectiveness of aspirin and the relative low cost of NSAIDs may represent an efficient strategy for the primary chemoprevention of non-gastrointestinal cancer. However, the effect of non-aspirin NSAIDs on the incidence of non-gastrointestinal cancer is not well established [6], and there are possible increased risks with their prolonged use. The objective of this work was to present an up-to-date overview of the existing evidence of the effects of non-aspirin NSAIDs on the incidence of non-gastrointestinal cancer. Before, however, we highlight the historical features of NSAIDs and cancer chemoprevention.

HISTORICAL PERSPECTIVE AND PHARMACOLOGIC RATIONALE

Since 1897, when the German chemist Felix Hoffman prompted Bayer to produce acetylsalicylic acid, the non-steroidal anti-inflammatory agents have to be the drugs most widely prescribed and used throughout the world. NSAIDs — which include aspirin (acetylsalicylic acid), indomethacin, piroxicam, ketoprofen, naproxen, diclofenac, ibuprofen, celecoxib and others — are a structurally diverse group of similarly acting compounds that are used to treat rheumatic diseases as well as the signs and symptoms of inflammation [7].

In 1971, Vane and colleagues first demonstrated that aspirin and indomethacin inhibited prostaglandin production by blocking cyclooxygenase (COX, prostaglandin H synthase, PGHS) enzyme [8]. Sune K. Bergström, Bengt I. Samuelsson and John R. Vane were awarded the Nobel Prize in Physiology or Medicine of 1982 for their discoveries concerning prostaglandins and related biologically active substances. They were able to show that prostaglandins are involved in a diverse range of biochemical functions and processes; for this reason their research opened up a new arena of medical research and pharmaceutical applications [9]. Some years later, it has been found that NSAIDs directly affect cyclooxygenase activity, either by covalently modifying the enzyme (as in the case of aspirin) or by competing with the substrate for the active site (as all other NSAIDs) [10]. Significant advances have been made in understanding the role of these enzymes in certain biologic processes.

Two important COX enzymes have been described: the cyclooxygenase-1 isoform (COX-1) and cyclooxygenase-2 isoform

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(COX-2). COX-1 was first purified from bovine vesicular glands in 1976 [11]. It is constitutively expressed in most tissues, where it mediates physiologic functions such as gastric mucosal cytoprotection and regulation of platelet aggregation. Between 1989 and 1991 Simmons *et al.* (1989) and Kujubu *et al.* (1991) independently isolated a cDNA encoding of second isoform by different screening in fibroblasts [12, 13]. This second isoform, now known as cyclooxygenase-2 isoform shares significant sequence homology and catalytic activity with COX-1. However, its expression pattern is markedly different. Most tissues do not constitutively express COX-2 [14]. In addition, a variety of extracellular and intracellular stimuli will rapidly induce COX-2. That is induced in response to cytokines and growth factors and is expressed in inflammatory disease, premalignant lesions (such as adenomas), and colon cancer [15]. The inhibition of COX-1 but not to COX-2 may account for many of the common side effects of NSAIDs, including gastric ulceration and gastrointestinal hemorrhage [16].

Cyclooxygenase affects the synthesis of prostaglandin (eicosanoids, oxygenated-lipid) signaling molecules, products of arachidonic acid metabolism, have a central role not only in inflammation but also are involved in a numerous others biologic processes including angiogenesis, immunologic function, platelet aggregation [7]. Neoplastic tissues contain high concentrations of prostaglandins [17]. Prostaglandin E2 (PGE2) seems to have a key role in carcinogenesis: activation of several types of PGE2 receptors triggers other signaling pathways, such as the epidermal-growth factor-receptor pathway [18, 19]. The production of these potent signaling molecules is stringently regulated at the levels of expression for COX-2 and catalysis for both COX-1 and COX-2 [7].

From the mid-90s, researchers from several countries began to study the expression of COX-2 in the process of carcinogenesis and its correlation with the prognosis of the disease. COX-2 has been found to be expressed in up to 90% of colorectal carcinomas, but not in hyperplastic polyps or normal colorectal mucosa [20]. According to Koki *et al.* [21], COX-2 is expressed in cancer in 40% to 80% of neoplastic cells, and this more intense expression in these cells than in non-neoplastic. However, there are still many questions about their participation in the development of disease. As Dempke *et al.* [22] stated, the increased expression COX-2 contributes to carcinogenesis in several ways, for example, the formation of new vessels blood, conversion of procarcinogens into carcinogens, inhibition of apoptosis, modulation of inflammatory response and immune by the addition of prostaglandin synthesis and increased the invasive capacity of cancer cells. Table 1 summarizes the main chronologic events concerning to NSAIDs.

Cohesive scientific evidence supports the hypothesis that aberrant induction of COX-2 and up-regulation of the prostaglandin cascade play a significant role in carcinogenesis: i. expression of constitutive COX-2-catalyzed prostaglandin biosynthesis is induced by most cancer-causing agents including tobacco smoke and its components; ii. COX-2 expression is a characteristic feature of all premalignant neoplasms; iii. COX-2 expression is a characteristic feature of all malignant neoplasms, and expression intensifies with stage at detection and cancer progression and metastasis and, iv. animal studies show that COX-2 up-regulation (in the absence of genetic mutations) is sufficient to stimulate the transformation of normal cells to invasive cancer and metastatic disease [23].

Evidence supports the concept that the chemopreventive effects of NSAIDs may be due at least in part to inhibition of COX-2 [15, 24]. Although many of the initial studies indicated that COX-2 might be the central player in COX-induced colorectal carcinogenesis, evidence from mouse experiments now also implicates COX1 as a causal agent [25], probably through effects on PGE2 concentrations [19].

It is not surprising that regular use of aspirin and other NSAIDs is related to a decreased risk of several types of cancer. Evidence

clearly shows a chemopreventive effect for aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) on colorectal cancer and probably other cancer types [4]; however, data on the risk-benefit profile for cancer prevention are insufficient and no definitive recommendations can be made. Other very important question that remains to be answered is whether these observations in other cancers are attributable to factors that are correlated with NSAID use — for example, behaviors that might reduce cancer risk, such as exercise or dietary behaviors, or conditions that cause an individual to use NSAIDs, such as some autoimmune diseases.

METHODS

Study Design

This is a summary of evidence with a systematic approach on search, selection and data extraction processes.

Study Eligibility Criteria

We considered eligible narrative reviews, systematic reviews and clinical guidelines that assessed the influence of non-aspirin NSAIDs on cancer prevention in healthy individuals. We also included primary controlled studies that had not been previously considered on included secondary studies. There were no restrictions on publication date, accessibility, language, and country of publication.

Data Sources and Search Strategy

We searched Guidelines.gov, BMJ Clinical Evidence, the TRIP database, UpToDate, MEDLINE, CANCELIT, Embase, CINAHL, ISI Web of Science and the Scopus database. The latest search date was November 2011. Our search strategy on Medline (via PubMed) was: (((("anti-inflammatory agents, non-steroidal"[mesh] or "anti-inflammatory"[tiab] or "nsaid"[tiab] or "nsaids"[tiab] or "non-steroidal"[tiab] or "aine"[tiab] or "anti-inflammatory agents, non-steroidal"[pharmacological action] or "nonsteroidal antiinflammatory agents"[tiab] or "non-steroidal anti-inflammatory agents"[tiab] or "non steroidal anti inflammatory agents"[tiab] or "nonsteroidal anti-inflammatory agents"[tiab] or "nonsteroidal anti inflammatory agents"[tiab] or "non-steroidal antirheumatic agents"[tiab] or "anti-inflammatory analgesics"[tiab]) and ("neoplasms"[mesh] or "neoplasm"[tiab] or "neoplasms"[tiab] or "tumors"[tiab] or "tumor"[tiab] or "benign neoplasms"[tiab] or "benign neoplasm"[tiab] or "cancer"[tiab] or "cancers"[tiab]) and ("incidence"[mesh] or "incidence"[tiab] or "incidences"[tiab] or "prevention and control"[subheading] or "prevention and control"[tiab] or "prevention"[tiab] or "preventions"[tiab] or "preventive therapy"[tiab] or "prophylaxis"[tiab] or "preventive measures"[tiab] or "prevention"[tiab] or "control"[tiab])) not ("gastrointestinal neoplasms"[mesh])) and humans. We adapted our search strategy to other databases. We also screened references from the included studies to identify potentially eligible studies not found during the initial database searches.

Study Selection and Data Extraction

Two reviewers independently selected studies by screening titles and abstracts (IRZ, MTS). Relevant data were extracted by one reviewer (MTS) and cross-checked by two others (IRZ, TFG). We also contacted the authors of the studies as needed to retrieve unavailable full texts or other information.

We extracted from studies: authors, publication data, country, year, enrollment dates, population, sample size, type of non-aspirin NSAIDs, follow-up and outcomes.

Data Analysis and Risk of Bias

We extracted the data available in the eligible studies, and recalculation was not performed. For each cancer type we presented a summary of evidence table with results from primary research and systematic reviews only.

Table 1. Chronologic Event About NSAIDs and Cancer

Year	Event
1897	Felix Hoffman prompted Bayer to produce acetylsalicylic acid
1971	Vane and colleagues first demonstrated that aspirin and indomethacin inhibited prostaglandin production by blocking cyclooxygenase
1976	Cyclooxygenase 1 isoform was first purified from bovine vesicular glands.
1980	Early studies using animal models of colon cancer indicated that NSAIDs were chemopreventive
1982	Sune K. Bergström, Bengt I. Samuelsson and John R. Vane were awarded the Nobel Prize in Physiology or Medicine for their discoveries concerning prostaglandins and related biologically active substances.
1989	Cyclooxygenase 2 isoform was screened in fibroblast
1991	Study investigating the relationship between aspirin use and colon cancer involved following colon cancer fatality rates prospectively among 600,000 individuals

As we intended to evaluate all available evidence, we included all eligible studies despite their risk of bias, and we critically appraised them based on study design. We did not rate the quality of the evidence with a traditional score and did not perform meta-analysis due to the wide clinical and methodological heterogeneity of study designs. Nonetheless, we collected information on possible sources of bias for each study design along with statistical methodology and data quality features, i.e.: sample size and confidence interval, appropriated pooling method, and potential biases (selection, measurement and confounding). Finally, we summarized the available evidence for each cancer type as follows: conflicting (when the evidence showed conflicting results regarding the effects of NSAIDs); inconclusive (when there were concerns about the significance of the results or size effects); favorable (when there was evidence suggesting potential benefits of the use of NSAIDs); or unfavorable (when there was evidence suggesting potential risks of the use of NSAIDs, outweighing any benefits). This approach was centered on the fundamentals of critical appraisal of medical literature [26].

RESULTS AND DISCUSSION

Our literature search retrieved 4,984 unique records. After selection, 67 were assessed for eligibility, and 56 were included in our review (Fig. 1). Of those, 30 were primary studies (one randomized clinical trial, 12 cohorts, 16 case-control and one cross-sectional), and 27 were secondary studies (13 systematic reviews of observational studies, 12 narrative reviews and two consensus/guideline studies).

We found secondary studies for the following cancer types: lung, breast, ovary, endometrial, bladder, renal cell carcinoma, prostate, skin and head and neck. Table 2 presents a summary of the results found. Most of the studies reported conflicting (both positive and negative effects) or inconclusive (without statistical significance) results. An increased risk of cancer incidence was observed for renal cell carcinoma and reduced cancer incidence for breast cancer. Some of these results were obtained from large population studies, and their results would therefore not likely be changed by further studies. Most subtypes and stages of cancer were not detailed or distinguished because this information was not generally provided by the evaluated source records. Details of the primary incidence of each cancer type and non-aspirin NSAID use are detailed in the next subsections.

Lung Cancer

Worldwide, lung cancer accounted for 13% (1.6 million) of the total cancer cases and 18% (1.4 million) of all cancer deaths in

2008 [1]. In males, lung cancer is the most commonly diagnosed cancer and is the leading cause of cancer death. The highest incidence rates for males are in eastern and southern Europe, North America, Micronesia and Polynesia, and eastern Asia, whereas rates are low in sub-Saharan Africa. In females, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death. The highest incidence rates for females are found in North America, northern Europe, and Australia/New Zealand. A number of environmental and lifestyle factors have been associated with the subsequent development of lung cancer, of which cigarette smoking is the most important. Other known risk factors include exposure to several occupational and environmental carcinogens, such as asbestos, arsenic, radon, and polycyclic aromatic hydrocarbons [1].

