Use of Nonsteroidal Anti-Inflammatory Agents and Risk of Melanoma and Non-Melanoma Skin Cancer

by

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Abstract

Skin cancer (melanoma and non-melanoma skin cancer) is one of the common types of cancer in most of the countries. Several studies have assessed the chemoprevention effect of NSAIDs in melanoma and non-melanoma skin cancer. A few studies support the chemopreventive effect of NSAIDs on skin cancer and some do not. There is conflicting evidence regarding NSAID use and risk of skin cancer risk. In view of these inconsistent results, a detailed meta-analysis to explore the role of NSAIDs in melanoma and non-melanoma skin cancer prevention was undertaken.

The present study assessed the role of NSAIDs (both aspirin and non-aspirin NSAIDs) as chemopreventive agents for melanoma and non-melanoma skin cancer. Meta-analysis of 15 studies showed that NSAIDs might have a chemopreventive effect in prevention of melanoma skin cancer. A secondary analysis showed only that aspirin possesses the chemopreventive effect. A similar trend was observed for NSAIDs use and risk of non-melanoma (BCC and SCC) skin cancers by pooling the results of 14 studies.

Usage of NSAIDs (especially aspirin) might reduce the risk of melanoma and non-melanoma skin cancer. However, there is insufficient understanding of effective time periods and dosing of NSAIDs as chemopreventive agents. Pharmacogenetic investigations may also help to establish the individual NSAIDs risk–benefit ratio for specific subtypes of skin cancer and therefore allow tailoring of chemoprevention. Future research is recommended towards finding the subcellular targets of NSAIDs' action in skin cancer subtypes before venturing into large clinical studies.

Keywords: Aspirin, basal cell carcinoma, melanoma, nonsteroidal anti-inflammatory agents, squamous cell carcinoma.

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Chapter 1: Background

The burden of cancer is increasing across the globe. Skin cancer is one of the most common types of cancer in most countries. There has been a recent rise in the incidence of skin cancer in the US (American Cancer Society, 2018). Melanoma contributes to 5.2% of all new incident cancer cases each year in the US (National Cancer Institute – Surveillance).

Skin cancer could be of many types. However, two major classes of skin cancer are important because of their prevalence, impact on patients' finances, and burden on quality of life: melanoma skin cancer and non-melanoma skin cancer.

Melanoma contributes to only ~1% of total skin cancers. However, melanoma causes majority of deaths in skin cancer patients. Melanoma is the fifth and sixth leading cause of new cancer cases in men and women, respectively (American Cancer Society, 2018). The prevalence of melanoma has been rising for the last three decades. The American Cancer Society forecasted that in the US for 2018, at least 91,000 new melanoma cases will be diagnosed, and at least 9000 melanoma-related deaths are expected. The risk of melanoma varies based on ethnicity of patients. Melanoma is about 20 times more prevalent in Caucasians (2.6%) than in African Americans (0.1%; National Cancer Institute – Surveillance, 2018). Several factors that increase the risk of melanoma have been identified, including exposure to ultraviolet light, presence of a nevus, lighter skin (skin with lower melanin pigmentation), presence of freckles, personal and family history of skin cancer, immunocompromised state, age, gender, and Xerodermapigmentosum (an inherited condition characterized by an extreme sensitivity to ultraviolet [UV] rays from sunlight). Survival at five years in patients with malignant melanoma is found to be 91.7% (National Cancer Institute – Surveillance, 2018). There is a significant improvement in 5-year survival

probability in the past two decades, mainly attributed to early diagnosis, use of some chemopreventive drugs, and advances in chemotherapy.

Non-melanoma skin cancer is also a commonly diagnosed skin cancer in the US. However, assessment of actual prevalence and incidence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) is difficult in most countries, as there is no mandate to report/register these non-melanoma skin cancers in cancer registries. This makes it difficult to understand the true burden of non-melanoma skin cancer. BCC is more common than SCC and alone contributes to 80% of non-melanoma skin cancer (Cancer.Net, 2018). It was found that more than 4 million and 1 million BCC and SCC cases are diagnosed in the US each year, and approximately 2000 patients die every year from these cancers (Cancer.Net, 2018). Most of BCC and SCC cases can be treated if they are detected early. The five-year survival rate of patients with cancer in the localized stage (99%) is very high compared to the regional stage (63%) and distant-stage disease (20%; American Cancer Society).

In the past two decades, much research has been done on chemoprevention, as there is an increased burden of cancer, low success (cure) rate with chemotherapy, and deteriorated quality of life in cancer patients. According to Chhabra, Ndiaye, Garcia-Peterson, and Ahmad (2017), several potential chemoprevention agents were explored, including

- Sunscreens (organic and inorganic UV filters)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Statins
- Dietary agents (Resveratrol, Curcumin, Epigallocatechin-3-gallate (EGCG), Fisetin)
- Vitamins A, C, D, E and K

However, none of these reported agents has positive confirmative results in clinical trials. Few epidemiological studies showed the chemoprevention effect of NSAIDs on various cancers. NSAIDs were explored as chemoprevention agents for gastric, esophageal, and adenocarcinomas (Huang et al., 2017), and the following cancers: prostate (Vidal et al., 2015), breast (Yiannakopoulou, 2015), colorectal (Chan et al., 2005), lung (McCormack et al., 2011), bladder (Daugherty et al., 2011), and ovarian (Baandrup et al., 2013).

Several studies have assessed the chemoprevention effect of NSAIDs in melanoma and non-melanoma skin cancer. Evidence of observational studies from the past two decades has shown that the NSAIDs have the potential to act as chemoprevention therapy due to the alteration of cellular mechanisms that could delay or prevent the occurrence or recurrence of several types of cancers. There is a special focus on two potential classes of oral drugs, including NSAIDs and statins as chemoprevention agents. As NSAIDs are the most widely used drugs (and they are available even as over-the-counter therapies in many countries), they remain a preferred chemoprevention drug to explore.

Few observational studies support the hypothesis of a chemoprevention effect of NSAIDs in the prevention of melanoma and non-melanoma skin cancer; however, few observational studies do not support it. There is conflicting evidence regarding NSAID use and risk of melanoma and non-melanoma skin cancer. There are multiple attempts made by several researchers to perform meta-analysis to assess the role of NSAIDs in prevention of melanoma and non-melanoma skin cancer Table 1 (Muranushi, Olsen, Green, & Pandeya, 2016; Muranushi, Olsen, Pandeya, & Green, 2015; Zhu, Chen, Luo, & Li, 2015; Hu, Xie, Yang, Jian, & Deng, 2014; Zhang, Liang, Ye, & Wang, 2014; Li, et al., 2013). There is a conflicting evidence exist in these meta-analyses. Zhang et al., 2014 and Hu et al., 2014

concluded that NSAIDs does not have any protective role in skin (melanoma and non-melanoma) cancer (Zhang et al., 2014; Hu et al., 2014). Whereas, Muranushi et al., 2015 and Zhu et al., 2015 concluded that NSAIDs have protective role in prevention of skin cancer (Muranushi et al., 2015; Zhu et al., 2015).

Table 1

Summary of Previous Meta-Analysis Conducted by Various Researchers

First author (Year)	Drug/drug class	Indication	Searched till	Studies included (CC/COH/RCT)	Notes
Muranushi C (2016) (Muranushi et al., 2016)	NSAIDs	BCC	December 2014	11 (5/5/1)	Support the role of NSAIDs in prevention of BCC
Muranushi C (2015) (Muranushi et al., 2015)	NSAIDs	SCC	February 2014	9 (5/3/1)	Support the role of NSAIDs in prevention of SCC
Zhu Y (2015) (Zhu et al., 2015)	Aspirin	Skin cancer (melanoma and non-melanoma skin cancer)	March 2013	11 (8/5/0)	Supported the role of aspirin in prevention of melanoma and non-melanoma skin cancer
Zhang B (2014) (Zhang et al., 2014)	NSAIDs	Non-melanoma skin cancer	September 2012	8 (4/3/1)	Does not support the role of NSAIDs in prevention of non-melanoma skin cancer
Hu H (2014) (Hu et al., 2014)	NSAIDs	Melanoma skin cancer	July 2012	10 (5/4/1)	Does not support the role of NSAIDs in prevention of melanoma skin cancer
Li S (2013) (Li et al., 2013)	NSAIDs	Melanoma skin cancer	March 2013	13 (6/6/1)	Does not support the role of NSAIDs in prevention of melanoma skin cancer

There are limitations exist in these meta-analyses as follows:

a. These meta-analyses are not up to date as they have included studies until 2014. There are several studies got published on the topic of interest between the time-period of 2014 to 2018.

b. These meta-analyses assessed either melanoma or non-melanoma skin cancer without giving complete information on skin cancer except Zhu et al. 2015
c. These meta-analyses included lesser number of primary studies than the present study. Therefore, lesser number of primary studies means less number of patients and lesser power to assess effect estimate. Present study includes higher number of studies. Therefore, have higher number of patients and power.

In view of these inconsistent results in primary studies and limitations in the previous meta-analysis, a detailed meta-analysis to explore the role of NSAIDs in melanoma and non-melanoma skin cancer prevention was studied.

Chapter 2: Aim and Objectives

Aim

To assess the chemoprevention effect of NSAIDs in prevention of skin cancer.

Objectives

1. To assess the risk of melanoma skin cancer in NSAIDs users
    a. To assess the risk of melanoma skin cancer in aspirin users
    b. To assess the risk of melanoma skin cancer in non-aspirin NSAIDs users
2. To assess the risk of non-melanoma skin cancer including BCC and SCC in NSAIDs users
    a. To assess the risk of non-melanoma skin cancer in aspirin users
    b. To assess the risk of non-melanoma skin cancer in non-aspirin NSAIDs users

Chapter 3: Methods

Literature Search

A separate literature search was carried out for melanoma and non-melanoma skin cancer. A systematic search strategy was used to identify all published studies reporting an association between NSAIDs use and risk of skin cancer. Electronic databases, including Medline (via Ovid), EMBASE (via Embase.com), and Cochrane library, were searched to identify relevant studies. Search terms and keywords were altered as per specification of individual databases. The search strategies in detail are presented in Appendix A: Supplementary Tables for melanoma and non-melanoma skin cancer. The reference lists of studies that examine the topic of interest were checked for additional publications.

Study Selection

Search results from the three databases were exported into EndNote X8.0.1 software to identify and remove potential duplicate studies that appeared in more than one database. After removing duplicate studies, all unique studies were exported into an Excel spreadsheet for initial screening, which involves a screening of the titles and/or abstracts of unique studies in Excel to exclude any clearly irrelevant studies. Initial screening resulted in identifying relevant studies. For secondary screening, the full texts were read and included or excluded based on selection criteria.

Inclusion and Exclusion Criteria

Studies were included if they (a) were observational studies (case-control or cohort studies) or clinical trials; (b) analyzed NSAIDs usage as the main variable of interest or as a covariate; or (c) analyzed melanoma skin cancer or non-melanoma skin cancer incidence as the dependent variable. Studies were excluded if they (a) included subjects with melanoma at

baseline; (b) assessed the progression of melanoma skin cancer or non-melanoma skin cancer without the data of the incidence; (c) were conference abstracts (as published conference abstracts do not provide all necessary information); (d) were duplicate publications from the same population of included study; or (e) did not provide enough raw data or data regarding assessment of the risk factor or outcome.

Data Extraction

All full-text articles were reviewed to extract the following information: (a) first author's name, country, and year of publication, (b) study design, (c) study population characteristics, (d) number of participants, (e) effect estimates and 95% confidence interval (CI), (f) results of the studies, and (g) number of confounding factors adjusted.

Quality Assessment

Randomized controlled clinical trials are assumed to be of higher quality than observational studies. Quality assessment of each observational study was performed using the Newcastle-Ottawa Scale (NOS). This scale consists of three parameters of quality, and a score of 0–10 is given.

For case-control studies, quality depends upon three parameters: selection, comparability, and exposure. For cohort studies, quality depends upon three parameters: selection, comparability, and outcome.

A study receiving nine points is regarded as a high-quality study; if it gets seven to eight points, it is considered a medium quality study; and if the score is ≤6, it is considered a low-quality study. To remove the effect of low quality studies on the final effect estimate, we performed subgroup analysis according to the quality of included studies.

Data Synthesis and Analysis

A separate analysis was conducted for melanoma and non-melanoma skin cancer. Meta-analysis (pooling) of studies was performed using two following methods (Borenstein, Hedges, Higgins, & Rothstein, 2010):

1. Fixed effects model (Mantel-Haenszel method) and;
2. Random effects model (Der Simonian-Laird method)

In fixed effects model, it was assumed that there is one true effect size that underlies all the studies in pooled analysis, and that all differences in observed effects are due to sampling error (Borenstein, et al., 2010). In other way, in random effects model, it was assumed that the included studies represent a random sample from a numerous studies. Random effects model allows both intra and inter-study variability. Therefore, it gives a conservative result with wider confidence intervals and less statistical significance than fixed effects model (Borenstein, et al., 2010).

The decision to choose the pooling method among fixed and random effects model depend up on the heterogeneity among the included studies. Heterogeneity was assessed using Cochrane Q test, and I^2 statistic (Higgins, Thompson, Deeks, & Altman, 2003). A Q statistic with a p value of <0.01 and an I^2 value $>50\%$ was considered a measure of heterogeneity (Higgins, et al., 2003). In absence of significant heterogeneity, a fixed-effects model was used; otherwise, a random effects model was used.

Relative risk was considered the effect estimate for pooling. The combination of relative risk and odds ratios are allowed, as the risk of dementia is low and the relative risk in prospective cohort studies will mathematically approximate the odds ratio.

Results of pooled analysis was represented in forest plot which helps to summarize the individual and pooled effect estimates. Forest plot is a graphical depiction of individual and pooled study effect estimates with their corresponding confidence intervals. In a forest plot, the effect estimate of the individual study is depicted as a square, and a horizontal line represents its corresponding confidence interval; the size of the square represents the weight of the individual study used for pooling. Pooled effect estimate, at the bottom of the forest plot, is represented as a diamond, and the horizontal lines represent confidence intervals (Impellizzeri & Bizzini, 2012). A forest plot helps in the quick summarization of trends of effect estimates across the studies and indicating summary effect estimates.

Subgroup analysis was performed to assess the sources of heterogeneity. Subgroup analyses were performed according to (a) study design, (b) quality of studies, (c) study location, and (d) exposure (NSAID usage) assessment method. Sensitivity analysis was performed to assess the influence of a single study on the pooled effect estimate.

The publication bias was assessed using following methods (Begg, & Mazumdar, 1994):

1. Funnel plot and
2. Begg and Mazumdar adjusted rank correlation test

The funnel plot helps to investigate the publication bias. It is a scatterplot having effect estimates of individual studies plotted against precision (standard error) of the corresponding study, and it looks like an inverted funnel. A symmetrical funnel represents no or insignificant publication bias and an asymmetrical funnel represent a significant publication bias (Impellizzeri & Bizzini, 2012).

The Begg and Mazumdar rank correlation test was used to assess publication bias in meta-analysis. It uses the correlation between the ranks of effect sizes and the ranks of their variances (Begg, et al., 1994). If the P value generated from the correlation test was <0.05 was considered as significant publication bias and vice versa.