A clinical practice guideline for individuals at risk or with a history of lung cancer, published in 2007, stated that there was insufficient data to recommend the use of any agent (including aspirin and COX-2 inhibitors), either alone or in combination, for primary, secondary, or tertiary lung cancer chemoprevention [40].

We found systematic reviews and observational studies with inconclusive or conflicting results (Table 3). A previous systematic review suggested an inverse association between NSAIDs—including aspirin—and lung cancer risk based on a combined relative risk (RR), adjusted for smoking history, of 0.79 (95% confidence interval [CI]: 0.66–0.95) [41]. This evidence does not suggest a causal relationship between NSAID use and lung cancer. Moreover, this study had methodological problems: independent reviewers were not used to minimize selection bias, there were no attempts to assess study quality, the literature search and selection results were not appropriately detailed, and there are concerns about the synthesis method used (i.e., pooling cohort and case-control studies for risk estimates).

Two additional meta-analyses found conflicting results [6, 24]. The first study suggested that the results for lung cancer were compatible with the finding that NSAIDs have no effect on prevention (RR = 0.65; 95% CI: 0.34–1.22) [6]. The other study reported that non-selective and selective COX-2 inhibitors, when used on a regular basis, reduce the risk of lung cancer (RR = 0.72; 95% CI: 0.61–0.85) [24]. These studies have important limitations and are critically reviewed in the next subsection (breast cancer) of this review.

We found two observational studies that were not previously considered in systematic reviews, with case group populations containing variable proportions of patients with adenocarcinoma, squamous cell, small-cell and non-small-cell carcinoma [42, 43]. The first examined the association between NSAID use and lung cancer risk based on pooled data from two case-control studies [42].

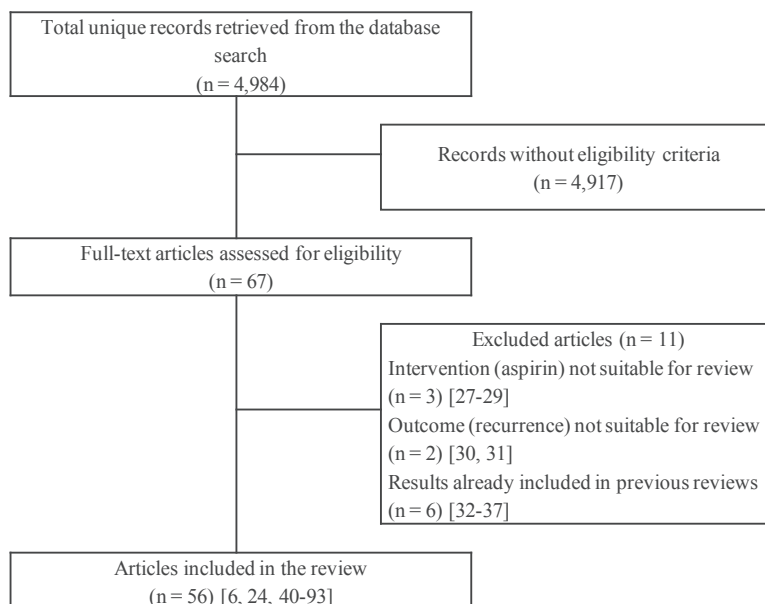


Fig. (1). Flow chart of the search, selection and inclusion of studies.

Table 2. Summary of Evidence for Non-aspirin NSAIDs in the Chemoprevention of Non-gastrointestinal Cancer Incidence

Cancer type	Randomized controlled trial	Systematic review of observational studies	Cohort study	Case-control study	Cross-sectional study	Guidelines or consensus	Narrative review	Comments
Lung	-	Conflicting [6, 24, 41, 44]	Inconclusive [43]	Inconclusive [42]	-	Inconclusive [40]	-	Large studies failed to show relevant effects
Breast	-	Favors [6, 24, 48-50]	-	-	-	Inconclusive [51]	Conflicting [45-47]	Results based on small effects; studies had important limitations
Ovarian	-	Conflicting [6, 55]	Inconclusive [61, 62]	Conflicting [56-60]	-	-	Inconclusive [46, 52-54]	Large studies failed to show relevant effects
Endometrial	-	-	Inconclusive [62-64]	Inconclusive [65, 66]	-	-	-	Large studies failed to show relevant effects
Bladder	-	Inconclusive [6]	Inconclusive [67]	-	-	-	-	Large studies failed to show relevant effects
Renal cell carcinoma	-	-	Unfavorable [69]	Unfavorable [70]	-	-	Unfavorable [68]	Large studies showed increased risk of cancer incidence
Prostate	-	Conflicting [6, 24, 71-73]	Conflicting [74-76]	Unfavorable [77-80]	Inconclusive [81]	-	-	Further well-conducted systematic reviews may influence the estimates
Skin	Inconclusive [83]	-	Inconclusive [84, 85, 87]	Inconclusive [86, 88, 92]	-	-	Conflicting [82, 89-91]	Large studies failed to show relevant effects, except in a very specific population
Head and neck	-	Conflicting [93]	-	-	-	-	-	Further well-conducted studies may change the estimates

Notes:

-: not available (publication type not found/included in this review)

Conflicting: The evidence showed conflicting results on the effects of NSAIDs.

Inconclusive: There are concerns about the significance of the results or size effects.

Favorable: There is evidence suggesting potential benefits of the use of NSAIDs.

Unfavorable: There is evidence suggesting potential risks of the use of NSAIDs that outweigh any benefits.

Table 3. Evidences About Non-aspirin NSAIDs and Prevention of Lung Cancer Incidence

Study	Design and Population	Outcomes	Results	Limitations
Khuder 2005 [41]	Systematic review with meta-analysis performed on 14 studies (6 case-control studies and eight 8 cohort studies)	Lung cancer	<p>NSAID use was associated with a small but statistically significant decrease in the risk of lung cancer. The combined estimate of RR derived from all the 14 studies showed that regular use of NSAID was associated with 21% reduction of the risk of lung cancer, RR = 0.79 (95% CI: 0.66–0.95)</p> <p>The analysis restricted to studies that adjusted the confounding effects of smoking found a 32% reduction of the risk, RR = 0.68 (95% CI: 0.55–0.85)</p> <p>The dose-response analysis revealed a significant relation between duration of use and the risk of lung cancer ($p = 0.04$), but a longer period of NSAID use was associated with greater reduction in lung cancer risk, OR of 6 months, 0.98 (95% CI: 0.96–0.99), 18 months, 0.94 (95% CI: 0.89–0.98) and 36 months, 0.88 (95% CI: 0.81–0.95)</p> <p>NSAID use was inversely associated with small cell lung cancer (OR = 0.48; 95% CI: 0.30–0.75) and non-small cell lung cancer (OR = 0.66; 95% CI: 0.56–0.79)</p> <p>No significant relationship was found between frequency of NSAID use and the risk of lung cancer ($p = 0.09$)</p>	<p>Results of search and selection not appropriately detailed</p> <p>Combined results from case-control and cohort studies</p>
González-Pérez 2003 [6]	Systematic review with meta-analysis with a total of 8 studies (5 case-controls and 3 cohort studies) that evaluated lung cancer chemoprevention	Lung cancer	<p>Results obtained were compatible with no effect or a possibly slight reduced risk.</p> <p>Overall RR: NSAIDs use, 0.65 (3 studies; 95% CI: 0.34–1.22), aspirin use, 0.84 (5 studies; 95% CI: 0.66–1.07), non-aspirin NSAIDs RR not evaluated</p>	Search restricted to studies published in English or Spanish indexed on MEDLINE; no attempts to identify unpublished data; case-control and cohort studies results were inadequately pooled; results with significant heterogeneity
Harris 2009 [24]	Systematic review with meta-analysis of 18 studies (randomized controlled trial, case control and cohort studies)	Lung cancer	A 28% reduction of the RR of lung cancer with regular use of aspirin or other non-prescription NSAIDs (RR = 0.72; 95% CI: 0.61–0.85)	Search strategy, selection criteria and their results not stated, what raises doubts about the results found; methodological quality assessment of the primary studies not stated; case-control and cohort studies results were inadequately pooled; scarce details about the included studies (population, design, intervention)
Olsen 2008 [42]	<p>Pooled data from two case-control studies (the Northern Jutland case-control study and other nested within the Danish Diet, Cancer and Health prospective cohort study; $n = 1,430$)</p> <p>573 cases and 857 sex and age-matched controls</p>	Lung cancer	The only significantly finding was that the study subjects who received the highest number of prescriptions per year, that is at least four, had the lowest risk estimate (OR = 0.49; 95% CI: 0.28–0.84)	Duration of prescribed NSAID use unknown; the presence or absence of potential conflicts of interest was not stated

(Table 3) Contd....

Study	Design and Population	Outcomes	Results	Limitations
Slatore 2009 [43]	Prospective cohort of 77,125 men and women, ages 50 to 76 years, from Washington state recruited in 2000 to 2002. 5 years of follow-up 665 subjects developed lung cancer	Lung cancer	Non-aspirin NSAIDs and regular aspirin use were each associated with a non-significant decreased lung cancer risk There was a borderline-significant inverse trend with total NSAID use (>4.2 doses/week for >10 years versus none): HR = 0.82; 95% CI: 0.64–1.04 The association was strongest for adenocarcinoma (HR = 0.59; 95% CI: 0.37–0.94) and seemed to be limited to men (HR = 0.66; 95% CI: 0.47–0.92) and to long-term (>10 years) former smokers (HR = 0.65; 95% CI: 0.44–0.96) There were no appreciable differences by NSAID type	The measurement of long-term use of NSAIDs is based on recall and did not include pills per day
Xu 2011 [44]	Systematic review with meta-analysis of 19 studies that included 20,266 lung cancer cases	Lung cancer	Aspirin use was not significantly associated with lung cancer incidence. Cohort studies: RR = 0.96 (95% CI: 0.78–1.19). Case-control studies: OR = 0.87 (95% CI: 0.69–1.09) Aspirin use to 7 tablets per week: OR = 0.80 (95% CI: 0.67–0.95) No significant association between non-aspirin NSAID or overall NSAID use and lung cancer risk	Complete data unavailable up to the time of elaboration of this review

Abbreviations:

NSAID: non-steroidal anti-inflammatory drugs

RR: relative risk

95% CI: 95% confidence interval

HR: hazard ratio

The only significant finding was a lower risk of lung cancer (odds ratio [OR] = 0.49; 95% CI: 0.28–0.84; $n = 1,430$; 10% of the case group of non-small-cell carcinoma) among subjects who received at least four courses per year. However, a non-statistically significant decrease in risk associated with any use of NSAIDs was observed after adjustment for smoking habits, length of education and concomitant use of acetaminophen. The second study evaluated the associations of a 10-year average use of NSAIDs with lung cancer incidence based on data from a large prospective cohort (77,125 men and women; most of the cases had non-small-cell carcinoma) [43]. Non-aspirin NSAIDs and regular aspirin use were each associated with non-significant decreased lung cancer risk. In conclusion, these broad findings converge with the clinical practice guideline recommendations to indicate a lack of evidence for using any NSAID agent in lung cancer chemoprevention [40].

A more recent meta-analysis included 19 case-control and cohort studies (20,266 lung cancer cases) [44]. No significant association between non-aspirin NSAID use and lung cancer risk was observed in the pooled analysis. The full text of this report was not available on the publisher's website or by contacting the authors, which prevented us from performing quality assessment and determining whether its primary studies were also assessed in our review.

Breast Cancer

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer deaths in females worldwide, accounting for 23% (1.38 million) of the total new cancer cases and 14% (458,400) of the total cancer deaths in 2008 [1]. In general, incidence rates are high in Western and Northern Europe, Australia/New Zealand, and North America, intermediate in South America, the Caribbean, and Northern Africa, and low in sub-Saharan

Africa and Asia. Reproductive factors that increase risk include a long menstrual history, nulliparity, recent use of postmenopausal hormone therapy or oral contraceptives and late age at first birth [1].

On this topic, we found three narrative reviews that were not restricted to the use of non-aspirin NSAIDs [45–47]. The first review cited NSAID studies that reported an approximately 20% risk reduction in the incidence of breast cancer [45]. However, this benefit may be confined to aspirin use alone and to hormone receptor-positive tumors. The authors suggest that future investigations should be performed to determine whether specific NSAIDs have efficacy in reducing breast cancer risk. The second study reported conflicting results from epidemiological studies and null findings from limited randomized trials [46]. The authors concluded that it was still too early to suggest that the regular use of NSAIDs can prevent breast cancer. Finally, the third review included cohort and case-control studies with individual results either favoring NSAIDs, including aspirin, or non-significant associations [47]. The authors also reflected on the possible consequences of long-term NSAID chemoprevention of breast cancer in healthy women, including negative effects such as cardiovascular events, infertility, teratogenicity, or the birth of infants with cardiovascular defects.

We also identified five systematic reviews that included many of the same studies related to any type of NSAID [6, 24, 48–50] Table 4. All these reviews concluded that the incidence of breast cancer in women was slightly reduced by the use of NSAIDs, mainly aspirin and ibuprofen. All studies had methodological flaws: restricted literature searches [6, 24, 48], no attempts to identify unpublished data or to avoid language bias [6, 24, 48, 49], no paired selection or data extraction to minimize bias [24, 48, 49], no attempts to assess study quality (or this quality assessment was not considered when pooling results) [6, 24, 48–50], and use of non-

adequate method of synthesis (e.g., pooling cohort and case-control studies for risk estimates) [6, 24, 48-50]. A high degree of heterogeneity was also observed across the results of the studies included in their analyses. Converging with these findings, a recent expert consensus statement on breast cancer prevention advised that to date, the level of evidence is insufficient to make any recommendations on the use of NSAIDs and COX-2 inhibitors for the prevention of breast cancer [51].

Ovarian Cancer

Approximately 225,500 women were diagnosed with ovarian cancer and 140,200 died from this disease worldwide in 2008 [1, 94]. Risk factors include a family history of ovarian cancer, increasing age, and low parity. Risks are reduced by the use of oral contraceptives for more than 5 years, tubal ligation, hysterectomy, breastfeeding, increased age at menarche and decreased age at menopause [94].

Four narrative reviews reported that the rationale for the use of NSAIDs as chemopreventive agents is lacking, despite some observational studies suggesting a reduction of ovarian carcinoma risk [46, 52-54]. Two systematic reviews did not support the use of non-aspirin NSAIDs for the chemoprevention of ovarian neoplasia [6, 55] (Table 5). The first review found no studies that evaluated the specific use of non-aspirin NSAIDs and ovarian cancer risk; nevertheless, the authors analyzed the use of NSAIDs—including aspirin—and found a slightly reduced risk (RR = 0.74; 95% CI: 0.61–0.90). This review was already critically examined in the breast cancer section [6]. The second review included three case-control studies and three cohort studies and found that the association between non-aspirin NSAIDs and ovarian cancer risk was not statistically significant [55]. This association was not observed among either the case-control studies (RR = 0.89; 95% CI: 0.53–1.49) or the cohort studies (RR = 0.84; 95% CI: 0.66–1.07). This review had some limitations: no attempts were made to identify unpublished data or avoid language bias; no paired selection or data extraction was used to minimize bias; no attempts were made to assess study quality, or quality assessment was not considered when pooling results; and an inadequate synthesis method was used (pooling cohort and case-control studies for risk estimates).

We found seven observational studies that were not considered in the latest reviews: five case-control studies [56-60] and two cohort studies [61, 62]. Three of the case-control studies suggested an inverse relationship between NSAIDs and ovarian cancer [56-58]. The first reported an adjusted OR of 0.72 (95% CI: 0.56–0.92), which is consistent with an inverse relationship between NSAID use and ovarian cancer; however, this result was not observed with non-aspirin NSAIDs alone (COX-2 inhibitor, OR = 0.72; 95% CI: 0.43–1.21; acetaminophen, OR = 0.78; 95% CI: 0.56–1.08) [56]. The second study observed an overall reduction in risk among women who had used any NSAID at least twice per week for 6 months or more (OR = 0.74; 95% CI: 0.59–0.92) [57]. NSAID effects were also investigated with considerations of oral contraceptive use and parity; such investigations found that users of any NSAID who were nulliparous (OR = 0.47; 95% CI: 0.27–0.82) or had never used oral contraceptives (OR = 0.58; 95% CI: 0.42–0.80) had the greatest risk reductions. The third study [58] found that the use of any NSAID, including aspirin, was significantly associated with decreased ovarian cancer risk (OR = 0.79; 95% CI: 0.67–0.95), but significant inverse associations were not observed among women who used only non-aspirin NSAIDs (0.79; 95% CI: 0.62–1.01). Two of the studies [57, 58] had specific target subgroups: women with the potential for higher background levels of inflammation from incessant ovulation [57], and women with the prostaglandin endoperoxide synthase 2 (PTGS2) rs5275 CC genotype [58]. The remaining two case-control studies provided little support for the use of NSAID drugs as chemopreventive agents [59, 60].

Surprisingly, one study observed an increased ovarian cancer OR among those who had used the following drugs for more than 10 years, even after adjusting for parity and hormonal contraception use: acetaminophen (OR = 1.8; 95% CI: 1.3–2.6), aspirin (OR = 1.6; 95% CI: 1.1–2.2) and any type of NSAID (OR = 1.3; 95% CI: 1.0–1.7) [59].

One large prospective cohort study (197,486 participants; 666 confirmed cases of epithelial ovarian cancer identified over 2,790,986 person-years of follow-up) did not support an association between regular non-aspirin NSAID use and ovarian cancer incidence (hazard ratio [HR] = 0.81; 95% CI: 0.64–1.01), although it suggested an inverse association between NSAID use duration and frequency and incidence of borderline ovarian tumors (HR = 0.58; 95% CI: 0.32–1.06) [61]. A more recent prospective cohort study (21,694 women, with 167 ovarian-incident malignancies identified over 15 years) showed that the frequency of aspirin use was inversely associated with ovarian cancer risk, although non-aspirin NSAIDs were not associated with reduced ovarian cancer incidence [62].

Endometrial Cancer

Endometrial cancer is the second-most common gynecological malignancy worldwide; in 2008, approximately 287,000 new cases and 74,000 deaths were expected [95, 96]. Differences in epidemiology and prognosis suggest that two forms of endometrial cancer exist: Type I (80%) is estrogen-related, associated with atypical endometrial hyperplasia and linked to obesity, nulliparity, excess estrogen, diabetes mellitus, and hypertension; Type II (20%) is unrelated to estrogen stimulation, associated with clear cell tumors, and linked to multiparity [96].

We located five observational studies that assessed NSAID use and endometrial cancer: three cohort [62-64] and two case-control studies [65, 66] (Table 6). The cohort studies found statistically significant associations between non-aspirin NSAID use and endometrial cancer risk [62-64]. The most recent cohort (17,697 women, 311 incident malignancies over 15 years) analyzed different frequency patterns, with no risk reduction observed (ever-use: adjusted HR = 0.89; 95% CI: 0.64–1.23; 6–7 days/week use: adjusted HR = 1.12; 95% CI: 0.71–1.78) [62]. In the larger cohort study (72,524 women in the National Institutes of Health-American Association of Retired Persons Diet and Health Study, neither any use (adjusted RR = 1.01; 95% CI: 0.79–1.29) nor daily use of non-aspirin NSAIDs (adjusted RR = 1.17; 95% CI: 0.85–1.62) showed significant results [63]. In the first published cohort study (82,971 women; 747 medical record-confirmed cases over 24 years), non-aspirin NSAID use was also not associated with endometrial cancer risk with any type of regular use (1 day/week: adjusted RR = 0.91; 95% CI: 0.65–1.27; 6–7 days/week: adjusted RR = 0.78; 95% CI: 0.56–1.08) [64].

One case-control study (n = 766) found that women who used any type of NSAID, including aspirin, were not at reduced risk of endometrial cancer compared with non-users of any type of NSAID (OR = 1.04; 95% CI: 0.76–1.42) [65]. The case and control groups were slightly different: cases were more likely to have a higher body mass index (BMI), not to have used oral contraceptives, and to have followed a high-risk menopausal hormone regimen, which could influence the potential protective effect of NSAIDs. In contrast, the other case-control study (n = 936), which assessed medicinal drug use, found that only NSAIDs were significantly associated with a decreased risk of endometrial cancer, but no indication of a duration-response trend was observed after adjustment for age and BMI (non-aspirin NSAID OR = 0.8; 95% CI: 0.5-1.3) [66].

Bladder Cancer

An estimated 386,300 new cases and 150,200 deaths from bladder cancer occurred worldwide in 2008 [1]. Bladder cancer is

Table 4. Evidences About Non-aspirin NSAIDs and Prevention of Breast Cancer Incidence

Study	Design and Population	Outcomes	Results	Limitations
González-Pérez 2003 [6]	<p>Systematic review with meta-analysis (search up to December 2002) with a total of 16 studies (9 case-control and 7 cohort study) that evaluated breast cancer chemoprevention.</p> <p>For the analysis, 9 studies provided data on the association between NSAID use and breast cancer incidence, 11 on aspirin use and 5 on non-aspirin NSAID use.</p>	Breast cancer	<p>Overall, there was slight reduced risk in breast cancer incidence among NSAIDs (RR = 0.77; 95% CI: 0.66–0.88), aspirin users (RR = 0.77; 95% CI: 0.69–0.86), and non-aspirin NSAIDs users (RR = 0.86; 95% CI: 0.73–1.00)</p> <p>The pooled estimate for hospital based case-control studies of NSAID use (n = 4) was 0.69 (95% CI: 0.62–0.77) whereas the pooled estimate for population based case-control studies (n = 4) was 0.89 (95% CI: 0.74–1.08). There was only one cohort study, RR = 0.57 (95% CI: 0.44–1.73)</p> <p>The combined estimate for the two studies that used mailed questionnaires to ascertain NSAID exposure was 0.67 (95% CI: 0.51–0.89). For studies using personal interview (n = 4) the overall estimate was similar (RR = 0.69; 95% CI: 0.62–0.77). The other three studies used automated databases and found no effect (RR = 0.95; 95% CI: 0.77–1.16)</p>	Search restricted to studies published in English or Spanish indexed on MEDLINE; no attempts to identify unpublished data; case-control and cohort studies results were inadequately pooled; results with significant heterogeneity
Harris 2009 [24]	Meta-analysis of 33 studies of OTC NSAIDs and breast cancer (mainly case-control and cohort studies)	Breast cancer	<p>The composite estimate shows a 25% reduction in the RR of breast cancer with regular use of aspirin or other OTC NSAIDs (combined RR = 0.75; 95% CI: 0.67–0.84)</p> <p>The risk reductions have been specifically observed for estrogen receptor positive breast cancer in recent studies (no data shown)</p>	Search strategy, selection criteria and theirs results not stated, what raises doubts about the results found; methodological quality assessment of the primary studies not stated; case-control and cohort studies results were inadequately pooled; scarce details about the included studies (population, design, intervention)
Zhao 2009 [48]	<p>Systematic review with meta-analysis (search up to 2008) of 26 studies: 16 case-control studies (7 hospital-based and 9 population-based) and 10 cohort studies. Studies from USA, Canada, UK and Denmark.</p> <p>528,705 participants were included: 241,050 were in the exposure group with 23,217 breast cancer; 287,655 were in the non-exposure group with 24,539 breast cancer</p>	Breast cancer	<p>There was observed a slight non-significant reduction on breast cancer incidence (RR = 0.94; 95% CI: 0.88–1.00).</p> <p>Case-control results (OR = 0.88; 95% CI: 0.77–1.01) and cohort studies results (RR = 0.96; 95% CI: 0.81–1.15) were also non-significant</p> <p>Population based case-control studies significantly reduced breast cancer incidence (OR = 0.84; 95% CI: 0.72–0.99), while hospital-based case-control studies did not (OR = 1.02; 95% CI: 0.80–1.29)</p> <p>A slight reduction of breast cancer by taking aspirin (RR = 0.91; 95% CI: 0.83–0.98) and ibuprofen (RR = 0.81; 95% CI: 0.67–0.97) was both observed</p> <p>No statistically significant associations about duration (>5 years and <5 years) were observed in both NSAIDs and aspirin use</p> <p>Statistically significant decreased risk was observed in both daily use group (RR = 0.88; 95% CI: 0.79–0.99) and no less than 4 times per week group (RR = 0.84; 95% CI: 0.74–0.94)</p>	Restricted search to MEDLINE and related databases and to studies published in English; Significant heterogeneity between-study variation was found Publication bias was found in the any NSAIDs meta-analysis; Studies based on self-reported (potential recall bias and misclassification of exposure); case-control and cohort studies results were inadequately pooled

(Table 4) Contd....