One-way sensitivity analysis was performed to assess the influence of individual studies on the summary effect estimate (Ressing, Blettner, & Klug, 2009). In this analysis, an influence analysis was performed by computing the meta-analysis estimates by omitting one study at a time. Pooled effect estimate was considered stable if it does not differ significantly by excluding any of the included studies. If the pooled estimate is significantly influenced by removing any of the included studies, it represents that the pooled analysis was influenced by that study and further detailed investigation was performed to understand the cause.

STATA 12.0 software was used to perform statistical analyses (Chaimani, Mavridis, & Salanti, 2014). STATA is a command line based multiple purpose statistical software package in which multiple customized publicly available statistical packages are available to perform simple to complex statistical analysis including meta-analysis. Data inputs and STATA commands used to perform statistical analysis are given in detail in Appendix B. STATA statistical packages used for analysis are listed in the Table 2 below:

Table 2

List of STATA Statistical Packages Used for Analysis

Statistical package	**Purpose**
Metan	• To perform main analysis and subgroup analysis
Metabias	• To assess publication bias (Begg and Mazumdar adjusted rank correlation test)
Metafunnel	• To draw funnel plot to assess publication bias
Metainf	• To perform one-way sensitivity analysis

Chapter 4: Results

Search Results

A summary of the initial database search results is shown in Table 3. A detailed search result of final included studies for meta-analysis is shown in Figure 1 for melanoma and Figure 2 for non-melanoma skin cancer.

Table 3

Summary of Search Results for Melanoma and Non-Melanoma Skin Cancer

Database	**Melanoma skin cancer**	**Non-melanoma skin cancer**
Medline (via Ovid)	536	751
EMBASE	4,696	1,287
Cochrane library	86	89
Total citations screened	5,318	2,127

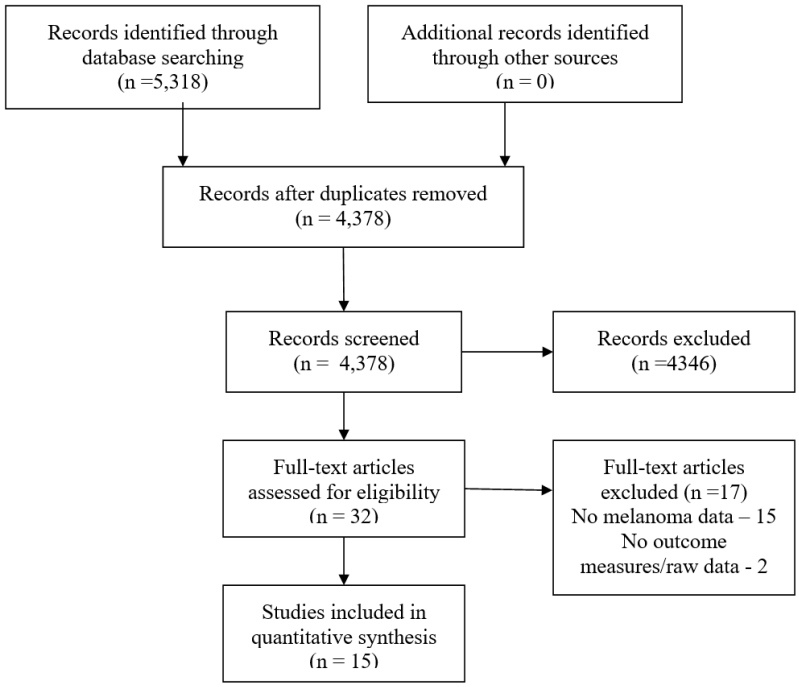

Figure 1. PRISMA flow chart representing detailed selection process for non-steroidal anti-inflammatory drugs use and risk of melanoma skin cancer.

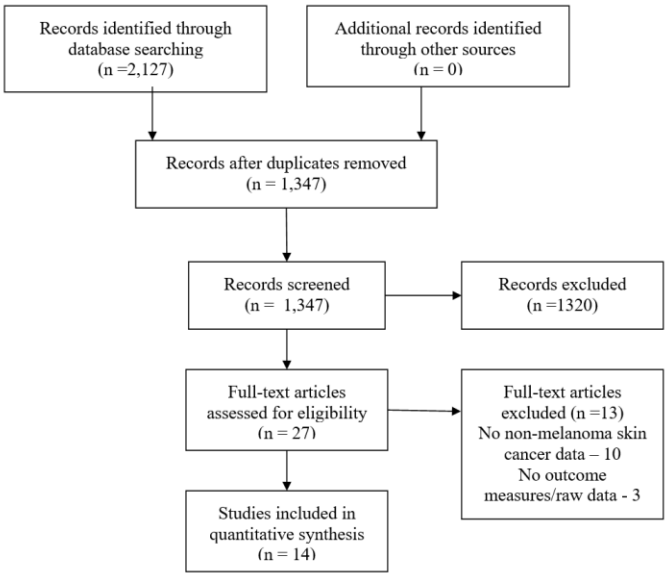

Figure 2. PRISMA flow chart representing detailed selection process for non-steroidal anti-inflammatory drugs use and risk of non-melanoma skin cancer.

Results for Melanoma Skin Cancer

Study characteristics - melanoma skin cancer. A total of 15 articles are selected for the meta-analysis, corresponding to one RCT, nine cohort and five case-control studies (Cook et al., 2005; Schreinemachers, & Everson, 1994; Sorensen et al. 2003; Friis, Sorensen, McLaughlin, Johnsen, Blot, & Olsen, 2003; Jacobs, Thun, Bain, Rodriguez, Henley, & Calle, 2007; Asgari, Maruti, & White, 2008; Jeter, Bonner, Johnson, & Gruber, 2011; Gamba et al., 2013; Shebl et al., 2014; Brasky et al., 2014; Harris, Beebe-Donk, & Namboodiri, 2001; Joosse et al., 2009; Curiel-Lewandrowski et al., 2011; Jeter, 2012; Johannesdottir et al., 2012). All fifteen studies are available in full text. Study characteristics are listed in Tables 4 and 5.

Table 4

Characteristics of Case-control Studies Assessing the Risk of Melanoma Skin Cancer in NSAIDs Users

Author, Published year (Country)	Source of study population	Recruitment period	Assessment of NSAID use/melanoma	Cases (NSAID users)/Controls (NSAID users)	Quality rating
Harris RA, et al., 2001 (USA; Harris et al., 2001)	Population based	NR	A/A	110 (NR)/609 (NR)	Low
Joosse A, et al., 2009 (UK; Joosse et al.,2009)	Population based	1991-2004	B/B	1,318 (799)/ 6,786 (3,857)	Medium
Curiel-Lewandrowski C, et al., 2011 (USA; Curiel-Lewandrowski et al.,2011)	Population based	2004-2007	A/A	400 (262)/ 600 (433)	Medium
Jeter JM, et al., 2011 (USA; Jeter et al., 2011)	Population based	2000-2003	C/C	327 (60)/ 119 (30)	Low
Johannesdottir SA, et al., 2012 (UK; Johannesdottir et al.,2012)	Population based	1991-2008	B/B	3,089 (932)/ 30,883 (9,898)	Medium

NR - Not reported.

A - Medical records; B - Database/registry; C - Interview/Self-reported

Table 5

Characteristics of Cohort Studies and Randomized Controlled Clinical Trial Assessing the Risk of Melanoma Skin Cancer in NSAIDs Users

Author, Published year (Country)	Name of the cohort	Cohort size	Follow-up period (Start-End year)	Assessment of NSAIDs use/melanoma	NSAID users (melanoma cases)/non-users (melanoma cases)	Quality rating
Schreinemachers DM, et al., 1994 (USA; Schreinemachers et al.,1994)	National Health and Nutrition Examination Survey I and NHANES I Epidemiologic Follow-up studies (NHEFS)	12,668	NR	C/A, C	7438 (38)/ 5230 (31)	Low
Sørensen HT, et al., 2003 (UK; Sorensen et al.,2003)	Not reported	172,057	9.1 (1989-1995)	B/B	172,057 (167)/ Expected value calculated from general population	Medium
Friss S, et al., 2003 (UK; Friis et al., 2003)	Not reported	29,470	9.1 (1989-1995)	B/B	29,470 (52)/ Expected value calculated from general population	Medium
Jacobs EJ, et al., 2007 (USA; Jacobs et al.,2007)	Cancer Prevention Study II Nutrition Cohort	146,113	10 (1992-1993)	C/A, B, C	112515 (NR)/ 33,598 (NR)	Medium
Asgari MM, et al., 2008 (USA; Asgari et al.,2008)	Vitamins and Lifestyle (VITAL) cohort study	63,809	5 (2000-2005)	C/B	40,506 (226)/ 23,303 (123)	Medium
Jeter JM, et al., 2012 (USA; Jeter et al., 2012)	Nurses' Health Study	76,181	18 (1990-2008)	C/A, B, C	NR (NR)	Medium
Gamba CA, et al., 2013 (USA; Gamba et al.,2013)	Women's Health Initiative (WHI) Observational Study (OS)	59,806	12 (NR)	C/C	24,277 (204)/ 35,529 (344)	High
Shebl FM, et al., 2014 (USA; Shebl et al.,2014)	NIH-AARP Diet and Health Study	314,522	10 (1996-2006)	C/B	NR (NR)	Medium
Brasky TM, et al., 2014 (USA; Brasky et al., 2014)	Women's Health Initiative	129,013	9.7 (1993-NR)	C/C	92,405 (390)/ 61,641 (248)	Medium
Cook NR, et al., 2005 (USA)*(Cook et al., 2005)	Women's Health Study	39,876	12 (1992-2004)	C/A, C	19,934 (68)/ 19,942 (70)	High

NR - Not reported. A - Medical records; B -Database/registry; C - Interview/Self-reported

* Randomized Controlled Clinical Trial

Characteristics of RCT – melanoma skin cancer. One RCT of US women, published in 2005, included 39,876 participants, of whom 19,934 were assigned to NSAIDs arm and 19,942 to control arm. They were followed for an average of 10.1 years, with 68 and 70 melanoma cases observed in the two arms, respectively (Cook et al., 2005).

Characteristics of cohort studies - melanoma skin cancer. Nine cohort studies were published from 1994 to 2014, involving more than 100,000 participants, more than 10,000 of whom were melanoma cases. The participants were followed for 5–18 years. Seven were conducted in the US and two in the United Kingdom (UK).

Characteristics of case-control studies - melanoma skin cancer. From 2001 to 2014, five case-control studies were published, involving more than 40,000 participants, of whom more than 10,000 were melanoma cases and 38,000 were controls. More than 16,000 NSAIDs users were present in five case-control studies. Three studies originated from the US population and two from the UK.

Quality assessment - melanoma skin cancer. When quality of included studies was assessed, there were two high, 10 medium, and three low quality studies present. RCT was considered a high-quality study based on the Jadad scale to assess quality of clinical trials. For cohort studies, there were one high, seven medium, and one low quality studies present. With regard to case-control studies, there were three medium and two low quality studies present.

NSAIDs and risk of melanoma skin cancer. When the p value of the Begg's ($p = 0.767$) and Egger's ($p = 0.589$) tests were analyzed, publication bias was not indicated, and

the funnel plot did not show any evidence of asymmetry (Figure 3). Random effects model was selected, as significant heterogeneity ($p_{heterogeneity}<0.05$, $I^2 = 59\%$) exists in included studies. Combined analysis of fourteen studies indicated that NSAIDs use was associated with a significant decrease in the risk of melanoma (RR 0.92, 95% CI 0.85-0.99, p <0.05). A forest plot depicting pooled and individual study effect estimates is shown in Figure 4.

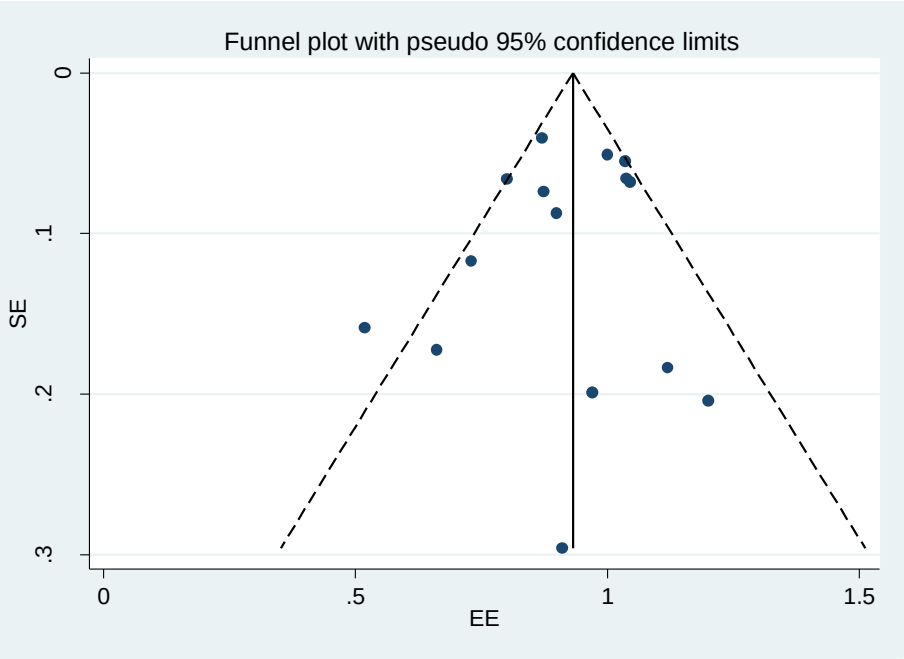

Figure 3. Funnel plot representing symmetry and no publication bias for use of NSAIDs and risk of melanoma.
EE - effect estimate; SE - standard error.

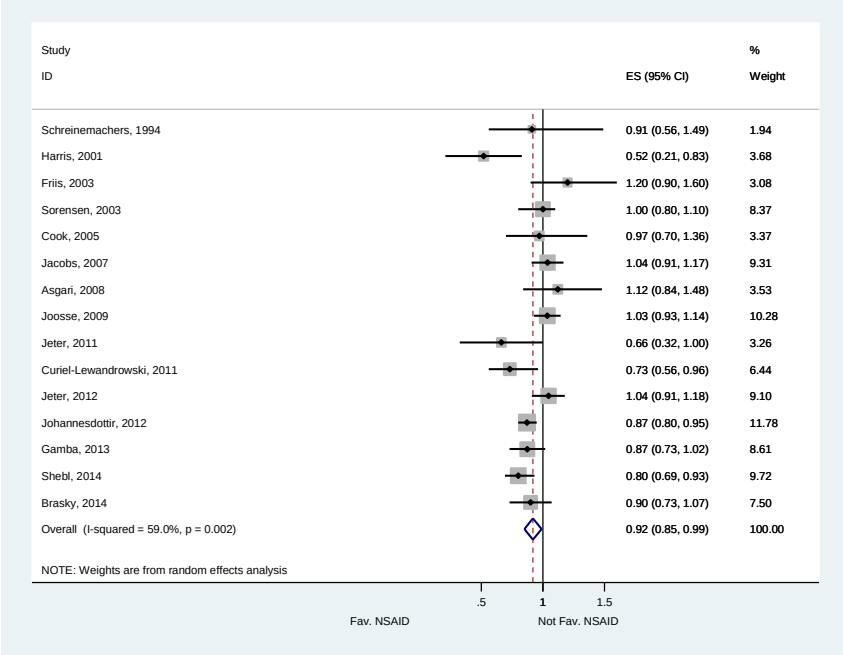

Figure 4. Forest plot depicting pooled and individual study effect estimates for use of NSAIDs and risk of melanoma.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Sensitivity analysis - NSAIDs and risk of melanoma. The pooled effect estimate is influenced by the studies of Curiel-Lewandrowski et al. (2011), Johannesdottir et al. (2012), and Shebl et al. (2014; Figure 5). It is explainable as these studies supported the hypothesis of the protective effect of NSAIDs in reducing the risk of melanoma. Removing these studies from analysis significantly influenced the pooled estimate because the effect estimate became non-significant. Overall, results of the sensitivity analysis show that the pooled effect estimate is stable (in any instance, effect estimate is <1).