Study	Design and Population	Outcomes	Results	Limitations
Khuder 2001 [49]	<p>Review, search up to 2000 on MEDLINE and on Cancer Abstract databases for studies that evaluated the association between NSAIDs and breast cancer</p> <p>Conferences abstracts were also searched</p> <p>Meta-analysis included 6 cohort studies (cases ranged from 14 to 2,414) and 8 case-control studies (cases ranged from 252 to 5,882)</p>	Breast cancer	<p>Any NSAID use significantly reduced breast cancer incidence (OR = 0.82; 95% CI: 0.75–0.89). The same was observed among cohort (OR = 0.78; 95% CI: 0.62–0.99) and case-control studies (OR = 0.87; 95% CI: 0.84–0.91)</p> <p>The risk reduction for highest duration of use (20 years or more) ranged from 40% to zero and in one study four or more pills of NSAID per week was associated with a 43% reduction in the risk of breast cancer (RR = 0.57; 95% CI: 0.44–0.74)</p>	Search strategy not appropriately stated; case-control and cohort studies results were inadequately pooled Significant heterogeneity among the studies (p = 0.001); in all studies the NSAID use was self-reported (potential recall bias and misclassification of exposure)
Takkouche 2008 [50]	<p>Systematic review with meta-analysis (search up to July 2008) of 38 studies from USA, Canada, UK, Spain and Denmark: 16 case-control studies (8 hospital-based and 8 population-based), 18 cohort studies and 3 case-control nested cohort and 1 clinical trial that were included in the cohort studies group</p> <p>In the cohort group, the cases ranged from 14 to 19,934) and in the case-control group, cases ranged from 11 to 1,443)</p>	Breast cancer	<p>In a global analysis, the use of any NSAID was associated with reduced risk of breast cancer (RR = 0.88; 95% CI: 0.84–0.93). The association was a little stronger for case-control studies (RR = 0.81; 95% CI: 0.74–0.89) than for cohort studies (RR = 0.93; 95% CI: 0.88–0.98)</p> <p>For high intakes (defined as either the highest dose or the highest duration as given in the study) of NSAIDs, there was a significantly reduced risk of breast cancer incidence (RR = 0.84; 95% CI: 0.77–0.91), similar to the corresponding risk associated with any intake. The association was stronger among case-control studies (RR = 0.70; 95% CI: 0.58–0.83) than among cohort studies (RR = 0.92; 95% CI: 0.85–1.00)</p> <p>Aspirin use was associated with a reduced risk (RR = 0.87; 95% CI: 0.82–0.92) and the association was stronger among case-control studies (RR = 0.79; 95% CI: 0.72–0.86) than cohort studies (RR = 0.92; 95% CI: 0.86–0.97). High intakes did not increase the magnitude of the association</p> <p>Use of ibuprofen was associated with reduced risk (RR = 0.79; 95% CI: 0.64–0.97). High intake did not increase the magnitude of the association</p> <p>Data on celecoxib and rofecoxib use were available in only two studies. The pooled RRs were 0.47 (95% CI: 0.10–2.25) for celecoxib use and 0.60 (95% CI: 0.27–1.32) for rofecoxib use</p>	Restricted search to published studies; heterogeneity was significant and did not subside after stratification by design or other characteristics; possible interactions with other drugs were not taken into account

Abbreviations:
 NSAID: non-steroidal anti-inflammatory drugs
 RR: relative risk
 95% CI: 95% confidence interval
 OR: odds ratio
 OTC: Over-the-counter (OTC)

the most common malignancy of the urinary tract. The majority of bladder cancer occurs in males. The highest incidence rates are found in Europe, North America, and Northern Africa. Smoking and occupational exposures are the major risk factors in Western countries, whereas chronic infection with *Schistosoma haematobium* accounts for approximately 50% of the total burden in developing countries, particularly in Africa and the Middle East [1].

The chemoprevention of bladder cancer consists of the use of various systemic agents to prevent or reverse diffuse changes in the urothelium that may result in bladder cancer [97]. Primary chemo-

prevention seeks to block the formation of *de novo* bladder cancers in healthy individuals, whereas secondary chemoprevention focuses on preventing the formation of additional tumors in patients who have already been treated for bladder cancer [97].

The best evidence related to non-aspirin NSAID use and bladder cancer comes from a pooled analysis of three large prospective U.S. cohort studies (508,842 individuals; 2,489 cases) [67] (Table 7). The authors found a non-significant reduction in bladder cancer risk in men and women who reported the regular use of non-aspirin

Table 5. Evidences About Non-aspirin NSAIDs and Prevention of Ovarian Cancer Incidence

Study	Design and Population	Outcomes	Results	Limitations
González-Pérez 2003[6]	Systematic review with meta-analysis with a total of 9 articles (1 cohort and 8 case-control studies) that evaluated ovarian cancer chemoprevention	Ovarian cancer	Overall RR: NSAIDs use, 0.74 (6 studies; 95% CI: 0.61–0.90), aspirin use, 0.91 (6 studies; 95% CI: 0.79–1.06). Non-aspirin NSAIDs risk was not evaluate	Restricted search to studies published in English or Spanish; combined results from case-control and cohort studies
Bonovas 2005 [55]	Systematic review with meta-analysis of 10 studies (6 case-control and 4 cohort studies) published between 1998 and 2004 3 case-control studies and 3 cohort studies evaluated exposure to non-aspirin NSAIDs and ovarian cancer risk	Ovarian cancer	The association of non-aspirin NSAID use with ovarian cancer was not statistically significant assuming either a fixed-effects model (RR = 0.88; 95% CI: 0.76–1.01), nor a random-effects model (RR = 0.86; 95% CI: 0.68–1.08) No association between nonaspirin NSAIDs use and ovarian cancer, either among case-control studies (random-effects model, RR = 0.89; 95% CI: 0.53–1.49), nor among cohort studies (random-effects model, RR = 0.84; 95% CI: 0.66–1.07)	Methodological quality assessment of the primary studies not stated; meta-analysis with different measures of effect estimative; sparse and heterogeneous data; most studies used personal interviews or self-administered questionnaires that rely on the subject's ability to recall; regular and irregular intake not very precise
Schildkraut 2006 [56]	Population-based, case-control study with 586 ovarian cancer cases (age 20 to 74 years) and 627 matched controls in North Carolina	Ovarian cancer	The adjusted OR of any NSAID was 0.72 (95% CI: 0.56–0.92) There was no evidence for differences in the association according to frequency or duration of NSAID use Any NSAID use appeared stronger for those who used both prescription and over-the-counter formulations (OR = 0.44; 95% CI: 0.25–0.79) For use of acetaminophen, the OR was 0.78 (95% CI: 0.56–1.08)	Self-report of analgesic use; the assessment of NSAID use was only within the last 5 years
Wernli 2008 [57]	Population-based case-control study conducted in Wisconsin and Massachusetts with a total of 487 invasive ovarian cancer cases and 2653 control women aged 20–74 years	Ovarian cancer	It was observed a reduction in risk among women who had ever used any type of NSAID compared to non-users, OR = 0.74 (95% CI: 0.59–0.92) According to oral contraceptive use, use of NSAIDs was inversely associated with ovarian cancer in never users, defined as use of NSAIDs for less than 6 months or less than twice per week (OR = 0.58; 95% CI: 0.42–0.80), but there was no association among ever users, defined as NSAID use for at least twice per week for 6 months or more (OR = 0.98; 95% CI: 0.71–1.35) Reduction in risk was seen for both current and former users among never oral contraceptive users. A reduced risk with NSAID use was limited to nulliparous women (OR = 0.47; 95% CI: 0.27–0.82), whereas there was little evidence of association among parous women (OR = 0.81; 95% CI: 0.64–1.04) There was a significant decreasing trend in risk with increasing years of NSAID use among nulliparous women alone ($p = 0.01$) Non-aspirin NSAIDs risk was not evaluated	Analysis relied on the subject's ability to recall the use of NSAIDs

(Table 5) Contd....

Study	Design and Population	Outcomes	Results	Limitations
Lurie 2010 [58]	Pooled analysis of two population-based case-control studies (the Hawaii Ovarian Cancer Case-Control Study and the New England Case-Control Study), including 1,025 women with invasive ovarian carcinoma and 1,687 cancer-free control	Ovarian cancer	<p>Any NSAID use was significantly associated with decreased ovarian cancer risk (OR = 0.79; CI: 0.67–0.95). Significant inverse associations were not observed among women who used one of the types exclusively (aspirin and non-aspirin NSAIDs)</p> <p>Among carriers of the CC genotype, patients who were users of only non-aspirin NSAIDs had the lowest risk (OR = 0.43; CI: 0.20–0.93)</p> <p>CC genotype carriers who were users of both aspirin and non-aspirin NSAIDs had a non-significantly decreased ovarian cancer risk (OR = 0.42; CI: 0.18–1.01), whereas women with the CC genotype who reported aspirin use alone had a non-significantly increased ovarian cancer risk (OR = 1.21; 95% CI: 0.60–2.44)</p>	Exploration of NSAID dose was not possible
Hannibal 2008 [59]	Population-based, case-control study in Washington State that included 812 women aged 35–74 years (cases) and 1,313 controls.	Ovarian cancer	<p>Use for more than 10 years, OR = 1.8 (95% CI: 1.3–2.6) for acetaminophen and 1.6 (95% CI: 1.1–2.2) for aspirin. For any type of NSAID, the OR was 1.3 (95% CI: 1.0–1.7)</p> <p>NSAID use for more than 20 years, the risk was more than two-fold higher: acetaminophen OR = 2.5 (95% CI: 1.5–4.0), aspirin OR = 2.1 (95% CI: 1.3–3.4)</p> <p>Among aspirin users, women who initiated regular use less than 5 years before the reference date were at a non-significant reduced risk (OR = 0.6; 95% CI: 0.4–1.0)</p>	Reporting of analgesic use may have been influenced by the presence of ovarian cancer symptoms in case women
Merritt 2008 [60]	Australia-wide population-based case-control study comprising 1,576 women with invasive and low malignant potential ovarian tumours and 1,509 population-based controls (aged 18–79 years).	Ovarian cancer	<p>Any use of aspirin was not associated with ovarian cancer risk for all subtypes combined (OR = 1.06; 95% CI: 0.92–1.23)</p> <p>Ever use of NSAIDs in the last 5 years also had no effect on risk of all subtypes of ovarian cancer (OR = 0.88; 95% CI: 0.76–1.02), while using two or more per week resulted in a OR = 0.83 (95% CI: 0.66–1.04)</p> <p>Risk of mucinous tumors was inversely associated with any use of NSAIDs (OR = 0.69; 95% CI: 0.50–0.94)</p> <p>There was a dose-response relationship for low malignant potential mucinous tumors (OR for 2 or more pills per week vs. no use = 0.46; 95% CI: 0.23–0.91)</p>	Low response rate for controls; analyses of medical conditions were based entirely on self-reported; cases were significantly less likely to have continued their education beyond high school
Pinheiro 2009 [61]	<p>Prospective cohort study with 197,486 participants from the Nurses' Health Study (NHS) and the Nurses' Health Study-II (NHS-II) over 24 and 16 years of follow-up, respectively</p> <p>A total of 666 (n = 552 [NHS]; n = 114 [NHS-II]) confirmed cases of epithelial ovarian cancer were identified</p>	Ovarian cancer	<p>Regular use of non-aspirin NSAIDs was not significantly associated with ovarian cancer incidence (for regular use vs. no regular use: HR = 0.81; 95% CI: 0.64–1.01)</p> <p>HR associated with regular use of aspirin was 1.11 (95% CI: 0.92–1.33, for non-aspirin NSAIDs was 0.81 (95% CI: 0.64–1.01), and for acetaminophen was 1.14 (95% CI: 0.92–1.43)</p> <p>There was observed no dose-response relation with increased frequency or duration of regular use of any of medications and ovarian cancer incidence</p>	Use of self-reported data

(Table 5) Contd....

Study	Design and Population	Outcomes	Results	Limitations
Prizment 2010 [62]	<p>Prospective cohort of women (Iowa Women's Health Study – IWHS) with ages from 58 to 76 years in 1992</p> <p>21,694 women were available for the ovarian cancer analysis</p> <p>Over 15 years, 167 ovarian incident malignancies were identified</p>	Ovarian cancer	<p>The HR of ovarian cancer for women who reported using aspirin <2 times per week, 0.83 (95% CI: 0.56–1.22); 2 to 5 times per week, 0.77 (95% CI: 0.48–1.24); and 6 times or more per week, 0.61 (95% CI: 0.37–0.99)</p> <p>Non-aspirin NSAIDs were not associated with ovarian cancer incidence. The multivariate-adjusted HR for women who used non-aspirin NSAIDs compared with no use of non-aspirin NSAIDs were 0.65 (95% CI: 0.40–1.05), for <2 times or less per week; 1.08, (95% CI: 0.62–1.90), for 2 to 5 times; and 1.12 (95% CI: 0.71–1.78) for 6 times or more per week</p>	Information about duration, dosage and reason for NSAIDs use was not collected; Exposure was assessed by self-report

Abbreviations:
 NSAID: non-steroidal anti-inflammatory drugs
 RR: relative risk
 OR: odds ratio
 95% CI: 95% confidence interval
 HR: hazard ratio

Table 6. Evidences About Non-aspirin NSAIDs and Prevention of Endometrial Cancer Incidence

Study	Design and Population	Outcomes	Results	Limitations
Prizment 2010 [62]	<p>Prospective cohort of women (Iowa Women's Health Study) with ages from 58 to 76 years in 1992</p> <p>17,697 women were available for the endometrial cancer analysis</p> <p>Over 15 years, 311 endometrial incident malignancies were identified</p>	Endometrial cancer	<p>The multivariate-adjusted HR for women who reported use of aspirin <2 times, 0.78 (95% CI: 0.58–1.04); 2 to 5, 0.89 (95% CI: 0.63–1.25) and 6+ times weekly 0.85 (95% CI: 0.61–1.18)</p> <p>The adjusted HR for non-aspirin NSAIDs users were 0.86 (95% CI: 0.63–1.18) for <2 times; 1.16 (95% CI: 0.78–1.72) for 2 to 5; and 0.85 (95% CI: 0.58–1.22) for 6+ times weekly</p> <p>Women using non-aspirin NSAIDs more frequently were more likely to be obese, have history of oral contraceptive and hormone replacement therapy use, have had a hysterectomy, and were somewhat more likely to report endometriosis</p>	Information about duration, dosage, and reason for NSAIDs use was not collected; exposure was assessed by self-report
Danforth 2009 [63]	<p>Prospective cohort study among 72,524 women in the NIH-AARP Diet and Health Study, ages 50 to 71 years.</p> <p>During the average 6.7 years of follow-up per woman, there were 732 incident endometrial cancers.</p>	Endometrial cancer	<p>NSAID use, compared with nonuse of NSAIDs, was not significantly associated with endometrial cancer risk (RR = 0.90; 95% CI: 0.74–1.09)</p> <p>No associations were observed by type of NSAID use (aspirin only: RR = 0.88; 95% CI: 0.70–1.11; non-aspirin NSAID only: RR = 1.01; 95% CI: 0.79–1.29; both aspirin and non-aspirin NSAIDs: RR = 0.85; 95% CI: 0.68–1.06)</p>	No information on dose or duration; exposure information not updated during follow-up
Viswanathan 2008 [64]	<p>Prospective cohort study with 82,971 women enrolled in the NHS (cohort of registered nurses between the baseline ages of 30 and 55 years, living in 11 states in the United States)</p> <p>747 women developed medical record-confirmed invasive endometrial cancer over a 24-year period</p> <p>Use of aspirin was ascertained from 1980 to 2004, and for other NSAIDs and acetaminophen, from 1990 to 2004</p>	Endometrial cancer	<p>In analyses from 1990 to 2004, non-aspirin NSAID use was not associated with endometrial cancer risk (analyses included 497 endometrial cancer cases)</p> <p>Similarly, no association was observed for use of either acetaminophen or aspirin use specifically from 1990 to 2004</p> <p>In age-adjusted analyses, the RR for past aspirin use was 1.22 (95% CI: 0.98–1.52) and for current aspirin users was 1.07 (95% CI: 0.87–1.32), and the association was only slightly attenuated after adjustment for important covariates, including BMI</p> <p>The frequency of aspirin use (days per week) from 1984 forward was not significantly associated with risk (for increasing number of days per week, p = 0.49)</p>	Possible residual confounding, such as BMI; limited ability to evaluate the acetaminophen exposures by duration of use

(Table 6) Contd....

Study	Design and Population	Outcomes	Results	Limitations
Bodelon 2009 [65]	Population-based, case-control study in western Washington State, 410 women diagnosed with invasive endometrial cancer, aged 50–74 years, and 356 controls	Endometrial cancer	Women who were users of any type of NSAID, including aspirin, were not at reduced risk of endometrial cancer compared with never users of any type of NSAID (OR = 1.04, 95% CI: 0.76–1.42) Use of neither aspirin nor acetaminophen altered the risk of endometrial cancer (aspirin: OR = 1.06, 95% CI: 0.73–1.53; acetaminophen: OR = 1.11; 95% CI: 0.70–1.77)	Data collection by interview (recall bias); no information on dose of analgesics was obtained; cases were more likely to not to have used oral contraceptives and to have taken a high risk menopausal hormone regimen
Fortuny 2009 [66]	Population-based case-control study (The Estrogen, Diet, Genetics, and Endometrial Cancer Study) northern New Jersey, including 469 endometrial cancer cases and 467 controls	Endometrial cancer	Use of non-steroidal anti-inflammatory drugs was related to a decreased risk (OR = 0.7; 95% CI: 0.5–0.97), no indication of a duration-response trend was observed after adjustment for age and BMI (p = 0.12; data not shown) No significant effect of non-aspirin NSAIDs (OR = 0.8; 95% CI: 0.5–1.3) in the age- and BMI-adjusted model Non-aspirin NSAIDs trend reduced risk was somewhat more apparent in women with lower BMI (OR = 0.7; 95% CI: 0.4–1.4) than in those with higher BMI (OR = 0.9; 95% CI: 0.4–1.9), after adjustment for age and BMI	Data collection by interview (recall bias); some conditions associated with use of NSAIDs, such as osteoarthritis, not evaluated

Abbreviations:

HR: hazard ratio

95% CI: 95% confidence interval

NSAID: non-steroidal anti-inflammatory drugs

NHS: National Institutes of Health

AARP: American Association of Retired Persons

RR: relative risk

BMI: body mass index

OR: odds ratio

NSAIDs (defined as a use frequency > 2 times/week) compared with those who reported no use (pooled HR = 0.99; 95% CI: 0.91–1.09). In addition, the pooled analysis supported the hypothesis that regular non-aspirin NSAID use was associated with a 42% reduction in the risk of bladder cancer, particularly for nonsmokers (HR = 0.58; 95% CI: 0.41–0.83).

A previous systematic review found limited results for the prevention of bladder cancer with the use of NSAIDs (RR = 0.91; 95% CI: 0.71–1.18) and aspirin (RR = 0.91; 95% CI: 0.73–1.13) [6]. These estimates were based on flawed methods and limited primary designs (cohort and case-control). Based on this evidence, the authors suggested that additional studies be conducted.

Renal Cell Carcinoma

Renal cell carcinoma (RCC) is a type of kidney cancer that usually originates in the lining of the kidney tubules and these tumors typically contains many blood vessels [30, 95, 98]. RCC accounts for 90% of kidney cancers and approximately 3% of all adult cancers [98]. Worldwide, there were an estimated 270,000 cases and 116,000 deaths in 2008 [95]. A number of environmental and clinical factors have been implicated in the etiology of RCC. These include smoking, hypertension, occupational exposure to toxic compounds, obesity, acquired cystic disease of the kidney (typically associated with dialysis), analgesic abuse nephropathy, and genetic predisposition [68].

A narrative review supports that the prolonged ingestion of analgesic combinations, particularly compounds containing phenacetin and aspirin, may lead to chronic renal failure [68]. Such patients are at increased risk of renal pelvic and urothelial tumors.

The prospective cohort Nurses' Health Study and Health Professionals' Follow-Up Study found an increased risk of RCC among subjects who used non-aspirin NSAIDs (RR = 1.46; 95% CI: 1.04–2.04) [69]. The study followed 95,967 women for 14 years and 49,401 men for 20 years and found 324 documented cases of RCC. Nevertheless, detailed information about this analysis was not accessible when this review was prepared. A previous population-based case-control study (1,204 RCC patients and an equal number of controls) found that regular analgesic use (defined as two or more times per week for 1 month or longer) was a significant risk factor for RCC (OR = 1.6; 95% CI: 1.4–1.9) [70]. More specifically, the regular use of non-aspirin NSAIDs presented an OR of 1.4 (95% CI: 1.1–1.8) for RCC. Another important finding was that within each class of analgesics, including the non-aspirin NSAIDs, there was a statistically significant increase in risk as the level of exposure increased. These findings support the evidence that the regular use of non-aspirin NSAIDs has no chemopreventive effect on RCC and may even increase the risk of developing the disease (Table 8).

Prostate Cancer

Prostate cancer is the second-most-frequently diagnosed cancer and the sixth leading cause of cancer death in males. Prostate cancer accounted for 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in males in 2008 [1]. Incidence rates vary by more than 25-fold worldwide, with the highest rates recorded primarily in the developed countries of Oceania, Europe, and North America. This may be largely credited to the wide utilization of prostate-specific antigen (PSA) testing, which detects clinically important tumors and other slow-growing cancers

Table 7. Evidences About Non-aspirin NSAIDs and Prevention of Bladder Cancer Incidence

Study	Design and Population	Outcomes	Results	Limitations
Daugherty 2011 [67]	Multicohort analysis of combined data from 3 large cohorts studies (NIH-AARP Diet and Health Study; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and U.S. Radiologic Technologists Study) with a total of 508,842 individuals and baseline median age of 62.1 years 2,489 incident cases of bladder cancer were identified in a total of 3,582,284 person-years (overall follow-up from 1993 to 2005)	Bladder cancer Urothelial carcinomas Tumor grade and morphology behavior	Bladder cancer: A reduction in risk was observed for regular use (>2 times/week) of non-aspirin NSAIDs in the fixed-effect meta-analysis (HR = 0.90, 95% CI: 0.80-1.02; p = 0.10). No significant trend in risk with increasing frequency of non-aspirin NSAID use (p = 0.30) A significant reduction in risk for nonsmokers with regular use of non-aspirin NSAIDs was found (HR = 0.58, 95% CI: 0.41-0.83; p = 0.008); no association for former smokers (HR = 0.98, 95% CI: 0.85-1.14), current smokers (HR = 0.98, 95% CI: 0.74-1.29), people who quit smoking more than 10 years ago (HR = 0.96, 95% CI: 0.80-1.15) or quit in the last 10 years (HR = 1.01, 95% CI: 0.78-1.32) was observed No significant association was observed for exclusive users of non-aspirin NSAIDs (HR = 0.98, 95% CI: 0.79-1.21) and for users of both aspirin and non-aspirin NSAIDs (HR = 1.03, 95% CI: 0.91-1.16). Exclusive regular aspirin users had a trend to a higher risk (HR = 1.12, 95% CI: 0.99-1.27) Urothelial carcinomas: Associations similar to the overall findings (HR = 0.92, 95% CI: 0.81-1.04) Tumor grade and morphology behavior: No association between regular use of non-aspirin NSAIDs and low-grade <i>in situ</i> tumors (HR = 1.03, 95% CI: 0.73-1.45), suggestive inverse associations with intermediate (HR = 0.83, 95% CI: 0.68-1.01) and high-grade bladder cancers (HR = 0.92, 95% CI: 0.75-1.13)	Small number (n = 106) of exclusive users of aspirin or non-aspirin NSAIDs (limited statistical power); Use frequency obtained by a self-administered questionnaire
González-Pérez 2003 [6]	Systematic review with meta-analysis with a total of 5 studies (3 case-controls and 2 cohort studies) that evaluated bladder cancer chemoprevention.	Bladder cancer	Results obtained were compatible with no effect. NSAIDs use: RR = 0.91 (3 studies, 95% CI: 0.71-1.18). Aspirin use: RR = 0.91 (3 studies, 95% CI: 0.73-1.13). Non-aspirin NSAIDs risk not evaluated	Restricted search to studies published in English or Spanish; Combined results from case-control and cohort studies

Abbreviations:

NIH: National Institutes of Health

AARP: American Association of Retired Persons

HR: hazard ratio

95% CI: 95% confidence interval

NSAID: non-steroidal anti-inflammatory drugs

RR: relative risk

that might otherwise escape diagnosis. Greater age, ethnicity (black), and family history remain the only well-established risk factors, and there are no confirmed preventable risk factors for prostate cancer [1].