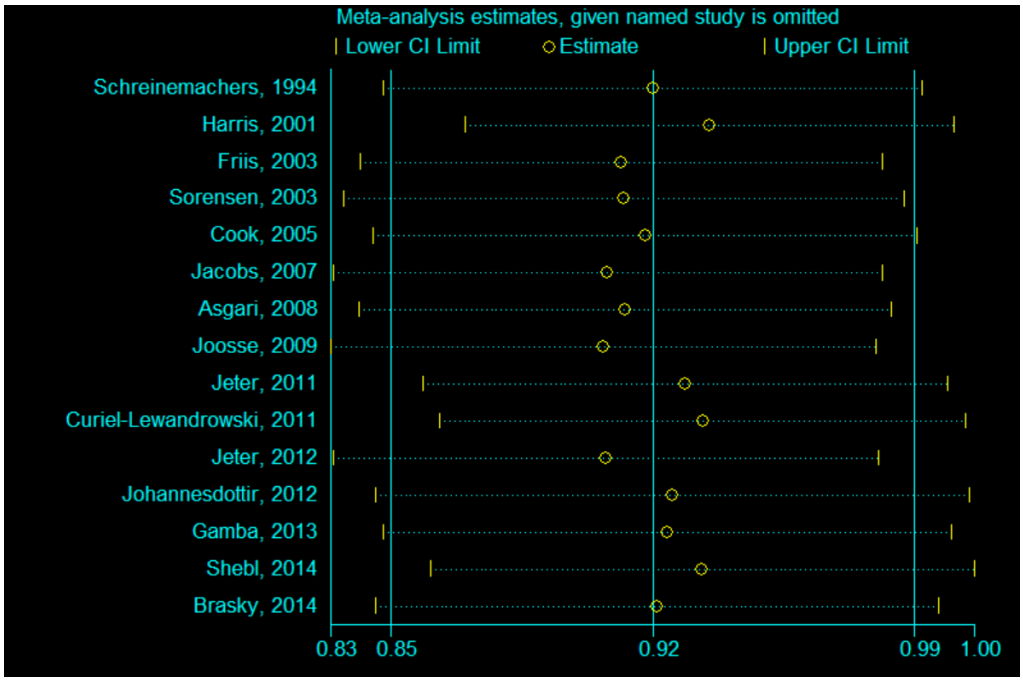

Figure 5. Sensitivity analysis depicting the influence of each single study on pooled effect estimate to assess risk of melanoma skin cancer in NSAIDs users.
CI - confidence interval.

Subgroup analysis - NSAIDs and risk of melanoma.

Quality - NSAIDs and risk of melanoma. A subgroup analysis according to study quality of 14 studies, including three low and 11 high, is shown in Figure 6. The pooled effect estimate obtained by pooling low quality studies results a non-significant pooled effect estimate of 0.84 (95% CI, 0.48-1.20). However, pooling low quality studies resulted in a significant pooled effect estimate of 0.92 (95% CI, 0.85-0.99), indicating that use of NSAIDs significantly reduces the risk of melanoma. Visual inspection of the forest plot reveals a significant influence (source of heterogeneity) on the pooled effect estimate.

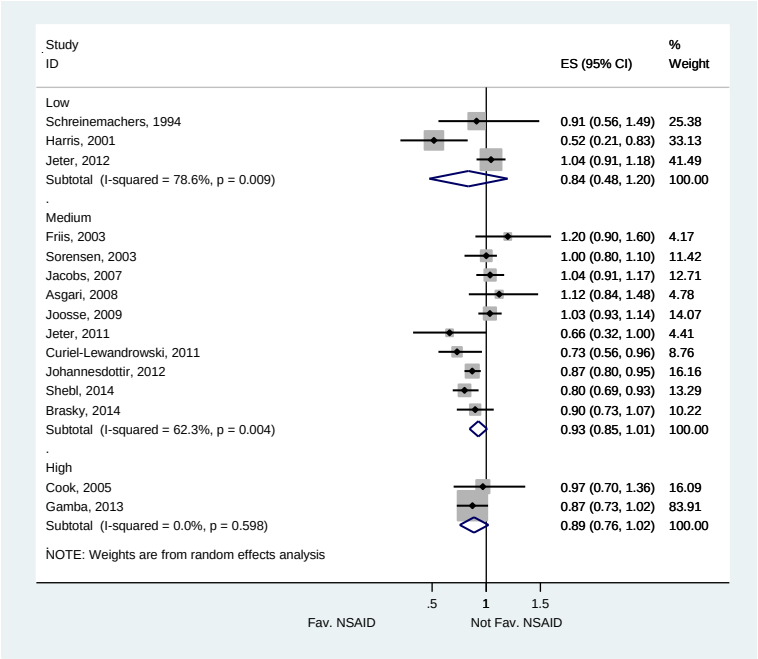

Figure 6. Forest plot representing subgroup analysis according to study quality of included studies to assess risk of melanoma skin cancer in NSAIDs users.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Study design - NSAIDs and risk of melanoma. A subgroup analysis according to the study design of 15 studies, including one RCT, five case-controls, and nine cohort studies, is shown in Figure 7. The effect estimate for RCT is found to be 0.97 (95% CI, 0.70-1.36). A pooled effect estimate, obtained by pooling cohort studies, resulted in a non-significant pooled effect estimate of 0.96 (95% CI, 0.88-1.04). However, pooling case-control studies resulted in a significant pooled effect estimate of 0.81 (95% CI, 0.67-0.96), indicating that use of NSAIDs significantly reduces the risk of melanoma. Visual inspection of the forest plot reveals a significant influence (source of heterogeneity) on the pooled effect estimate.

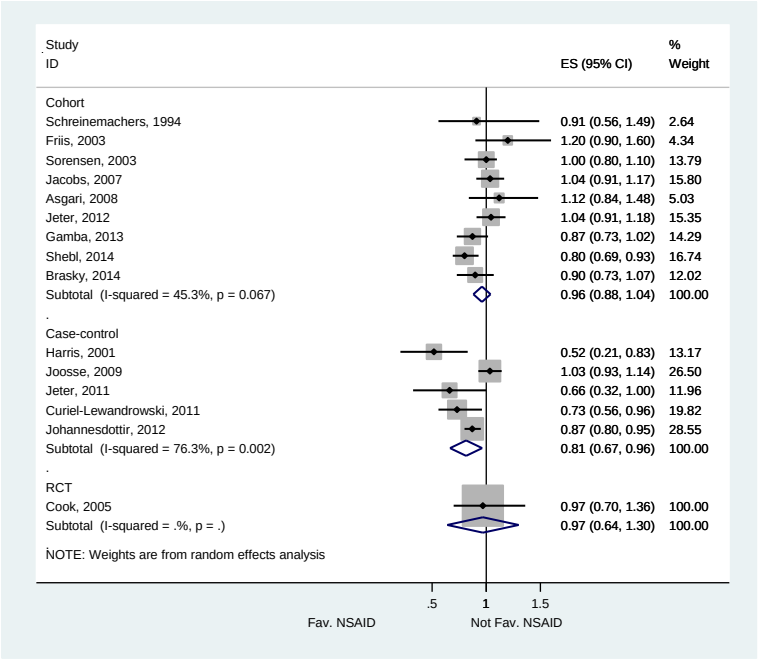

Figure 7. Forest plot representing subgroup analysis according to study design of included studies to assess risk of melanoma skin cancer in NSAIDs users.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Exposure assessment - NSAIDs and risk of melanoma. A subgroup analysis according to the exposure assessment of 15 studies, including nine self-reported and six databases, is shown in Figure 8. There is no significant difference in pooled estimates between studies, which used database vs. self-reported method to assess NSAID.

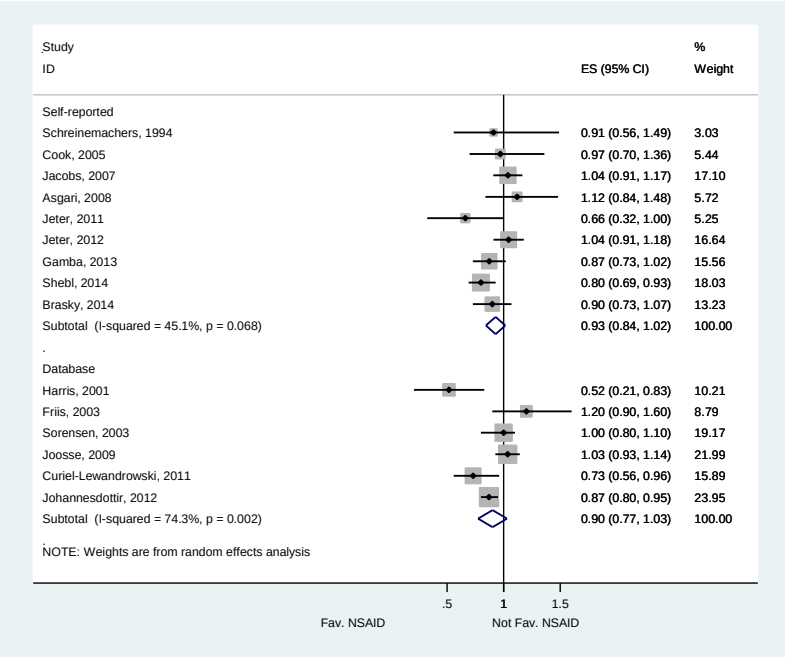

Figure 8. Forest plot representing subgroup analysis according to exposure (NSAID use) assessment and risk of melanoma skin cancer used in included studies.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Study location - NSAIDs and Risk of Melanoma. A subgroup analysis according to study location, with 15 studies including 11 North American and four European Union, is shown in Figure 9. Pooling studies conducted in North America showed a significantly decreased risk of melanoma in NSAIDs users. However, studies conducted in EU have reported a non-significant decreased risk of melanoma in NSAIDs users.

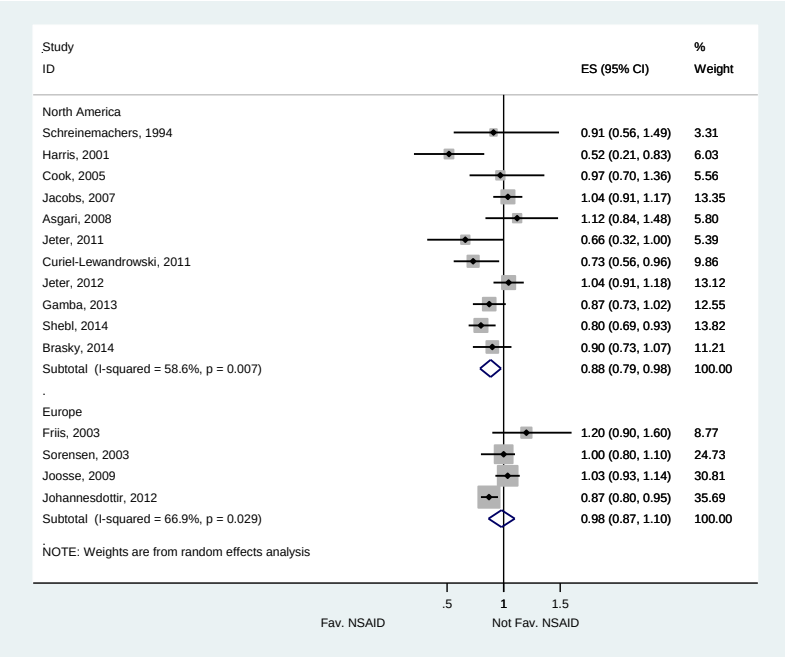

Figure 9. Forest plot representing subgroup analysis according to study location of included studies to assess risk of melanoma skin cancer in NSAIDs users.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Aspirin and risk of melanoma skin cancer.

Main analysis - aspirin and risk of melanoma. When the p value of the Begg's (p = 0.999) and Egger's (p = 0.976) tests were analyzed, publication bias was not indicated, and the funnel plot did not show any evidence of asymmetry (Figure 10). A random effects model was selected, as significant heterogeneity ($p_{heterogeneity}<0.05$, $I^2 = 54\%$) exists in included studies. A combined analysis of 11 studies indicated that aspirin use was associated with a significant decrease in the risk of melanoma (RR 0.88, 95% CI 0.78-0.97, p <0.05). A forest plot depicting pooled and individual study effect estimates is shown in Figure 11.

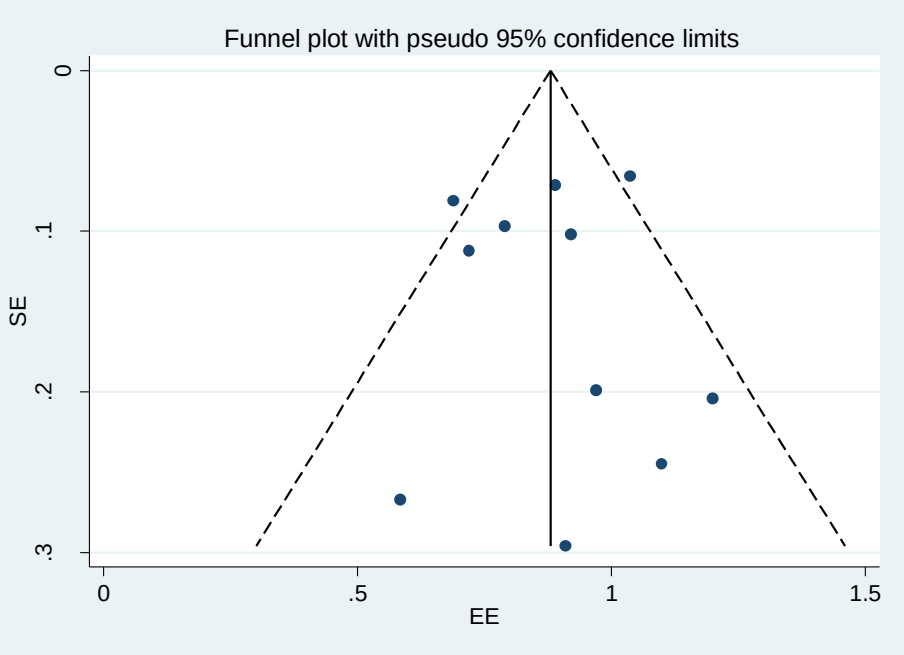

Figure 10. Funnel plot representing symmetry and no publication bias for use of aspirin and risk of melanoma.

EE - effect estimate; SE - standard error.

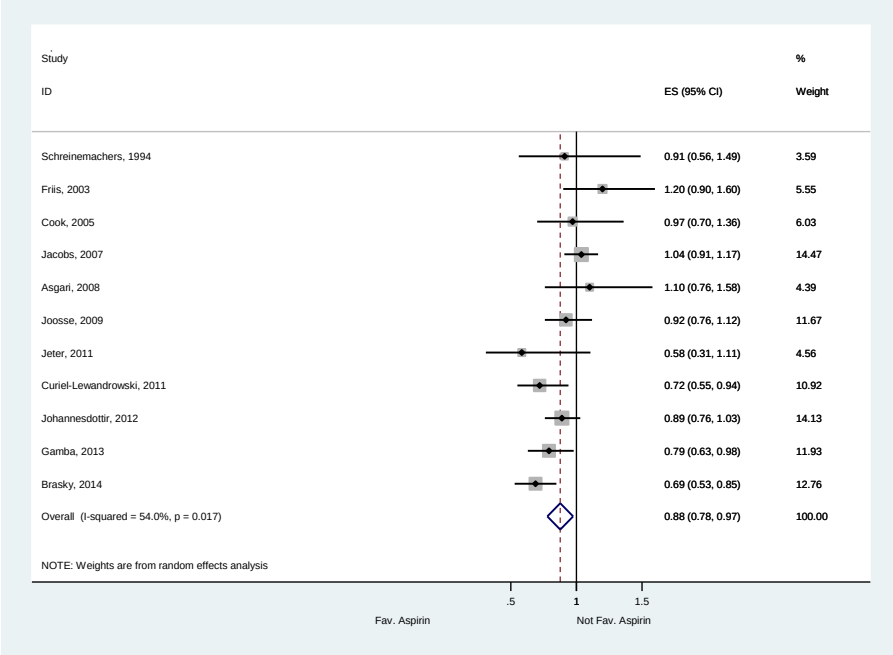

Figure 11. Forest plot depicting pooled and individual study effect estimates for use of aspirin and risk of melanoma.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Sensitivity analysis - aspirin and risk of melanoma. Sensitivity analysis by was done by pooling all studies and then excluding each study, one at a time. This showed that the pooled effect estimate is not influenced by any of the included studies (Figure 12). Sensitivity analysis revealed that the effect estimate varied between 0.84 and 0.91. Overall, results of sensitivity analysis show that the pooled effect estimate is stable (in any instance, effect estimate is <1).

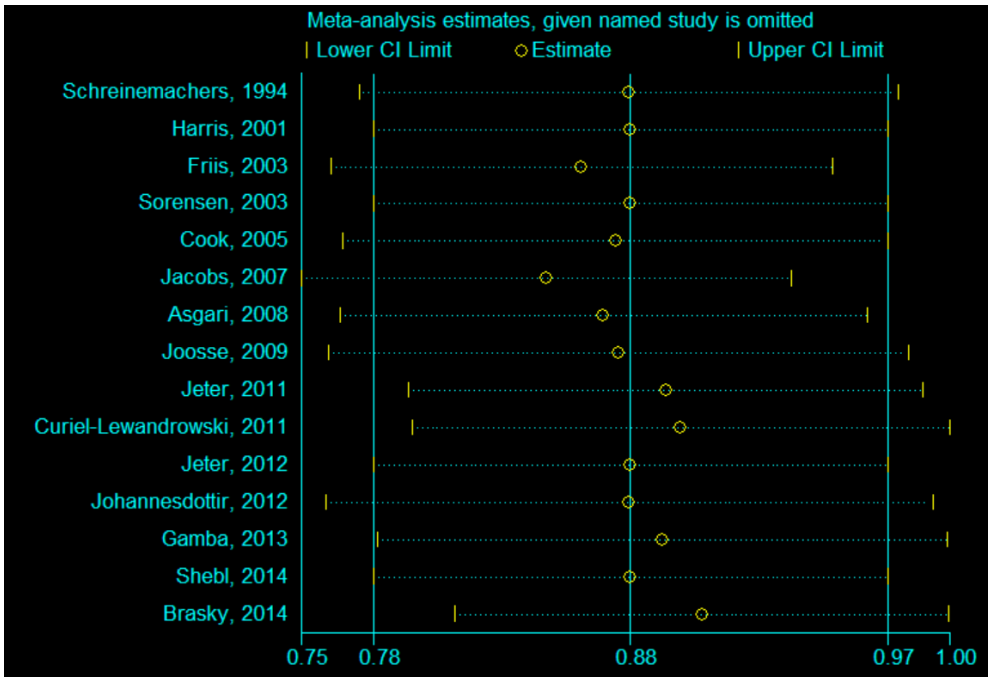

Figure 12. Sensitivity analysis depicting the influence of each single study on pooled effect estimate for use of aspirin and risk of melanoma.
CI - confidence interval.

Subgroup analysis - aspirin and risk of melanoma.

Quality - aspirin and risk of melanoma. A subgroup analysis according to study quality of 11 studies, including one low, two high, and 8 medium, is shown in Figure 13. A pooled effect estimate, obtained by pooling high quality studies, results a significant decreased risk 0.83

(95% CI, 0.67–0.96). However, by pooling low quality and medium studies results a non-significant pooled effect estimate.

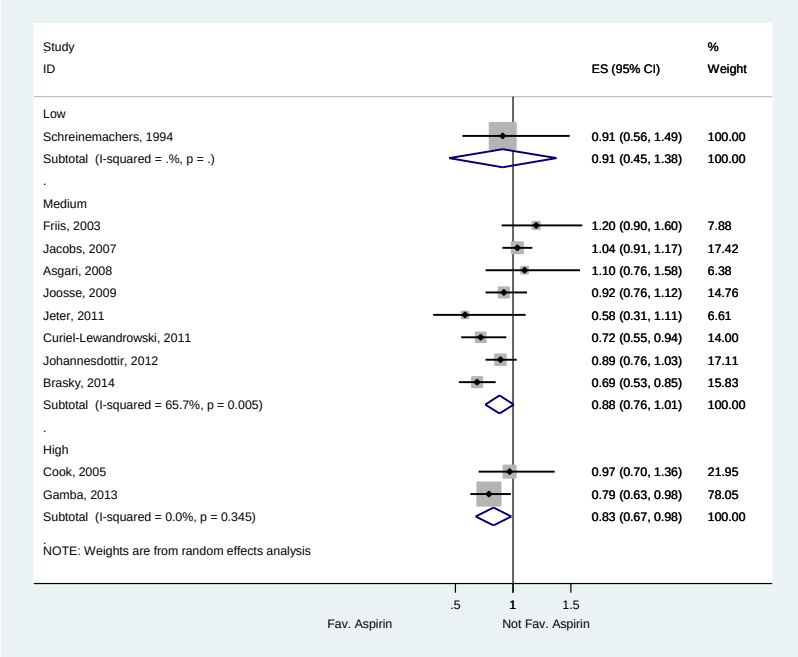

Figure 13. Forest plot representing subgroup analysis according to study quality of included studies for use of aspirin and risk of melanoma.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Study design - aspirin and risk of melanoma. Subgroup analysis according to study quality of 11 studies, including one RCT, four case-controls, and six cohorts, is shown in Figure 14. A pooled effect estimate obtained by pooling case-control studies results a significant decreased risk of 0.83 (95% CI, 0.71–0.95). However, pooling cohort or RCT studies resulted in a non-significant pooled effect estimate.

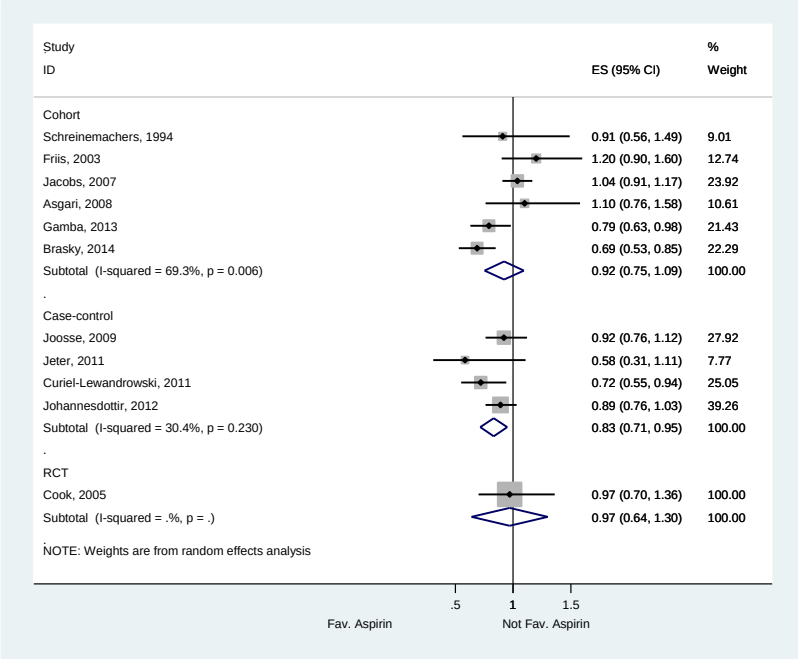

Figure 14. Forest plot representing subgroup analysis according to study design of included studies for use of aspirin and risk of melanoma.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Exposure assessment - aspirin and risk of melanoma. A subgroup analysis according to exposure assessment of 11 studies, including seven self-reported and four databases, is shown in Figure 15. There is no significant difference in pooled estimates between studies that used database and those that use a self-report method to assess NSAID.

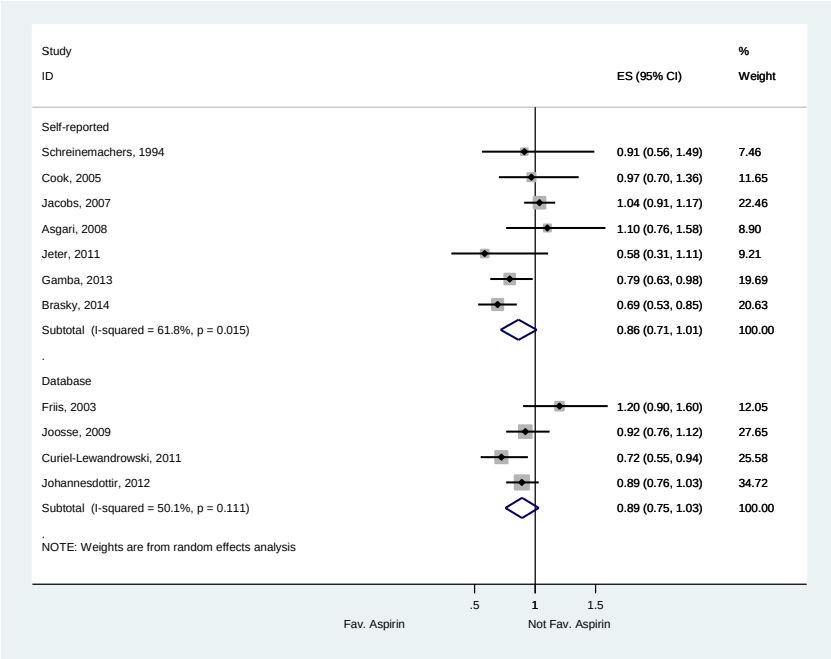

Figure 15. Forest plot representing subgroup analysis according to exposure (aspirin use) assessment used in included studies for use of aspirin and risk of melanoma.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Study location - aspirin and risk of melanoma. A subgroup analysis according to study location of 11 studies, including eight North American and three European Union, is shown in Figure 16. Pooling studies conducted in North America showed a significantly decreased risk of melanoma in aspirin users. However, studies conducted in the EU have reported a non-significant decreased risk of melanoma in aspirin users.

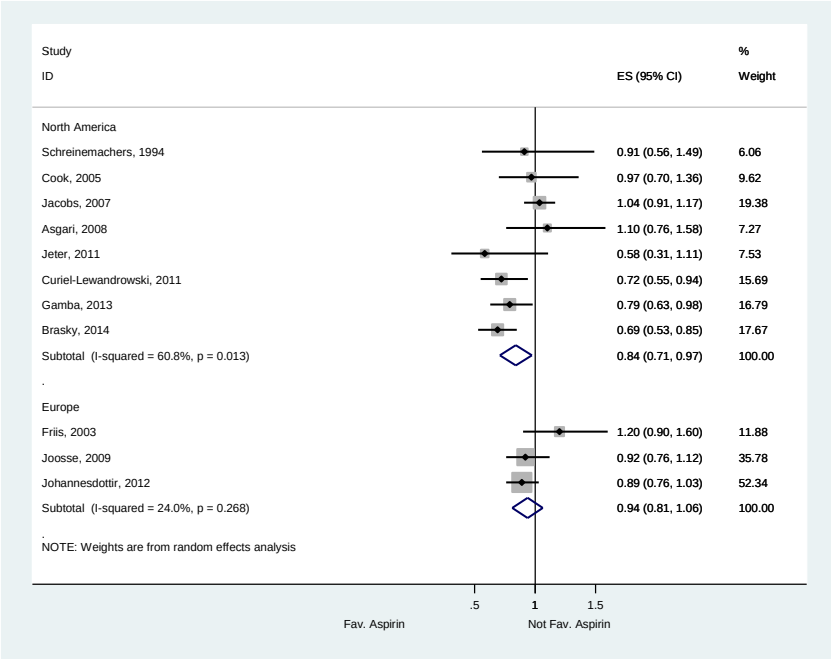

Figure 16. Forest plot representing subgroup analysis according to study location of included studies for use of aspirin and risk of melanoma.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Non-aspirin NSAID use and risk of melanoma skin cancer. When the p value of the Begg's (p = 0.602) and Egger's (p = 0.596) tests were analyzed, publication bias was not indicated, and the funnel plot did not show any evidence of asymmetry (Figure 17). The fixed-effects model was chosen, as the heterogeneity ($p_{heterogeneity}$ = 0.054, I^2 = 48%) value was observed to be not significant. Combined analysis of nine studies indicated that non-aspirin NSAID use was not associated with a decrease in the risk of melanoma (RR 0.96, 95% CI 0.90-1.03, p =0.070). A forest plot depicting pooled and individual study effect estimates is shown in Figure 18.

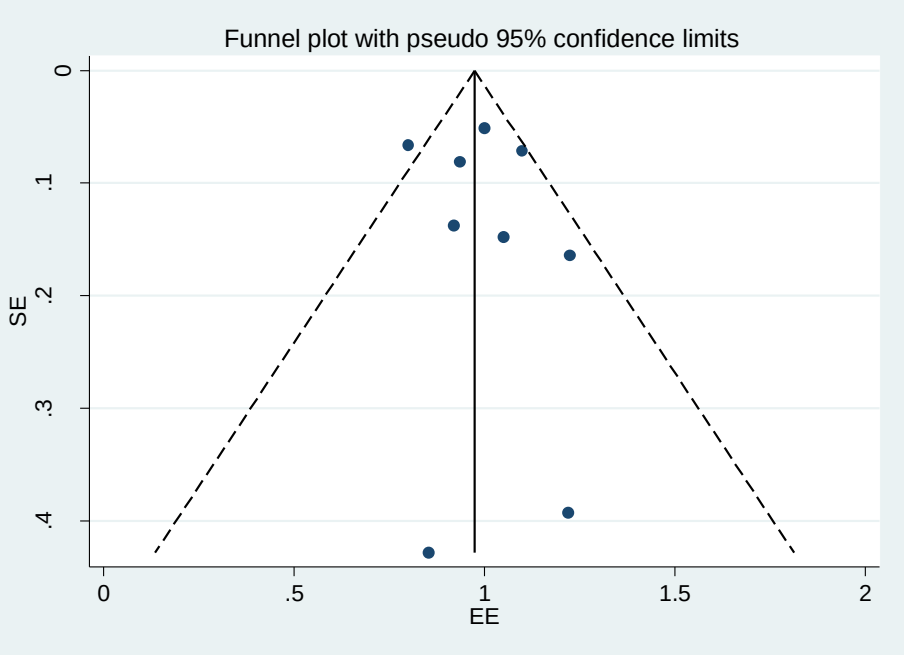

Figure 17. Funnel plot representing symmetry and no publication bias for use of non-aspirin NSAID and risk of melanoma.