Three factors have contributed to the rationale for prostate cancer chemoprevention: the long latency period between the initial diagnosis of prostate cancer and the development of evident or fatal disease, the androgen dependency of these tumors, and the availability of intermediate endpoints for use in clinical trials. Elevated prostaglandin levels and upregulation of COX-2, a key enzyme in the conversion of arachidonic acid to prostaglandins, are found in prostate cancer cell lines, and apoptosis follows the withdrawal of arachidonic acid and/or its metabolites. Experimental evidence suggests differential expression of COX-2 in normal prostatic stroma, with upregulation in both premalignant and malignant prostate epithelium, and regression of prostatic intraepithelial neoplasia has been observed in murine models after NSAID administration. These data provide evidence for considering the use of NSAIDs as chemopreventive agents. However, a planned prostate cancer pre-

vention trial with rofecoxib was canceled when the drug was withdrawn from the market due to unexpected cardiovascular toxicity [99].

We found five systematic reviews that evaluated this issue [6, 24, 71-73] (Table 9). The most current (including studies up to June 2008) included 10 case-control and 14 cohort studies (24,230 prostate cancer cases) [71]. Their findings did not show significant inverse associations when evaluating the non-aspirin NSAIDs across cohort and case-control studies (OR = 0.90; 95% CI: 0.80-1.01; 12 studies) or cohort studies only (OR = 0.99; 95% CI: 0.89-1.11, 5 studies); however, an analysis of the case-control studies only revealed significant findings (OR = 0.79; 95% CI: 0.68-0.92, 7 studies). The lack of information on drug dosage and duration, along with the limited quality of the included studies, may make it difficult to apply these findings in practice. The same problem was found in a similar analysis of 5 cohort and 7 case-control studies (n = 12,238) that was previously performed by the same group; their results also revealed no significant associations [72].

Table 8. Evidences About Non-aspirin NSAIDs and Prevention of Renal Cell Carcinoma Incidence

Study	Design and Population	Outcomes	Results	Limitations
Cho 2009 [102]	Prospective cohort of women and men in the Nurses' Health Study and Health Professionals Follow-up Study 324 cases of renal cell carcinoma documented (146 women and 178 men) among 95,967 women with a follow-up of 14 years and among 49,401 men with a follow-up of 20 years	Renal cell carcinoma	The pooled multivariate RR for renal cell carcinoma were significantly increased for use twice per week or more compared with those who used them less often of non-aspirin NSAIDs (RR = 1.52; 95% CI: 1.11–2.09) and acetaminophen (RR = 1.46; 95% CI 1.04–2.04)	Complete data unavailable (full text not published)
Gago-Dominguez 1999 [70]	Population-based case-control study in Los Angeles, California, with 1,204 non-Asian patients with renal cell carcinoma, aged 25-74 (mean age at diagnosis of 58.8 years) and an equal number of sex-, age- and race-matched neighborhood controls	Renal cell carcinoma	Regular use of analgesics was a significant risk factor for RCC in both men and women combined (OR = 1.6; 95% CI: 1.4–1.9) For regular use (defined as two or more times a week for 1 month or longer) of non-aspirin NSAID, the risk was significantly increased (OR = 1.4; 95% CI: 1.1–1.8) Risks were elevated across all four major classes of analgesics (aspirin, non-aspirin NSAIDs, acetaminophen and phenacetin). Compared with non- or irregular users of analgesics, increased risks of RCC were observed among exclusive users of aspirin (OR = 1.4; 95% CI: 1.1–1.9), non-aspirin NSAID (OR = 1.5; 95% CI: 1.0–2.2), and acetaminophen (OR = 1.6; 95% CI: 1.1–2.4) after adjustment for other risk factors There was statistically significant higher risk with increasing level of exposure: Non-aspirin NSAID, OR = 1.3 (95% CI: 0.9–1.9), for maximum weekly dose (g) of < 2; 1.5 (95% CI: 1.0–2.3), for 2 to < 4 g; 1.3 (95% CI: 0.8–2.3), for 4 to < 8 g; and 1.9 (95% CI: 1.1–3.5), for > 8 g	Personal interviews, questionnaires that rely on the subject's ability to recall

Abbreviations:

NSAID: non-steroidal anti-inflammatory drugs

RR: relative risk

OR: odds ratio

95% CI: 95% confidence interval

Two previous reviews revealed that NSAIDs provide some degree of protection against prostate cancer [24, 73]. However, the higher-quality studies included in such reviews do not support these conclusions. One review also included a pooled analysis of case-control and cohort studies ($n = 25,768$) and found that non-aspirin NSAIDs use was associated with a slightly reduced chance of prostate cancer (OR = 0.92; 95% CI: 0.85–1.00; 13 studies) [73]. In a subgroup analysis based on the study design, only the case-control findings including aspirin were significant (OR = 0.91; 95% CI: 0.84–0.99; 13 studies) [73]. The other meta-analysis did not separately evaluate the use of non-aspirin NSAIDs. Therefore, there were no conclusions specifically related to this issue [24]. Another systematic review (including studies up to December 2002 and restricted to those published in English and Spanish), warned that the limited number of studies involved and the heterogeneity observed in these estimates precluded a conclusive analysis [6].

Our literature search retrieved eight observational studies that had not been previously considered: three cohort studies [74–76], four case-control studies [77–80] and one cross-sectional study [81]. Two of the cohort studies ($n = 7,621$ and $n = 34,132$) found that non-aspirin NSAID use was not associated with prostate cancer risk [74, 75]. A recent large cohort study (78,485 men in the Cancer Prevention Study II Nutrition Cohort) suggested that long-term, regular acetaminophen use (> 5 years) may be associated with lower prostate cancer risk [76]. Two case-control studies (140 and 1,001 cases, respectively) found no association between non-aspirin

NSAIDs and prostate cancer risk (measured by the cancer incidence and PSA increase) [77, 78]. Another case-control study (1,367 cases and 2,007 controls) did not support a protective effect associated with statin and NSAID use [79]. In the last case-control study (1,016 cases and 5,043 controls), non-aspirin NSAID use was associated with an increased risk of PSA-detected prostate cancer (OR = 1.32; 95% CI: 1.04–1.67) [80]. However, potential bias was identified: the interview was based on mailed, self-completed questionnaires, and the data did not include information about past NSAID use or its duration. Finally, a cross-sectional study ($n = 1,372$) found that NSAID use including aspirin was not significantly associated with either cancer grade at biopsy ($p = 0.84$) or prostate volume ($p = 0.16$) [81].

Skin Cancer

There are two main types of skin cancer: non-melanoma and malignant melanoma. Non-melanoma includes two main types: basal-cell carcinoma (BCC) and the more serious squamous-cell carcinoma (SCC). BCC is rarely fatal, but if it is not diagnosed early enough or is not properly treated, it can result in tumors that destroy important anatomical structures, such as the nose, eye, ear and lip. SCC can be disfiguring and can be fatal if it spreads; its development is associated with chronic ultraviolet radiation exposure in the earlier decades of life. Malignant melanoma is the most serious and is responsible for the majority of skin cancer deaths; it

Table 9. Evidences About Non-aspirin NSAIDs and Prevention of Prostate Cancer Incidence

Study	Design and Population	Outcomes	Results	Limitations
Mahmud 2010 [71]	<p>Systematic review with meta-analysis, including (search up to June 2008) including 10 case-control and 14 cohort studies with a total of 24,230 prostate cancer cases</p> <p>The mean age of study participants ranged from 63 to 75 years</p> <p>8 studies reported RRs for use of non-aspirin NSAIDs</p>	Prostate cancer	<p>Aspirin use significantly reduced total prostate cancer incidence (all 17 studies: OR = 0.83; 95% CI: 0.77–0.89; 9 cohort studies: OR = 0.83; 95% CI: 0.76–0.91; 8 case-control studies: OR = 0.82; 95% CI: 0.71–0.94) and advanced prostate cancer incidence (all 10 studies: OR = 0.81; 95% CI: 0.72–0.92; similar results for cohort and case control studies)</p> <p>Non-aspirin NSAIDs use and total prostate cancer incidence were not significantly associated (all 12 studies: OR = 0.90; 95% CI: 0.80–1.01; 5 cohort studies: OR = 0.99; 95% CI: 0.89–1.11; 7 case-control studies: OR = 0.79; 95% CI: 0.68–0.92), as well as advanced prostate cancer (all 7 studies: OR = 1.00; 95% CI: 0.63–1.58; similar results for cohort and case control studies)</p>	Included studies were different in terms of design, populations, outcomes, and types of drugs investigated; although the subgroup analysis did not show significant changes on the results due to study design, pooling case-control and cohort was not an adequate method
Mahmud 2004 [72]	<p>Systematic review with meta-analysis (search up to January 2003) of 12 studies (n = 12,238): 5 cohort studies (n = 5,416), 2 nested case-control studies (n = 4,034) and 5 case-control studies (n = 2,788)</p> <p>The mean age of study participants ranged from 64 to 75.7 years</p>	Prostate cancer	<p>Aspirin use significantly reduced total prostate cancer incidence (OR = 0.90; 95% CI: 0.82–0.99)</p> <p>Non-aspirin NSAIDs use and total prostate cancer incidence were not significantly associated (OR = 0.87; 95% CI: 0.61–1.24) and for all NSAIDs (OR = 0.68; 95% CI: 0.37–1.22)</p>	<p>No information on the duration of drug use or time since first NSAID use; no search for unpublished studies; studies were different in terms of design, populations, outcomes, and types of drugs investigated</p> <p>Summary effect estimates based on sparse and heterogeneous data; the authors did not describe how the studies were assessed for validity; although the subgroup analysis did not show significant changes on the results due to study design; pooling case-control and cohort was not an adequate method</p>
Harris 2009 [24]	<p>Meta-analysis of 17 studies of non-prescription NSAIDs and prostate cancer (case-control and cohort studies)</p>	Prostate cancer	<p>The composite estimate shows a 27% reduction in the RR of prostate cancer with regular use of aspirin or other non-prescription NSAIDs (RR = 0.73; 95% CI: 0.62–0.87)</p>	<p>Search strategy, selection criteria and their results not stated, what raises doubts about the results found; methodological quality assessment of the primary studies not stated; case-control and cohort studies results were inadequately pooled; scarce details about the included studies (population, design, intervention)</p>
Jafari 2009 [73]	<p>Systematic review (search up to March 2008) including 20 observational studies (7 cohort, 5 nested case-control, 7 case-control and 1 cross-sectional study) with a total of 25,768 participants (all observational design)</p> <p>The mean age of study participants ranged from 63 to 75.7 years.</p>	Prostate cancer	<p>There was a statistically significant protective effect for NSAIDs on risk of prostate cancer (OR = 0.92; 95% CI: 0.86–0.97)</p> <p>Non-aspirin NSAIDs was associated with a slightly reduced likelihood of prostate cancer (OR = 0.92; 95% CI: 0.85–1.00)</p> <p>The summary OR for 13 case-control studies was 0.91 (95% CI: 0.84–0.99)</p> <p>The summary OR for 7 cohort studies was 0.94 (95% CI: 0.86–1.02)</p> <p>Analysis of 15 high-quality studies revealed a pooled OR of 0.96 (95% CI: 0.91–1.01). There was no significant difference in effect size based on the quality scores</p> <p>A small protective effect was seen among the questionnaire studies (OR = 0.93; 95% CI: 0.88–0.98) compared with database studies (OR = 1.04; 95% CI: 0.93–1.16)</p> <p>Results of separate analysis for aspirin revealed a pooled OR of 0.95 (16 studies, 95% CI: 0.91–1.00)</p>	<p>Although the subgroup analysis did not show significant changes on the results due to study design, pooling case-control and cohort was not an adequate method; there was moderate heterogeneity in the results of the included studies (statistical significant)</p>

(Table 9) Contd....