EE - effect estimate; SE - standard error.

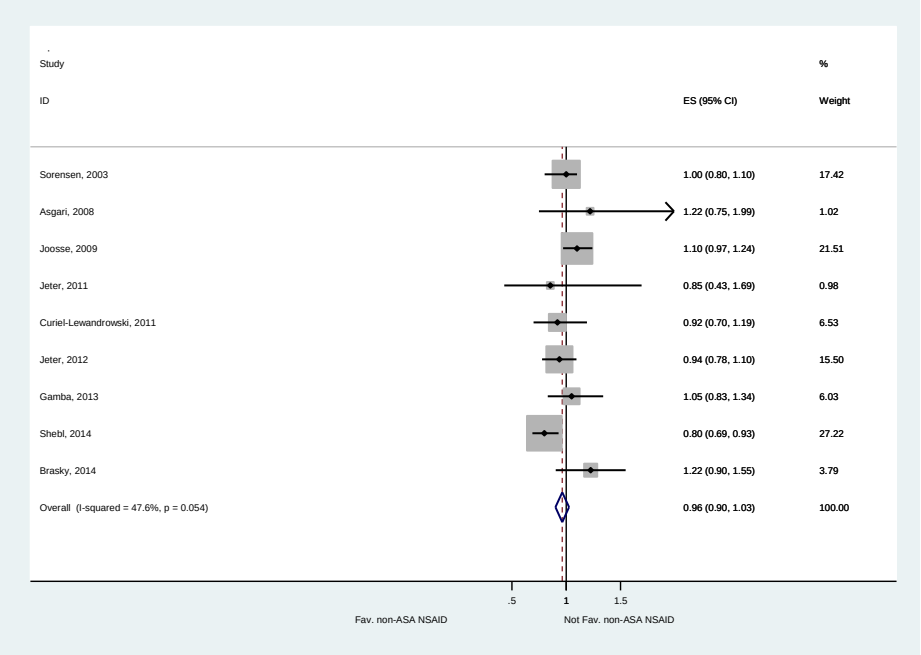

Figure 18. Forest plot depicting pooled and individual study effect estimates for use of non-aspirin NSAID and risk of melanoma.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Sensitivity analysis - non-aspirin NSAID and risk of melanoma. Sensitivity analysis done by pooling all studies and excluding one study at a time showed that the pooled effect estimate is not influenced by any of the included studies (Figure 19). Sensitivity analysis revealed that the effect estimate varied between 0.95 and 1.

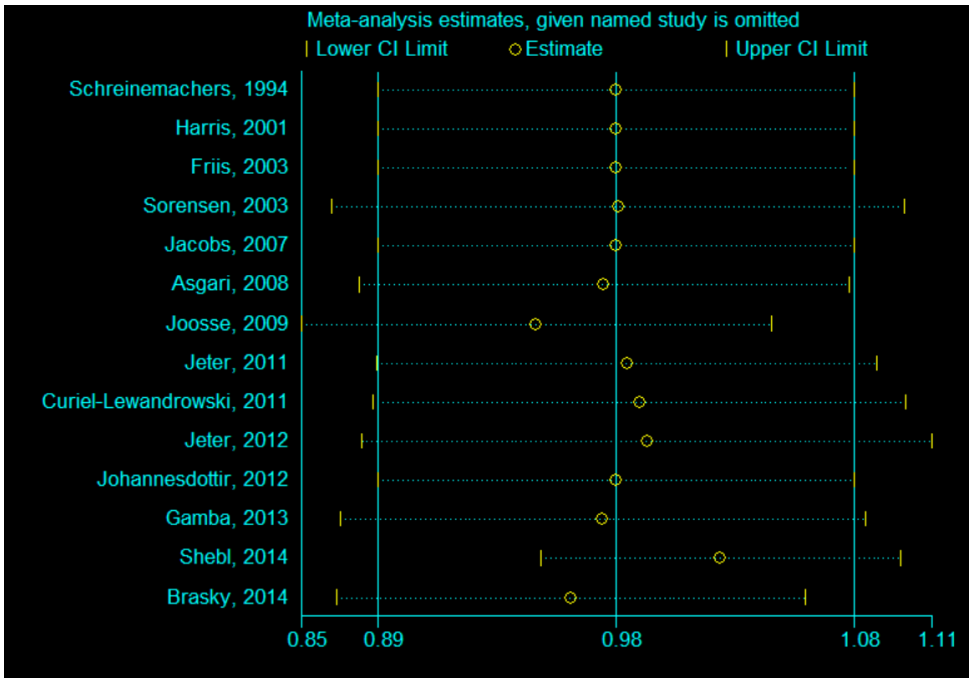

Figure 19. Sensitivity analysis depicting the influence of each single study on pooled effect estimate for use of non-aspirin NSAID and risk of melanoma.
CI - confidence interval.

Subgroup analysis - Non-aspirin NSAID and risk of melanoma.

Quality - non-aspirin NSAID and risk of melanoma. Subgroup analysis according to study quality of nine studies, including one low, one high, and seven medium, is shown in Figure 20. There was no significant difference observed in pooled effect estimates (non-significant reduced risk) obtained by high quality vs. medium vs. low quality studies.

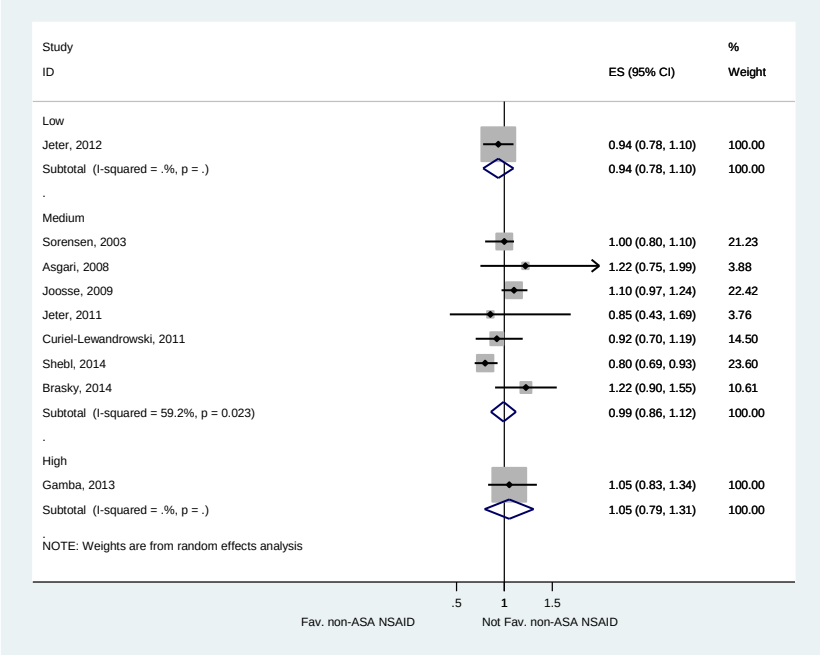

Figure 20. Forest plot representing subgroup analysis according to study quality of included studies for use of non-aspirin NSAID and risk of melanoma.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Study design - non-aspirin NSAID and risk of melanoma. The subgroup analysis according to study design of six cohort and three case-control studies is shown in Figure 21. There was no significant difference observed in the pooled effect estimate (non-significant reduced risk) obtained by pooling case-control versus cohort studies.

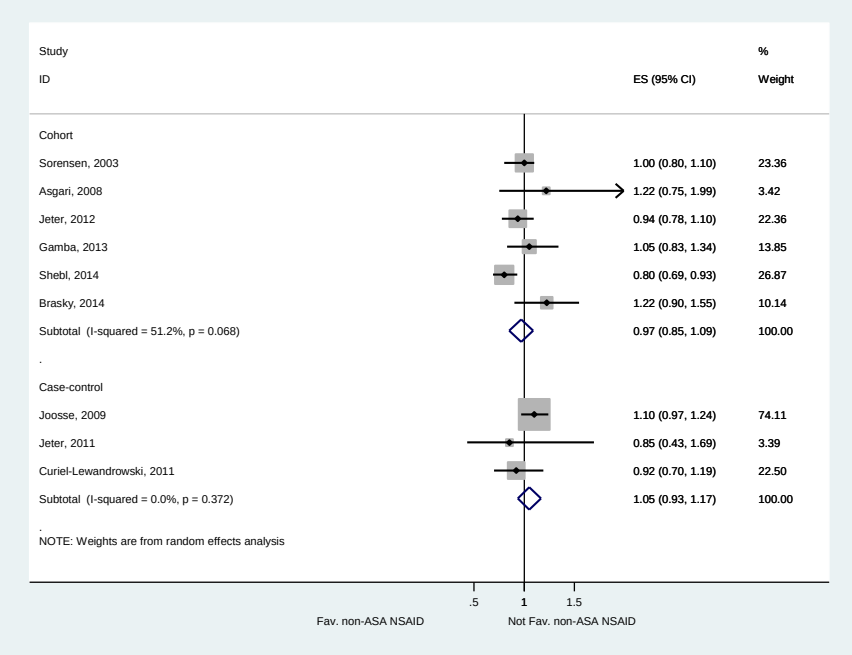

Figure 21. Forest plot representing subgroup analysis according to study design of included studies for use of non-aspirin NSAID and risk of melanoma.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Exposure assessment - non-aspirin NSAID and risk of melanoma. The subgroup analysis according to exposure assessment of nine studies including six self-reported and three database exposure assessment studies is shown in Figure 22. There is no significant difference in pooled estimates between studies that used database and those that used the self-reported method to assess NSAID.

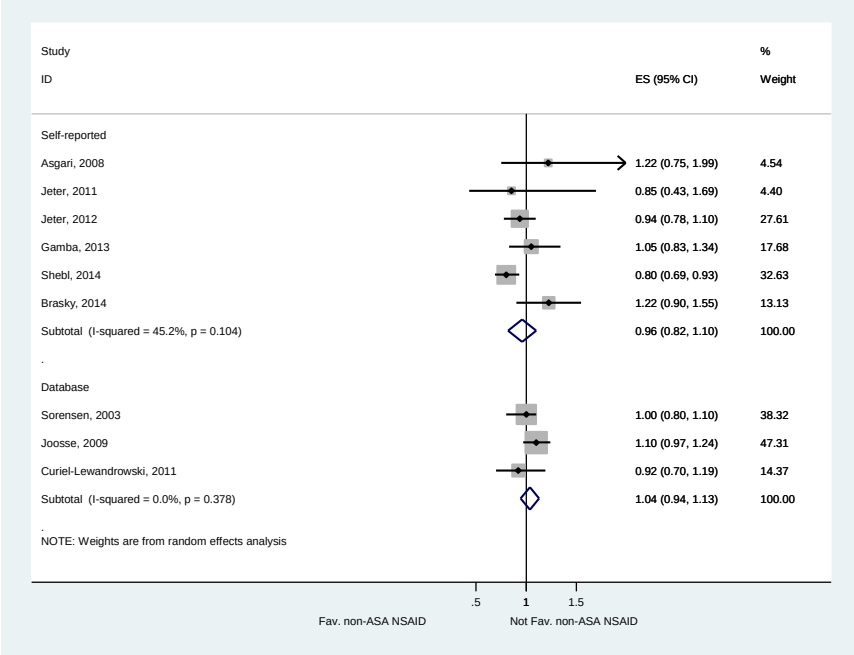

Figure 22. Forest plot representing subgroup analysis according to exposure (non-aspirin NSAID use) assessment used in included studies for use of non-aspirin NSAID and risk of melanoma.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Study location - non-aspirin NSAID and risk of melanoma. The subgroup analysis according to study location of nine studies, including seven North American and two European Union, is shown in Figure 23. No significant difference in pooled estimates was observed between studies conducted in North America and those conducted in the EU for risk of melanoma in non-aspirin NSAIDs users.

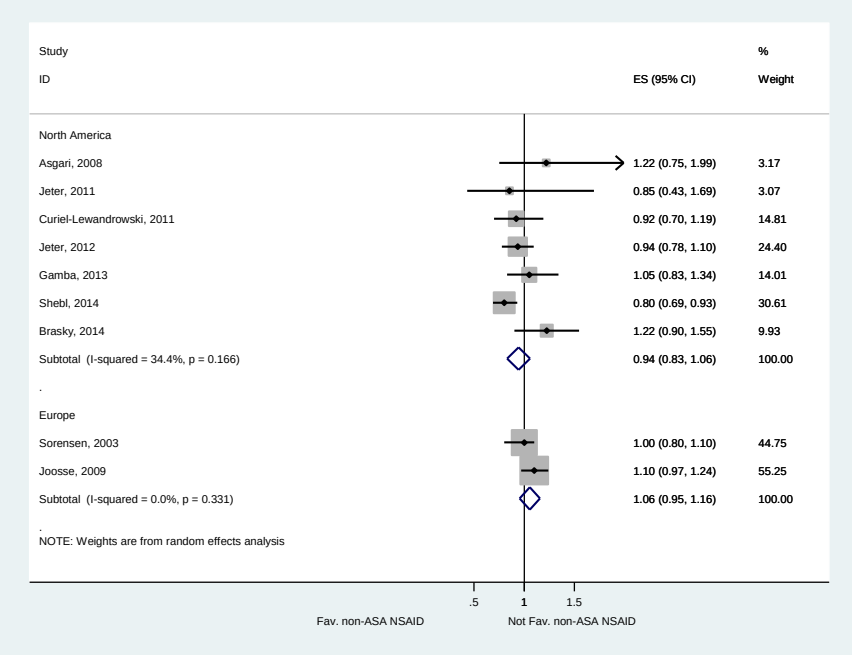

Figure 23. Forest plot representing subgroup analysis according to study location of included studies for use of non-aspirin NSAID and risk of melanoma.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Results for non-melanoma skin cancer

Study characteristics - non-melanoma skin cancer. A total of 14 articles were selected for the meta-analysis, corresponding to one RCT, four cohort, and nine case-control studies (Milan, Verkasalo, Kaprio, & Koskenvuo, 2003; Butler, Neale, Green, Pandeya, & Whiteman, 2005; Clouser, Roe, Foote, & Harris, 2009; Elmets et al., 2010; Grau et al., 2006; Cahoon et al., 2012; Vogel et al., 2007; Nunes, Lapane & Weinstock, 2011; Asgari, Chren, Warton, Friedman & White, 2010; Jeter et al., 2012; Torti et al., 2011; de Vries et al., 2012; Johannesdottir et al., 2012; Reinau, Surber, Jick, & Meier, 2015). All 14 studies are available in full text, and study characteristics are listed in Table 6.