Study	Design and Population	Outcomes	Results	Limitations
González-Pérez 2003 [6]	Systematic review with meta-analysis with a total of 11 articles (6 cohort and 5 case-control studies)	Prostate cancer	No significant association was found. NSAIDs use: RR 0.64 (4 studies, 95% CI: 0.34–1.21); Non-aspirin NSAIDs use: RR 0.84 (2 studies, 95% CI: 0.68–1.05)	Restricted search studies published in English or Spanish indexed on MEDLINE; no attempts to identify unpublished data; case-control and cohort studies results were inadequately pooled; results with significant heterogeneity
Siemes 2008 [74]	Population-based prospective cohort study with a total of 7,621 participants of the “The Rotterdam Study”, aged 55 years and older During a mean follow-up time of 9.7 years, 720 cancers occurred Mean age of the study population was 70 years	Prostate cancer	Adjusted analysis of any NSAIDs use showed a non-significant HR of 1.02 (95% CI: 0.76–1.37); use of more than 365 days: HR = 1.07 (95% CI: 0.75–1.54) Adjusted analysis of non-aspirin NSAIDs use showed a non-significant HR of 1.01 (95% CI: 0.74–1.40); use of more than 365 days: HR = 1.41 (95% CI: 0.71–2.83) In summary, total cancer risk seemed not to be associated with use or duration of use of any of the NSAID group	Possible sources of information bias (no information about stage, grade and therapy and other competing risk indicators); more frequently smoker had shorter follow-up time frame
Brasky 2010 [75]	Prospective cohort study with male members of the VITAL cohort (Vitamins And Lifestyle) including 34,132 men, aged 50-76 years, living in western Washington State Between October 2000 and December 2007, there were 1,550 incident prostate cancer cases diagnosed	Prostate cancer	Adjusted analysis of non-aspirin NSAIDs uses was not associated to prostate cancer incidence (HR = 1.01; 95% CI: 0.89–1.15) Adjusted analysis of 10-year average use of non-aspirin NSAIDs were also non-significant (HR = 0.99; 95% CI: 0.86–1.14, for low use [< 4 days/week or < 4 years]; HR = 1.08; 95% CI: 0.86–1.37, for high use [≥ 4 days/week and ≥ 4 years]) Low-dose aspirin, regular-strength aspirin, ibuprofen, and any non-aspirin NSAID (ibuprofen, naproxen, and COX-2 inhibitors) were not associated with prostate cancer risk	Specific population (western Washington State inhabitants)
Jacobs 2011 [76]	Prospective cohort study with 78,485 men in the Cancer Prevention Study II Nutrition Cohort, evaluating acetaminophen use and prostate cancer incidence During follow-up from 1992 through 2007, 8,092 incident prostate cancer cases were identified Mean age of the study population was about 70 years.	Prostate cancer	Regular use (30 or more pills per month) of less than 5 years was not associated with overall prostate cancer risk (RR = 1.00; 95% CI: 0.89–1.12) Regular use of acetaminophen for 5 or more years was associated with lower risk of overall prostate cancer (RR = 0.62; 95% CI: 0.44–0.87) and aggressive prostate cancer (RR = 0.49; 95% CI: 0.27–0.88). No association for non-aggressive prostate cancer (RR = 0.75; 95% CI: 0.49–1.15)	Low prevalence of long-term regular acetaminophen use (limited precision); no information was available on dose per tablet; acetaminophen use and frequency was based on self-reported questionnaires.
Algotar 2010 [77]	Case-control study with data from 140 men with prostate cancer enrolled in a phase 2 clinical trial (the Watchful Waiting – WW study), average follow-up time of 3.2 years) Blood was drawn to assess PSA at randomization and at every subsequent quarterly follow-up visit	Mean PSA velocity	Analysis of aspirin use demonstrated a non-significant negative association with PSA velocity (0.51 ng/ml/year vs. 0.95 ng/ml/year, $p = 0.56$) Non-aspirin NSAID use revealed a non-significant negative association with PSA velocity (0.64 ng/ml/year vs. 0.73 ng/ml/year, $p = 0.90$)	Dose-response not evaluated

(Table 9) Contd....

Study	Design and Population	Outcomes	Results	Limitations
Salinas 2010 [78]	Population-based case-control study with 1,001 cases (Seattle–Puget Sound Surveillance, Epidemiology, and End Results – SEER cancer registry) and 942 age-matched controls from King County, Washington (35–74 years of age)	Prostate cancer	Ever use of aspirin (OR = 0.82; 95% CI: 0.68–0.99), daily use (OR = 0.78; 95% CI: 0.64–0.95) and daily low-dose use (OR = 0.71; 95% CI: 0.56–0.90) were significantly associated with reduced prostate cancer incidence. The same was observed with current users of aspirin with greater than 5 years of use (OR = 0.74; 95% CI: 0.58–0.94) and current users reporting 5 or fewer years of use (OR = 0.85; 95% CI: 0.67–1.08). Prostate cancer risk was not related to use of either non-aspirin NSAIDs (OR = 1.05; 95% CI: 0.84–1.32) No association was found for ibuprofen alone (ever use: OR = 0.94; 95% CI: 0.69–1.27) No association was found for acetaminophen alone (ever use: OR = 1.03; 95% CI: 0.75–1.41; > 5 years' use: OR = 1.15; 95% CI: 0.71–1.48)	Potential selection bias (of the 1,507 eligible controls identified, only 942, 62.5%, completed the interview) Potential detection bias (cases were more likely to report first-degree family history of prostate cancer and to have undergone PSA testing prior to the reference date) Potential recall bias
Coogan 2010 [79]	Case control study of patients admitted to participating hospitals in New York, Philadelphia, and Baltimore from 1992 to 2008 Cases were 1,367 men with prostate cancer and controls were 2007 men with diagnoses unrelated to statin or NSAID use (people living within 50 miles of a participating hospital) Cases median age of 62 years and controls median age of 54 years	Prostate cancer	The OR among joint statin and NSAID users was 1.1 (95% CI: 0.7–1.6), with no difference by duration or cancer stage The OR among the 84% of joint statin/NSAID users who used a hydrophobic statin was 1.2 (95% CI: 0.8–1.8)	-
Murad 2011 [80]	Case-control study nested in cross-section phase of a multicenter, randomized controlled trial (The Prostate testing for cancer and Treatment – ProtecT study) including 1,016 cases and 5,043 controls Mean age of cases was 63.03 years and of controls was 62.81 years	Prostate cancer	No significant association on adjusted analysis of NSAIDs use and prostate cancer incidence (all NSAIDs: OR = 1.24; 95% CI: 1.06–1.46; non-aspirin NSAIDs: OR = 1.30; 95% CI: 1.02–1.65; aspirin: OR = 1.13; 95% CI: 0.94–1.35; acetaminophen: OR = 1.15; 95% CI: 0.86–1.53)	-
Fowke 2009 [81]	Cross-sectional study with 1,372 eligible consenting patients men scheduled for diagnostic prostate biopsy between 2002 and 2008 (The Nashville Men's Health Study, a multicenter rapid recruitment protocol) Of the NSAID user participants, 18.8% were less than 50 years old and 56.0% were 80 years old or greater (p < 0.01)	Prostate volume PSA Cancer grade at biopsy	Prostate volume: adjusted analysis showed that prostate volume was not significantly associated with NSAID use (47.6 mL vs. 46.0 mL, p = 0.17) PSA: adjusted analysis showed that PSA was not significantly associated with NSAID use (7.3 ng/mL vs. 7.8 ng/mL, p = 0.09) Cancer grade at biopsy: NSAID use was not significantly associated with cancer grade at biopsy (p = 0.84)	Cross-sectional design; the frequency and duration of use not included in the analysis; the frequency of selective COX-2 inhibitors or other non-aspirin NSAID use was insufficient to analyze thoroughly (low statistic power); potential detection bias (aspirin)

Abbreviations:
NSAID: non-steroidal anti-inflammatory drugs
RR: relative risk
OR: odds ratio
95% CI: 95% confidence interval
HR: hazard ratio
PSA: prostate-specific antigen

has most strongly and consistently been associated with reported intermittent sun exposure, mostly accrued through recreational

activities [98]. The reported incidences of BCC and SCC are imprecise because of the difficulties in collecting (and counting) such

tumors and the consequent variability of available data [95]. BCC is the most common cancer found in humans, and SCC is the second-most common [89, 100] Worldwide, an estimated 197,000 cases and 46,000 deaths in 2008 were related to malignant melanoma [95].

Considering non-melanoma skin cancers (NMSC), a narrative review concluded that there is mounting evidence that NSAIDs may be chemopreventive agents and suggests a clinical trial for high-risk patients [82]. We identified some primary evidence related to this issue (Table 10). A double-blind, placebo-controlled randomized trial (240 subjects at high risk) found that 200 mg of celecoxib administered orally twice daily for 9 months was not effective in preventing new actinic keratosis when compared with a placebo. These results suggests that celecoxib may prevent some NMSCs in patients who have extensive actinic damage [83]. However, this hypothesis has important limitations, as NMSC development was not a primary or secondary endpoint (it was only studied in the exploratory analyses) [83]. A current, good-quality cohort study ($n = 1,051$) [84] neither confirmed nor refuted the hypothesis that NSAIDs are protective against NMSC. A significant protective effect was associated with sporadic NSAID use but not with continuous use (time-varying analysis). This study may have misclassified exposure levels, as over-the-counter use was not evaluated [84]. A cohort study ($n = 1,402$) [85] also reported conflicting results: new users experienced some protective effect against BCC (HR = 0.33; 95% CI: 0.13–0.80) but continuous users did not (HR = 1.26; 95% CI: 0.61–2.59). Among this study's limitations are concerns about the possible recall bias and problems with the self-reporting of NSAID use (this validation study demonstrated probable misclassification) [85]. A recent population-based case-control study ($n = 1,484$) found no association between NSAID use and BCC (OR = 0.91; 95% CI: 0.69–1.21) or SCC (OR = 0.78; 95% CI: 0.59–1.03) [86]. Nevertheless, when stratifying cases according to the presence of molecular alteration (involving suppressor genes in the pathogenesis of NMSC), the use of NSAIDs, including aspirin, was associated with a lower risk of developing tumors with altered p53 (OR = 0.32; 95% CI: 0.14–0.73).

More specifically, for BCC, a recent larger cohort study ($n = 58,213$) established that none of the evaluated NSAIDs (aspirin, non-aspirin or acetaminophen) was associated with a reduced risk of BCC; no association was observed when stratified by NSAID type (aspirin and other NSAIDs), nor did dose-response patterns emerge in relation to frequency of use [87]. Despite being a questionnaire-based study, the study's large sample size and its consequent statistical power strengthened these results (based on the United States Radiological Technologists cohort). A case-control study (322 BCC cases and the same number of controls) found that NSAID use was associated with a slightly (non-significantly) reduced risk of BCC (with an incidence rate ratio [IRR] = 0.85; 95% CI: 0.66–1.10) [88]. This study also employed a molecular approach, reporting that two polymorphisms in COX-2 were associated with the risk of BCC: carriers of the A-1195G variant allele of COX-2 had a lower BCC risk than homozygous wild-type carriers (IRR = 0.54; 95% CI: 0.47–0.89), and homozygous carriers of the T8473C variant allele had a higher BCC risk (IRR = 2.27; 95% CI: 1.31–3.92). For SCC, a narrative review suggested that additional studies are needed to explore the efficacy of celecoxib and other NSAIDs for the prevention of SCC and to determine whether the beneficial effects on SCC risk would outweigh the risks of long-term NSAID therapy [89].

For malignant melanoma, we found two narrative reviews [90, 91] and one case-control study that had not been previously considered [92]. One narrative review reflected the conflicting evidence between observational studies [90], and the other [91] revealed that NSAIDs should demonstrate sufficiently convincing evidence before they are explicitly recommended for the chemoprevention of melanoma. A recent case-control study (327 cases of incident

melanoma and 119 controls) found that non-aspirin NSAIDs were not associated with a reliable reduction in melanoma risk (adjusted OR = 0.71; 95% CI: 0.23–2.02) [92].

Head and Neck Cancer

Head and neck cancer (HNC) describes a range of tumors involving the oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses and the thyroid and salivary glands [101]. HNC is the fifth-most common cancer worldwide; more than 845,000 individuals were diagnosed with HNC in 2008 [95]. The incidence rate in males exceeds 20 per 100,000 in regions of France, Hong Kong, the Indian subcontinent, central and Eastern Europe, Spain, Italy and Brazil and among African-Americans in the United States. It has been estimated that tobacco and alcohol use accounts for up to 80 percent of cases. Other risk factors include viral infection (particularly Epstein-Barr virus [EBV] and human papillomavirus [HPV]), occupational exposure, radiation, dietary factors, and genetic susceptibility [101].