Table 6

Characteristics of Studies Included to Assess the Risk of Non-Melanoma Skin Cancer and NSAIDs Use

Study	Study location	Outcome assessment	Exposure assessment	Quality assessment
Case-control studies				
Milan,2003 (Milan et al., 2003)	Finland	A, B	C	Medium
Butler, 2005 (Butler et al., 2005)	Australia	B	C	Medium
Grau, 2006 (Grau et al., 2006)	US	A	C	Medium
Vogel, 2007 (Vogel et al., 2007)	Denmark	B	C	Medium
Asgari, 2010 (Asgari et al., 2010)	US	B	C	Medium
Torti, 2011 (Torti et al., 2011)	US	B	C	Medium
de Vries, 2012 (de Vries et al., 2012)	EU	B	C	Medium
Johannesdottir, 2012 (Johannesdottir et al., 2012)	Denmark	B	B	Medium
Reinau, 2014 (Reinau et al., 2014)	UK	B	B	Medium
Cohort studies				
Clouser, 2009 (Clouser et al., 2009)	US	A	C	High
Cahoon, 2011 (Cahoon et al., 2011)	US	B, C	C	Medium
Nunes, 2011 (Nunes et al., 2011)	US	A	B	Medium
Jeter, 2012 (Jeter et al., 2012)	US	C	C	Low
RCT				
Elmets, 2010 (Elmets et al., 2010)	US	A	C	High

A - Histological confirmation; B - database; C - self-reported

Quality assessment - non-melanoma skin cancer. When quality of included studies was assessed, there were two high, eleven medium, and one low. RCT was considered a high-quality study based on the Jadad scale to assess the quality of clinical trials.

Overview of results of non-melanoma skin cancer. Overall, results show that NSAIDs and aspirin especially have a significant chemoprevention effect in reducing the

incidence of both BCC and SCC (Table 7 & 8). However, non-aspirin NSAIDs do not have chemoprevention effect for both BCC and SCC (Table 9).

The subgroup analysis revealed that there is no significant heterogeneity between the groups compared based on study design, study location, exposure assessment, and study quality.

Table 7

Results of Meta-analysis of NAIDs Use and Risk of Non-Melanoma Skin Cancer

Estimate	**SCC**		**BCC**	
	N	**EE (95% CI)**	**N**	**EE (95% CI)**
All studies	11	0.84 (0.74-0.93)	7	0.94 (0.89-0.99)
Subgroup analysis				
Study design				
RCT	1	0.42 (0.19-0.93)	-	-
Cohort	3	0.83 (0.64-1.03)	4	0.89 (0.78-1.00)
Case control	7	0.86 (0.75-0.98)	3	0.98 (0.95-1.01)
Study location				
North America	7	0.81 (0.66-0.96)	6	0.93 (0.87-0.99)
EU	3	0.91 (0.81-1.02)	1	0.97 (0.91-1.02)
Australia	1	0.55 (0.25-0.84)	-	-
Study quality				
High	2	0.58 (0.31-0.85)	1	0.64 (0.30-0.98)
Medium	8	0.84 (0.73-0.95)	5	0.93 (0.87-1.00)
Low	1	0.98 (0.90-1.06)	1	0.99 (0.95-1.02)
Exposure assessment				
Self-reported	8	0.79 (0.63-0.96)	4	0.95 (0.89-1.02)
Database	3	0.87 (0.74-0.99)	3	0.92 (0.83-1.01)

BCC – basal cell carcinoma; EE – effect estimate; SCC – squamous cell carcinoma

Table 8

Results of Meta-analysis of Aspirin Use and Risk of Non-Melanoma Skin Cancer

Estimate	SCC		BCC	
	N	**EE (95% CI)**	**N**	**EE (95% CI)**
All studies	7	0.87 (0.77-0.97)	7	0.94 (0.89-0.99)
Subgroup analysis				
Study design				
RCT				
Cohort	3	0.82 (0.59-1.05)	4	0.89 (0.78-1.00)
Case control	4	0.90 (0.78-1.01)	3	0.98 (0.95-1.01)
Study location				
North America	5	0.86 (0.67-1.05)	6	0.93 (0.87-0.99)
EU	2	0.91 (0.84-0.98)	1	0.97 (0.91-1.02)
Study quality				
High	1	0.71 (0.30-1.11)	1	0.64 (0.30-0.98)
Medium	5	0.86 (0.73-0.98)	5	0.93 (0.87-1.00)
Low	1	0.99 (0.85-1.12)	1	0.99 (0.95-1.02)
Exposure assessment				
Self-reported	4	0.92 (0.70-1.13)	4	0.95 (0.89-1.02)
Database	3	0.85 (0.72-0.97)	3	0.92 (0.83-1.01)

BCC – basal cell carcinoma; EE – effect estimate; SCC – squamous cell carcinoma

Table 9

Results of Meta-analysis of Non-aspirin NSAIDs Use and Risk of Non-Melanoma Skin Cancer

Estimate	SCC		BCC	
	N	**EE (95% CI)**	**N**	**EE (95% CI)**
All studies	5	0.96 (0.90-1.01)	5	0.92 (0.83-1.01)
Subgroup analysis				
Study design				
Cohort	3	0.93 (0.82-1.03)	4	0.88 (0.73-1.03)
Case control	2	0.97 (0.90-1.04)	1	0.96 (0.92-1.00)
Study location				
North America	4	0.93 (0.84-1.02)	5	0.92 (0.83-1.01)
EU	1	0.98 (0.91-1.05)	-	-
Study quality				
High	1	0.80 (0.31-1.28)	1	0.60 (0.24-0.96)
Medium	3	0.93 (0.82-1.03)	3	0.89 (0.75-1.04)
Low	1	0.98 (0.87-1.08)	1	1.02 (0.98-1.05)
Exposure assessment				
Self-reported	3	0.96 (0.86-1.06)	3	1.00 (0.92-1.08)
Database	2	0.92 (0.78-1.07)	2	0.81 (0.52-1.11)

Results of BCC.

NSAIDs and risk of BCC. When the p value of the Begg's (p = 0.107) and Egger's (p = 0.239) tests were analyzed, publication bias was not indicated, and the funnel plot did not show any evidence of asymmetry (Figure 24). The random effects model was selected, as significant heterogeneity ($p_{heterogeneity}<0.05$, $I^2 = 71\%$) exists in included studies. Combined analysis of 13 studies indicated that NSAIDs use was associated with a significant decrease in the risk of BCC (RR 0.91, 95% CI 0.86-0.97, p <0.05). A forest plot depicting pooled and individual study effect estimates is shown in Figure 25.

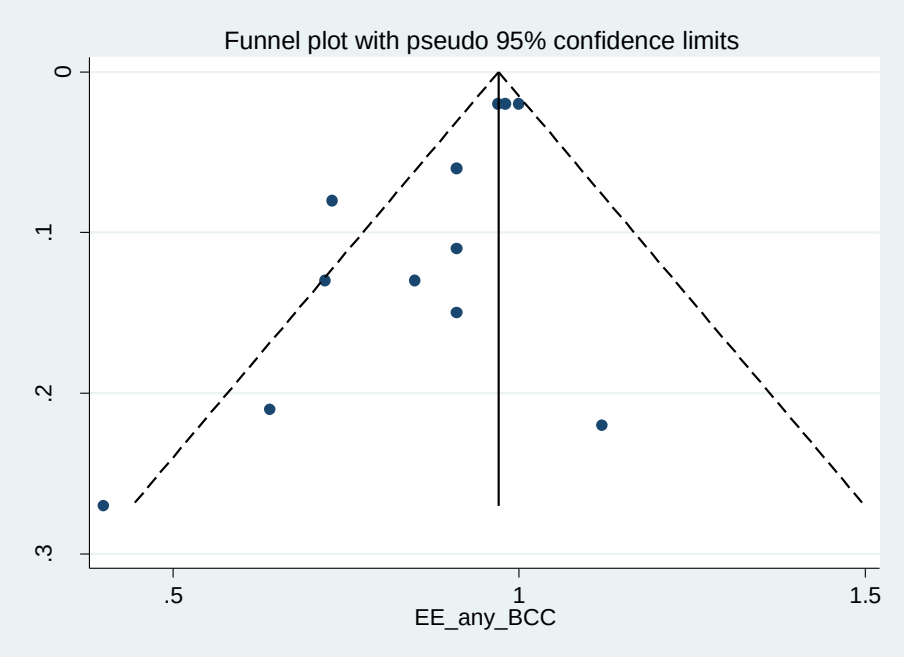

Figure 24. Funnel plot representing symmetry and no publication bias for use of NSAIDs and risk of BCC.

EE - effect estimate; SE - standard error.

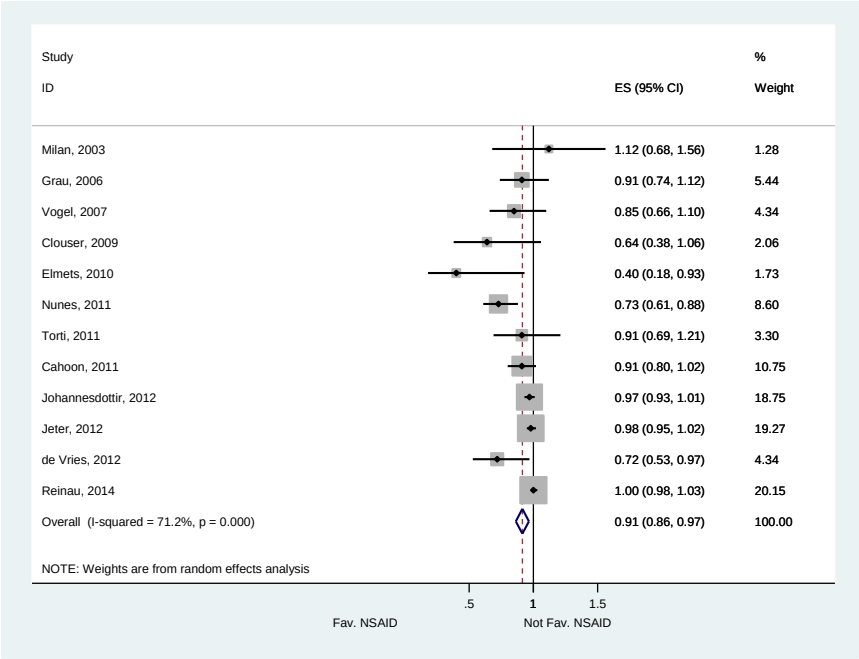

Figure 25. Forest plot depicting pooled and individual study effect estimates for use of NSAIDs and risk of BCC.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Sensitivity analysis - NSAIDs and risk of BCC. Overall, the results of the sensitivity analysis show that the pooled effect estimate is stable and ranged from 0.88–0.94 across the sensitivity analysis.

Figure 26. Sensitivity analysis depicting the influence of each single study on pooled effect estimate for NSAIDs use and risk of BCC.
CI - confidence interval.

Aspirin and risk of BCC. When the p value of the Begg's (p = 0.251) and Egger's (p = 0.304) tests were analyzed, publication bias was not indicated, and the funnel plot did not show any evidence of asymmetry (Figure 27). The random effects model was selected, as significant heterogeneity ($p_{heterogeneity}$<0.05, I^2 = 70%) exists in included studies. The combined analysis of seven studies indicated that aspirin use was associated with a significant decrease in the risk of BCC (RR 0.95, 95% CI 0.90-0.996, p <0.05). A forest plot depicting pooled and individual study effect estimates is shown in Figure 28.

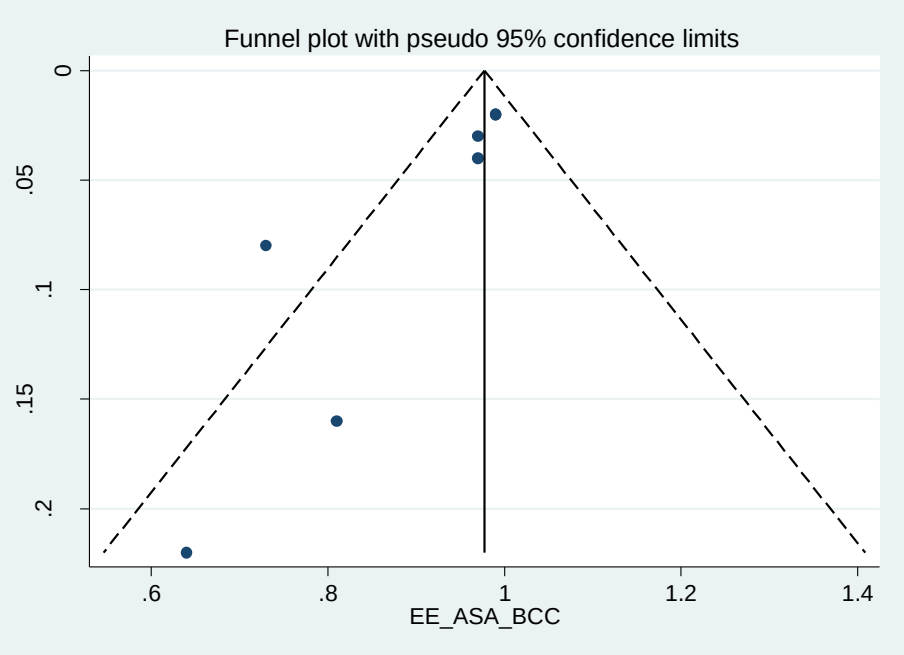

Figure 27. Funnel plot representing symmetry and no publication bias for use of aspirin and risk of BCC.

EE - effect estimate; SE - standard error.

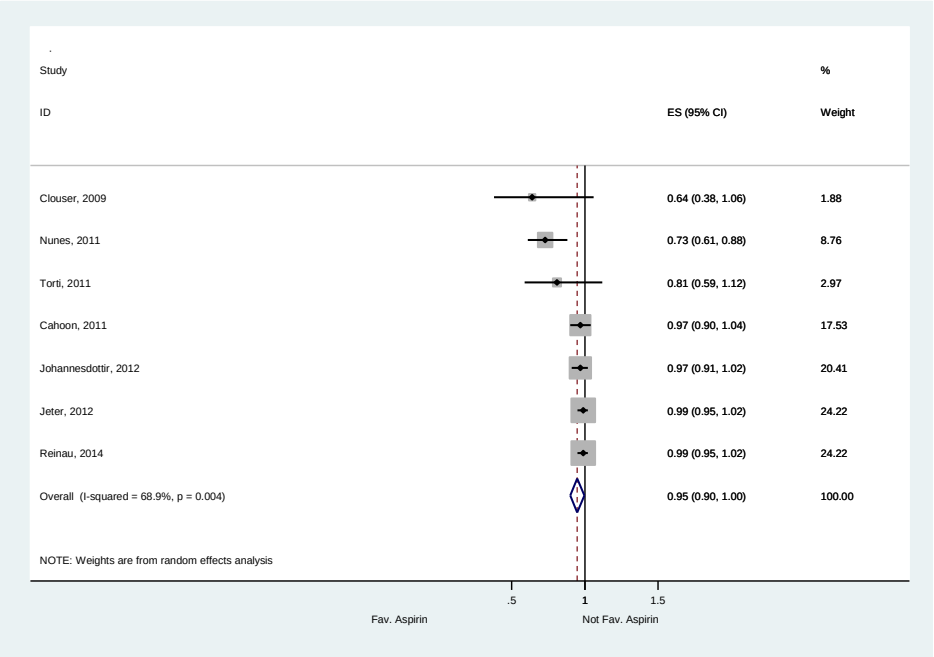

Figure 28. Forest plot depicting pooled and individual study effect estimates for use of aspirin and risk of BCC.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Sensitivity analysis - aspirin and risk of BCC. Overall, the results of the sensitivity analysis show that the pooled effect estimate is stable (Figure 29). The pooled effect estimate is influenced by Clouser et al., (2009); Nunes et al., (2011); Torti et al., (2011). The pooled effect estimate ranged from 0.92–0.98 across the sensitivity analysis.

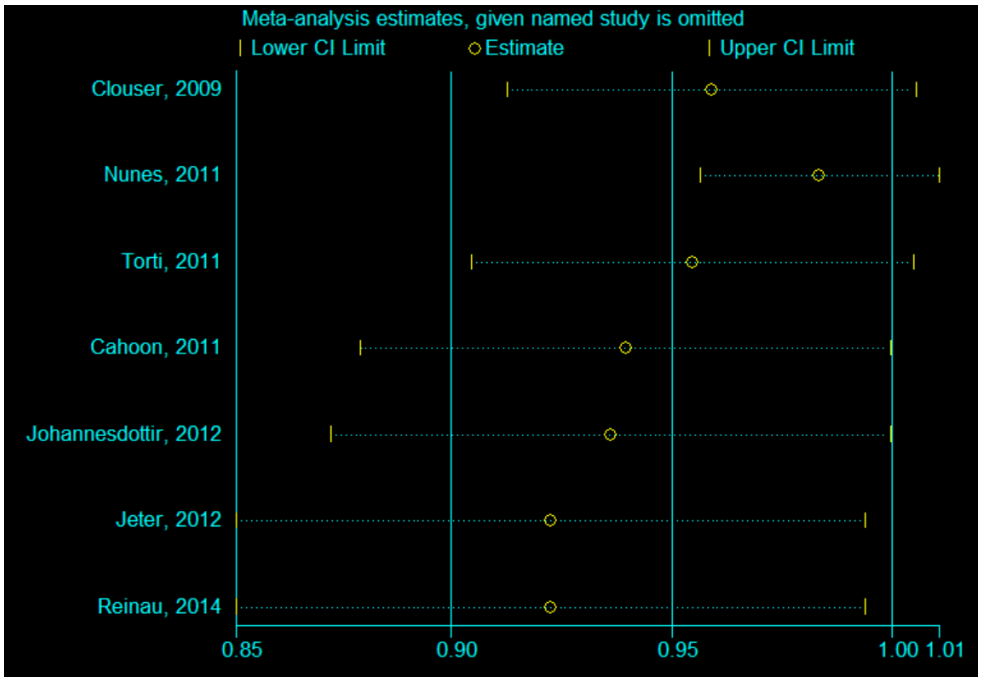

Figure 29. Sensitivity analysis depicting the influence of each single study on pooled effect estimate for aspirin use and risk of BCC.
CI - confidence interval.

Non-aspirin NASAID and risk of BCC. Assessment of publication bias is not relevant for this case, as the number of studies is less than ten. The random effects model was selected, as significant heterogeneity ($p_{heterogeneity}<0.05$, $I^2 = 89\%$) exists in included studies. A combined analysis of five studies indicated that non-aspirin NSAIDs use was not associated with the risk of BCC (RR 0.92, 95% CI 0.83-1.01). A forest plot depicting pooled and individual study effect estimates is shown in Figure 30.

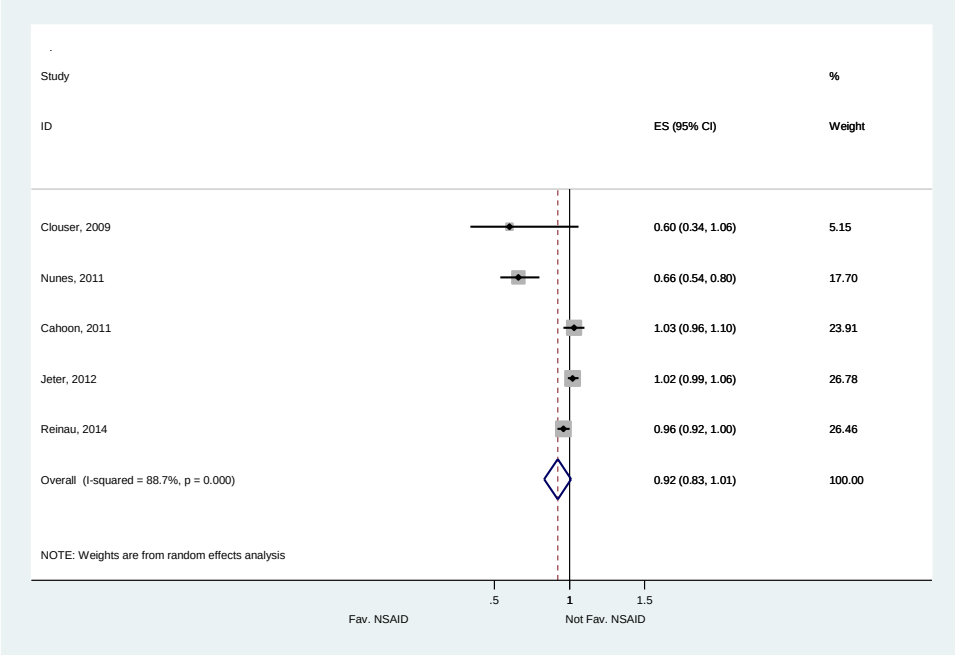

Figure 30. Forest plot depicting pooled and individual study effect estimates for use of non-aspirin NSAIDs and risk of BCC.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Sensitivity analysis - non-aspirin NASAID and risk of BCC. Overall, the results of the sensitivity analysis show that the pooled effect estimate is stable (Figure 31). The pooled effect estimate is influenced by (Cahoon et al., 2011; Jeter et al., 2012). The pooled effect estimate ranged from 0.86–0.99 across the sensitivity analysis.

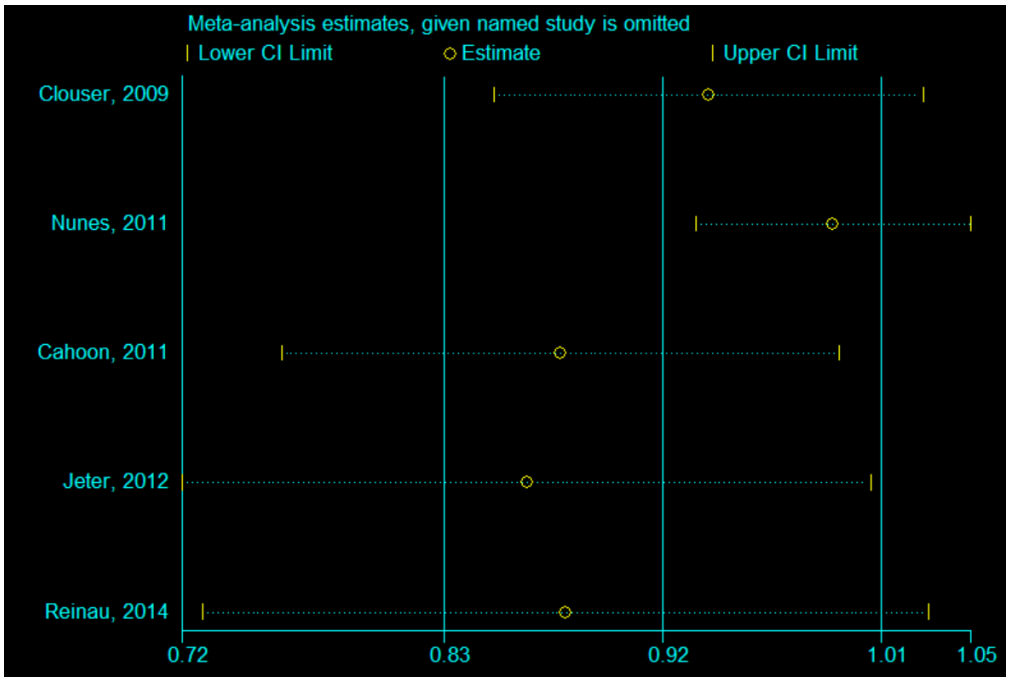

Figure 31. Sensitivity analysis depicting the influence of each single study on pooled effect estimate for non-aspirin NSAIDs use and risk of BCC.
CI - confidence interval.

Results of SCC.

NSAIDs use and risk of SCC. When the p value of the Begg's (p = 0.815) and Egger's (p = 0.080) tests were analyzed, publication bias was not indicated, and the visual inspection the funnel plot did not show any asymmetry (Figure 32). The random effects model was selected, as significant heterogeneity ($p_{heterogeneity}$<0.05, I^2 = 70%) exists in included studies. The combined analysis of 11 studies indicated that NSAIDs use was associated with a significant decrease in the risk of SCC (RR 0.84, 95% CI 0.74-0.93, p <0.05). A forest plot depicting pooled and individual study effect estimates are shown in Figure 33.

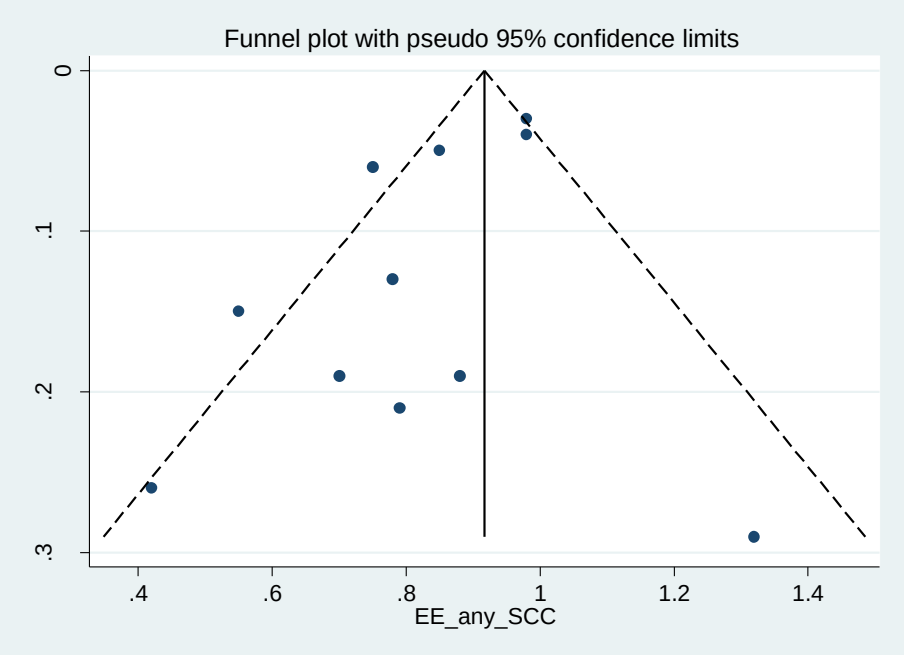

Figure 32. Funnel plot representing symmetry and no publication bias for use of NSAIDs and risk of SCC.

EE - effect estimate; SE - standard error.

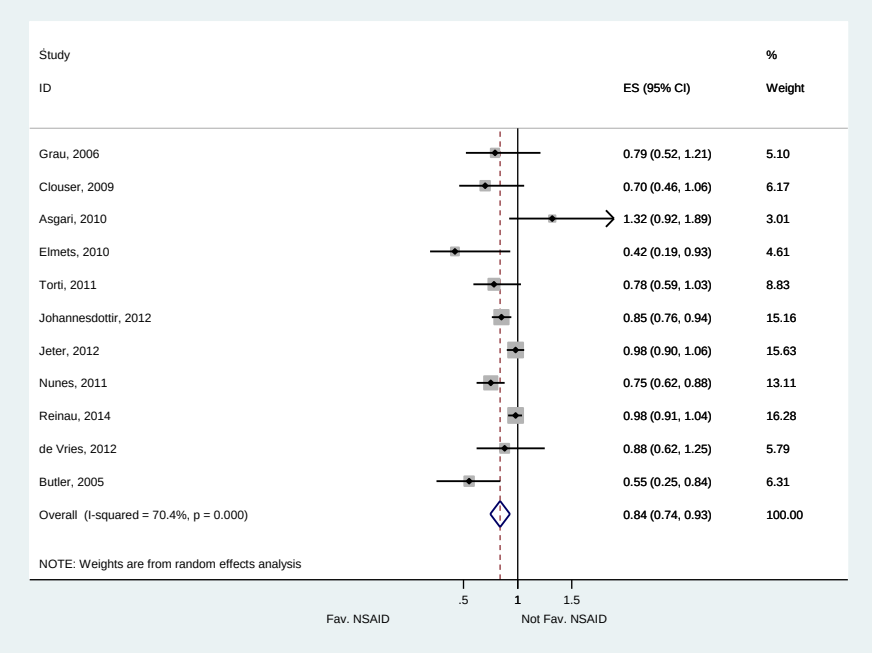

Figure 33. Forest plot depicting pooled and individual study effect estimates for use of NSAIDs and risk of SCC.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Sensitivity analysis - NSAIDs use and risk of SCC. Overall, the results of the sensitivity analysis show that the pooled effect estimate is stable (Figure 34) and ranged from0.88–0.94 across the sensitivity analysis.

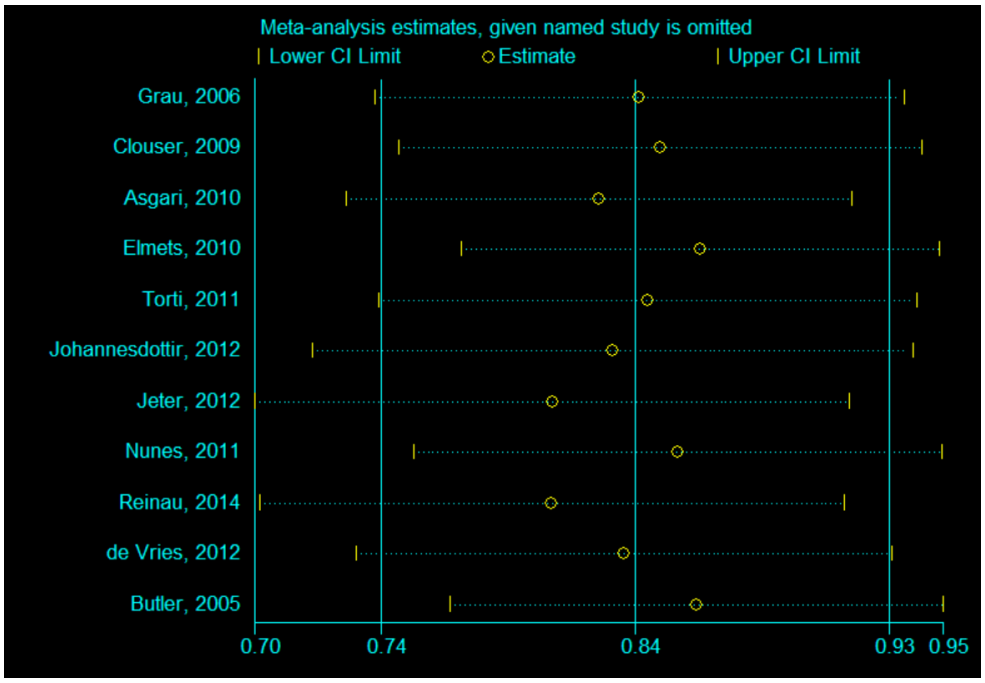

Figure 34. Sensitivity analysis depicting the influence of each single study on pooled effect estimate for NSAIDs use and risk of SCC.
CI - confidence interval.