A recent systematic review, which included only two population-based prescribing database studies and three case-control studies, found that no definitive conclusion could be reached on the use of NSAIDs (including aspirin) and HNC risk [93] (Table 11). Although no study quality analysis was performed, the reviewers found some evidence to suggest associations between non-aspirin NSAID use and an increased risk of HNC (oral cavity cancer [RR = 1.2; 95% CI: 1.0–1.6] and between NSAID use and increased risks of oral and oropharyngeal squamous cell carcinoma [OR = 3.5; 95% CI: 1.8–6.7]). They also observed a significantly higher risk of HNC with increasing numbers of NSAID prescriptions dispensed (RR = 1.3; 95% CI: 1.0–1.6). A significant reduction in HNC risk was observed with increased duration of NSAID use (> 5 years; OR = 0.21; 95% CI 0.05–0.85), compared with non-users. Studies investigating NSAIDs and the associated risk of HNC were limited by potential bias in the study group selection, recall bias, lack of information on the use of medicines without prescription and confounding by indication or a lack of vital information.

CONCLUSIONS

Overall, the effectiveness of chemoprevention of non-gastrointestinal cancer with non-aspirin NSAIDs is not supported by the available evidence. Conflicting or inconclusive evidence was found for lung, ovarian, endometrial, head and neck, bladder, and skin cancers. Renal cell carcinoma showed an increased risk of cancer incidence, while breast cancer had a reduced cancer incidence. In summary, the hypothesis of comparable biological actions among aspirin and non-aspirin NSAIDs was not supported by observations in clinical research. There are well-known risks associated with the use of non-aspirin NSAIDs (e.g., cardiovascular and gastrointestinal damage) and potentially unknown long-term risks.

Limitations of the studies reviewed herein indicate a need for further, well-designed, controlled research to elucidate these issues. New studies could increase confidence in the outcomes or even modify the estimates. However, uncertainty remains regarding the well-being of the study subjects, as there are important concerns about the potential risks of long-term exposure to NSAIDs.

AUTHORSHIP CONTRIBUTIONS

Marcus Tolentino Silva conceived the study design and performed study selection, data extraction and analysis and contributed to writing of the manuscript.

Tais Freire Galvao conceived the study design and confirmed the data extraction and analysis and contributed to writing of the manuscript.

Ivan Ricardo Zimmerman conceived the manuscript design and performed the study selection, confirmed the data extraction, conducted the analysis and contributed to writing of the manuscript.

Table 10. Evidences About Non-aspirin NSAIDs and Prevention of Skin Cancer Incidence

Study	Design and Population	Outcomes	Results	Limitations
Elmets 2010 [83]	<p>Double-blind placebo-controlled randomized trial involving 240 subjects aged 37-87 years, at eight study sites in the United States (academic medical centers)</p> <p>Subjects were evaluated at 3, 6, 9 and 11 months after randomization</p> <p>Celecoxib 200 mg orally twice daily as a chemopreventive agent for actinic keratoses</p>	<p>New actinic keratoses</p> <p>Exploratory analyses:</p> <p>Nonmelanoma skin cancers (combined)</p> <p>Squamous cell carcinoma (11 months)</p> <p>Basal cell carcinoma (11 months)</p> <p>Adverse events</p>	<p>There was no difference in the incidence of actinic keratoses between the two groups at 9 months</p> <p>At 11 months there were fewer non-melanoma skin cancers in the celecoxib arm than in the placebo arm (RR = 0.43; 95% CI: 0.24–0.75)</p> <p>After adjusting, the non-melanoma skin cancers RR = 0.41 (95% CI: 0.23–0.72) the numbers of basal cell carcinomas (RR = 0.40; 95% CI: 0.18–0.93) and squamous cell carcinomas (RR = 0.42, 95% CI: 0.19–0.93)</p> <p>Severe and cardiovascular adverse events were similar in the two groups (p = 0.95)</p>	<p>The development of nonmelanoma skin cancers was not a primary or secondary endpoint; all participants had extensive actinic damage (particular external validity); potential conflict of interest (with the manufacturer of celecoxib)</p>
Nunes 2011 [84]	<p>Prospective cohort study by linking data from the Veterans Affairs Topical Tretinoin Chemoprevention Trial and the VA Pharmacy Benefits Management database (n = 1,051)</p> <p>Median follow-up time of 2 years for basal cell carcinoma and 2.5 years for squamous cell carcinoma, with 472 occurrences of BCC and 309 occurrences of SCC</p>	<p>Basal cell carcinoma (face and ears)</p> <p>Squamous cell carcinoma (face and ears)</p>	<p>Basal cell carcinoma (face and ears): Non selective NSAIDs users had a 34% lower hazard (HR = 0.66; 95% CI: 0.54–0.80), and COX-2 selective NSAID users had a 43% lower hazard (HR = 0.57; 95% CI: 0.41–0.79)</p> <p>Squamous cell carcinoma (face and ears): Non selective NSAIDs users had an 18% lower hazard (HR = 0.82; 95% CI: 0.64–1.04), and COX-2 selective NSAID users had a 46% lower hazard (HR = 0.54; 95% CI: 0.36–0.81)</p> <p>Significant protective effect associated with incidental/sporadic NSAID use but not with continuous NSAID use. The initiation of NSAID use was more protective than the baseline use and the continuous use (time-varying analysis)</p>	<p>Potential misclassification of the exposure (over-the-counter use not evaluated); potential conflict of interest (Pfizer and OMJ funding)</p>
Clouser 2009 [85]	<p>Prospective cohort study using data from a double-blind, randomized, placebo-controlled trial of non-melanoma skin cancer (NMSC), including 1,402 subjects, mean time on study of 60.7 months (SD = 11.5, range 31.0–91.9)</p>	<p>Basal cell carcinoma</p> <p>Squamous cell carcinoma</p>	<p>Statistically significant protective effect for BCC among those who reported any NSAID use was observed (HR = 0.58; 95% CI: 0.39–0.85)</p> <p>For continuous users, the relationship was less protective and not statistically significant (HR = 0.88; 95% CI: 0.52–1.50)</p> <p>Use of non-aspirin NSAIDs was associated with being protective for BCC only in the new users group (HR = 0.33, 95% CI: 0.13–0.80)</p> <p>Statistically significant protective effect for development of SCC was observed only for the new user NSAID group (HR = 0.49; 95% CI: 0.28–0.87).</p> <p>The continuous user group had no effect for SCC development (HR = 1.11; 95% CI: 0.65–1.92)</p>	<p>Possible recall bias and problems with the self-report of NSAID use (validation study demonstrated probable misclassification).</p>
Cahoon 2011 [87]	<p>Prospective cohort study with caucasian participants (n = 58,213) from the United States Radiologic Technologists cohort</p> <p>Mean age at entry into the study was 47.5 (SD = 8.3) years. Follow-up of 509,465 person-years at risk, where 2,291 incident BCCs were reported</p>	<p>Basal cell carcinoma</p>	<p>Any NSAID use was not associated with subsequent incidence of BCC (HR = 1.04; 95% CI: 0.92–1.16) after adjusting</p> <p>Neither association was observed when stratifying by NSAID type (aspirin and other NSAIDs), nor did dose-response patterns emerge by frequency of use (average days per month)</p> <p>Increased risk of BCC for any acetaminophen use was observed (adjusted HR = 1.14; 95% CI: 1.04–1.25)</p>	<p>Self-administered second survey questionnaire</p>

(Table 10) Contd....

Study	Design and Population	Outcomes	Results	Limitations
Torti 2011 [86]	Case-control study with 1,484 participants: 535 with squamous cell carcinoma (SCC), 487 with basal cell carcinoma (BCC), and 462 control subjects, New Hampshire residents aged 25 to 74 years	Basal cell carcinoma Squamous cell carcinoma	BCC: There was little to no association between use of NSAIDs and BCC overall (OR = 0.91; 95% CI: 0.69–1.21); a reduced OR was found with use of paracetamol, especially among current users (OR = 0.56; 95% CI: 0.33–0.97) and those who reported a longer duration of use (OR = 0.54; 95% CI: 0.29–1.03) SCC: Use of NSAIDs (OR = 0.78; 95% CI: 0.59–1.03), aspirin (OR = 0.75; 95% CI: 0.55–1.02), and paracetamol was associated with reduced risk of SCC (OR = 0.62; 95% CI: 0.40–0.97), especially among current users (OR = 0.56; 95% CI: 0.33–0.97) and users of 7 years or less (OR = 0.51; 95% CI: 0.27–0.97) Stratifying cases by presence of molecular alteration, use of NSAIDs was associated with a lower risk of developing tumors with altered p53 (OR = 0.32; 95% CI: 0.14–0.73)	Self-reported drug use; Potential selection bias
Vogel 2007 [88]	Case-control study including 322 BCC cases and 322 controls was nested in a population-based prospective study (the Danish prospective study “Diet, Cancer and Health”)	Basal cell carcinoma	NSAID use was associated with a slightly, non-significant reduced risk of BCC (IRR = 0.85; 95% CI = 0.66–1.10). The variant allele of COX-2 T8473 was associated with lower risk of BCC, all variant allele carriers (IRR = 0.65; 95% CI = 0.47–0.89)	Dose-response not evaluated; sun exposure not measured.
Jeter 2011 [92]	Multicenter case-control study (Genes, Environment, and Melanoma – GEM) with 509 participants at the University of Michigan Melanoma patients accounted for 327 subjects; the remaining 119 were melanoma-free spouses of the patients	Melanoma (first primary invasive or in situ)	The unadjusted OR for use of non-aspirin NSAIDs was 0.58 (95% CI: 0.31–1.11). After adjustment for melanoma risk factors, the OR was 0.71 (95% CI: 0.23–2.02) In an exploratory analysis, the crude OR for melanoma in users of COX-2 specific inhibitors was 0.61 (95% CI: 0.28–1.31), and the adjusted OR was 0.42 (95% CI: 0.14–1.27) Aspirin users had an unadjusted OR of 0.85 (95% CI: 0.45–1.69) and an adjusted OR of 1.45 (95% CI: 0.44–4.74)	Reports of medication use not validate; sun exposure not assessed; potential selection bias in the control group (not all spouses participated); potential overmatching of spouse controls (OR may be attenuated).

Abbreviations:
 HR: hazard ratio
 95% CI: 95% confidence interval
 NSAID: non-steroidal anti-inflammatory drugs
 OR: odds ratio
 RR: relative risk
 BCC: basal-cell carcinoma
 SCC: squamous-cell carcinoma
 IRR: incidence rate ratio

Table 11. Evidences About Non-aspirin NSAIDs and Prevention of Head and Neck Cancer Incidence

Study	Design and Population	Outcomes	Results	Limitation
Wilson 2011 [93]	Systematic review with 9,268 articles identified, where 5 papers met all criteria and were included (2 population-based prescribing database studies and 3 case-control studies). Aside from a North American study, all were European based with an average	Head and neck cancer	Prescribing database studies: There was not find a protective association with NSAID usage, for low-dose aspirin (SIR = 1.2; 95% CI: 0.8–1.7 for the buccal cavity and pharynx and 1.4; 95% CI: 0.8–2.3 for larynx). Neither for non-aspirin NSAID use and oral cavity cancer risk (SRR = 1.2; 95% CI: 1.0–1.6) Case-control studies: No significant association between aspirin use and head and neck cancer, OR = 0.86 (95% CI: 0.46–1.61). No protective association with low-dose aspirin use, OR = 1.0 (95% CI: 0.6–1.7). One study reported a significant protective association of aspirin on overall head and neck cancer risk (adjusted OR = 0.75; 95% CI: 0.58–0.96). In subsite specific analyses, although all adjusted-ORs below 1.0, none significant A protective association of aspirin use in moderate smokers and drinkers only, adjusted OR = 0.67 (95% CI: 0.50–0.91). Unadjusted results similar to the adjusted models Significant increased risk of oral and oropharyngeal squamous cell carcinoma associated with NSAID use (OR = 3.5; 95% CI: 1.8–6.7). Significant increased risk of head and neck cancer with increased number of NSAID prescriptions dispensed (SRR = 1.3; 95% CI: 1.0–1.6)	Potential risk of recall bias (questionnaires and interview in case-control); no meta-analysis conducted (small numbers and heterogeneity of the studies); information on over-the-counter use or prescription adherence not collected

Abbreviations:
 SIR: standardized incidence ratio
 95% CI: 95% confidence interval
 NSAID: non-steroidal anti-inflammatory drugs
 OR: odds ratio
 SSR: standardized rate ratios

Mauricio Gomes Pereira conceived the study design, made important contributions to critical aspects of the research and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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