ASA use and risk of SCC. An assessment of publication bias is not relevant for this case, as the number of studies is less than ten. Random effects model was selected, as significant heterogeneity ($p_{heterogeneity}$<0.05, I^2 = 60%) exists in included studies. The combined analysis of seven studies indicated that ASA use was associated with a significant decrease in the risk of SCC (RR 0.88, 95% CI 0.78-0.98, p <0.05). A forest plot depicting pooled and individual study effect estimates is shown in Figure 35.

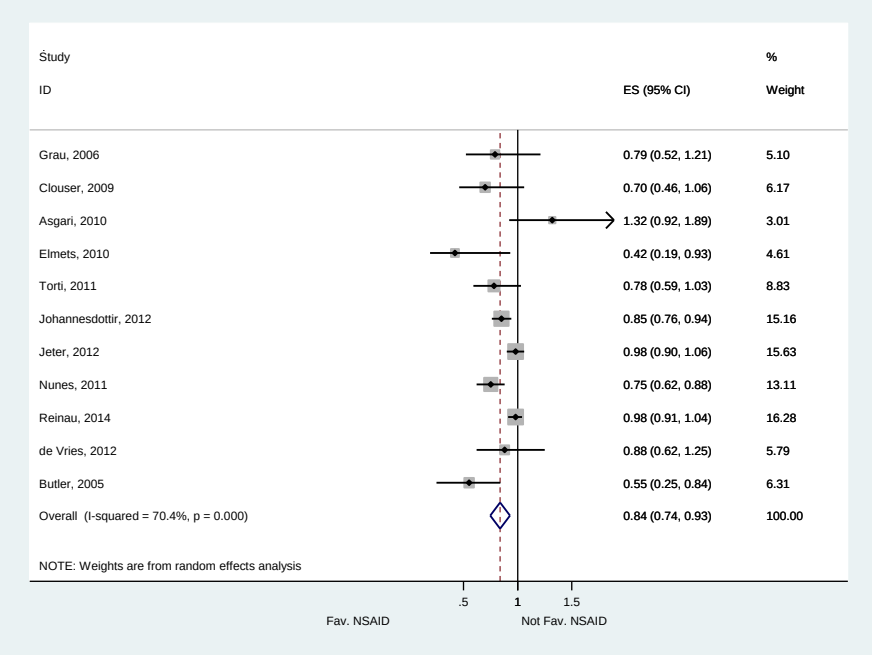

Figure 35. Forest plot depicting pooled and individual study effect estimates for use of aspirin and risk of SCC.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Sensitivity analysis - ASA use and risk of SCC. Overall, the results of the sensitivity analysis show that the pooled effect estimate is stable (Figure 36) and ranged from 0.85–0.91 across the sensitivity analysis.

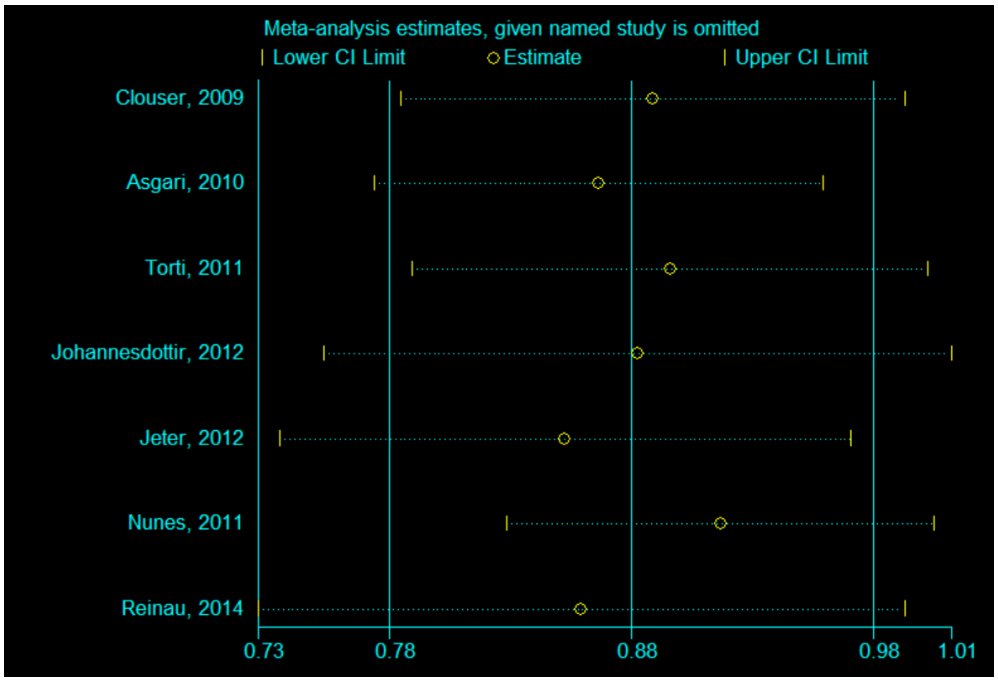

Figure 36. Sensitivity analysis depicting the influence of each single study on pooled effect estimate for aspirin use and risk of SCC.
CI - confidence interval.

Non-ASA NSAIDs use and risk of SCC. An assessment of publication bias is not relevant for this case, as the number of studies is less than ten. No significant heterogeneity ($p_{heterogeneity}>0.05$, $I^2 = 1\%$) was observed, so the fixed-effects model was considered. The combined analysis of five studies indicated that non-ASA NSAIDs use was associated with a significant decrease in the risk of SCC (RR 0.96, 95% CI 0.91-1.02). A forest plot depicting pooled and individual study effect estimates is shown in Figure 37.

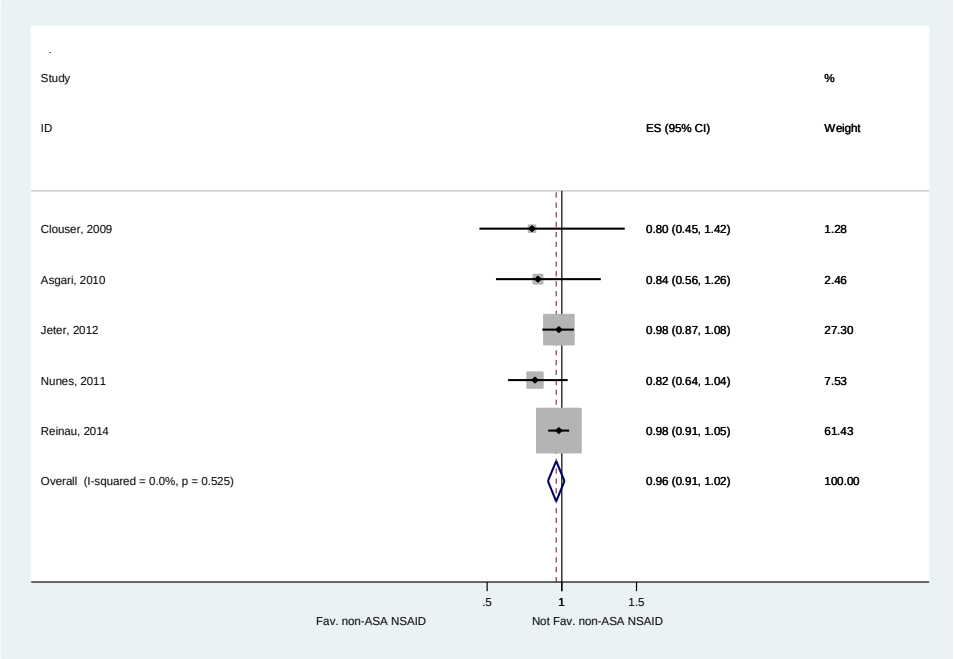

Figure 37. Forest plot depicting pooled and individual study effect estimates for use of non-aspirin NSAIDs and risk of SCC.
CI – confidence interval; ES - effect size; NSAID – Non-steroidal anti-inflammatory drug.

Sensitivity analysis - non-ASA NSAIDs and risk of SCC. Overall, the results of the sensitivity analysis show that the pooled effect estimate is stable (Figure 38) and ranged from 0.93–0.97 across the sensitivity analysis.

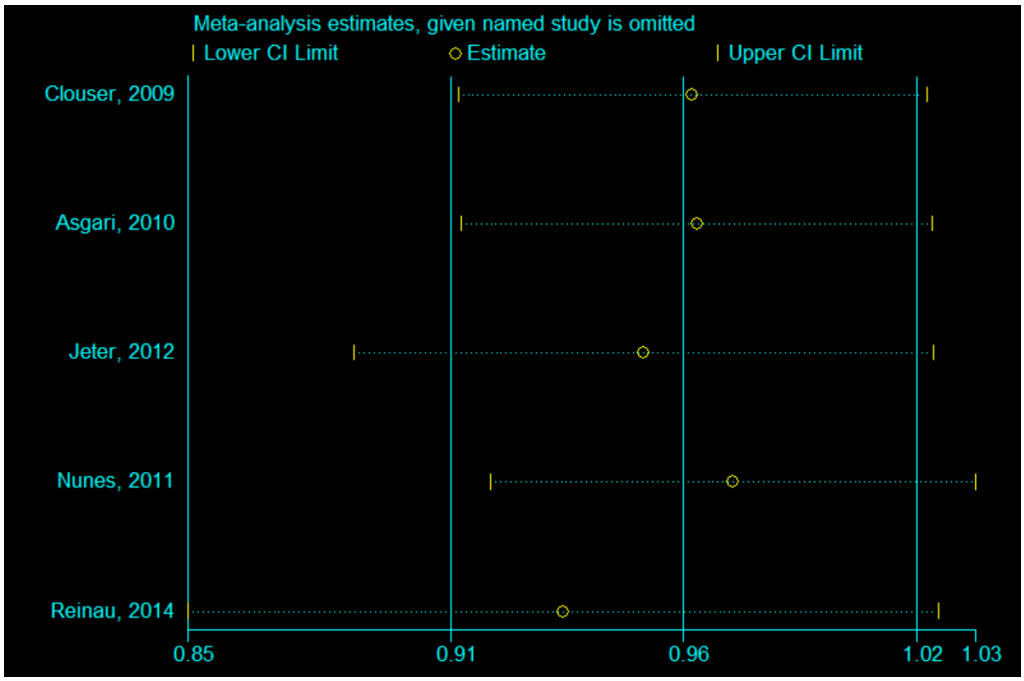

Figure 38. Sensitivity analysis depicting the influence of each single study on pooled effect estimate for non-aspirin NSAIDs use and risk of SCC.

CI - confidence interval.

Chapter 5: Discussion

Skin cancer, both melanoma and non-melanoma, poses huge financial burdens to society. The present study assessed the role of NSAIDs (both aspirin and non-aspirin NSAIDs) as chemoprevention agents for melanoma and non-melanoma skin cancer. And overview of the results is presented in Table 10. Meta-analysis of 14 studies showed that NSAIDs could have chemoprevention effects on melanoma skin cancer. A secondary analysis showed that aspirin alone possesses the chemoprevention effect. However, the non-aspirin NSAIDs do not. A similar trend is even observed for NSAIDs use and risk of non-melanoma (BCC and SCC) skin cancers.

Table 10

Overview of Results for NSAIDs Use and Risk of Skin Cancer

Drug	**Melanoma**		**BCC**		**SCC**	
	N	**RR (95% CI)**	**N**	**RR (95% CI)**	**n**	**RR (95% CI)**
NSAIDs	15	0.92 (0.85-0.99)	7	0.94 (0.89-0.99)	11	0.84 (0.74-0.93)
Aspirin	11	0.88 (0.78-0.97)	7	0.94 (0.89-0.99)	7	0.87 (0.77-0.97)
Non-Aspirin NSAIDs	9	0.96 (0.90-1.03)	5	0.92 (0.83-1.01)	5	0.96 (0.90-1.01)

The results of the present study are backed by mechanistic *invitro* and *invivo* studies (Goodman& Grossman, 2014). Evidence shows that NSAIDs, and in particular, aspirin, inhibits the cancer cell growth by affecting cell cycle control machinery (Block, 2005). However, the mechanism through which NSAIDs act as chemoprevention differs in different cancers. For example, in the case of colorectal cancer, NSAIDs target peroxisome proliferator-activated receptor δ (PPAR δ) and might show a chemoprevention effect (Chan et al., 2005). In the case of prostate cancer, NSAIDs inhibit anti-apoptotic kinase and thus show a chemoprevention effect (Vidal et al., 2015). NSAIDs induce cyclin-dependent kinase

inhibitor p27 and thus show a chemoprevention effect in lung cancer cases (McCormack et al.,2011).

The effect of NSAIDs chemoprevention on skin cancer could occur in two ways, including COX-dependent and COX-independent mechanisms. It is well known that the COX enzyme is abundantly present at inflammatory sites, and evidence shows that various forms of COX upregulates inflammation, hypoxia, and carcinogenesis (Block, 2005; Vane, Flower, & Botting, 1990). NSAIDs directly inhibit the production and/or action of COX enzymes and thus elicit COX-dependent chemoprevention effects (Block, 2005; Vane et al., 1990). The COX-dependent chemoprevention effect of NSAIDs is well recognized and presented in various animal studies (Zhang & Daaka, 2011; Jain, Chakraborty, Raja, Kale, & Kundu, 2008; Abrahao et al., 2010). However, there is no definitive evidence to suggest the COX-independent mechanism of chemoprevention effect of NSAIDs.

NSAIDs could also act through COX-independent mechanisms, including downregulation of EGF receptor signaling and inhibit the activation of NF-kB. This COX-independent mechanism could affect cell apoptosis, cancer cell adhesion, and metastasis and thus show chemoprevention effect (Pangburn, Ahnen, & Rice, 2010; Yamamoto, Yin, Lin, & Gaynor, 1999; Takada, Bhardwaj, Potdar, & Aggarwal, 2004).

Present study provides an up to date evidence compared to previously conducted meta-analysis in literature. Previous meta-analysis included a maximum of 13 studies. Therefore, lesser number of patients are included in pooled analyses. Lesser number of total patients represent lesser statistical power and lesser confidence on summary estimates. Results of the present study are in line with meta-analysis conducted by Muranushi et al., 2016, Muranushi et al., 2015 for non-melanoma skin cancer and Zhu et al., 2015 for

melanoma skin cancer (Muranushi et al., 2016; Muranushi et al., 2015; Zhu et al., 2015). Muranushi et al., 2016 included 11 studies to assess the risk of BCC in NSAID users and concluded that NSAIDs users could have reduced risk of BCC (Muranushi et al., 2016). Same research group in 2015 performed meta-analysis of 9 studies to assess the risk of SCC in NSAID users and concluded that NSAIDs users could have reduced risk of SCC (Muranushi et al., 2015).

Zhu et al., 2015 performed meta-analysis of 11 studies to assess the risk of melanoma and non-melanoma skin cancer in aspirin users and found that aspirin could have chemopreventive role (Zhu et al., 2015). Present study including 15 studies to assess the risk of melanoma skin cancer in NSAID users confirm that aspirin and non-aspirin NSAIDs have chemopreventive role in melanoma skin cancer. Present meta-analysis is the first to support the chemopreventive role of non-aspirin NSAIDs in melanoma skin cancer. Reason for observing the difference in results between the present meta-analysis and previous meta-analyses is that higher number of studies are included and several sub-groups analyses were performed to generate robust results.

Results of the present study should be considered carefully, as there is significant heterogeneity observed in terms of exposure assessment. It is difficult to assess and validate the NSAIDs use in large studies, making the evidence less robust. However, this bias is more common in most of the observational studies. The heterogeneity observed in the results of various analyses might be due to differences in study duration and duration of exposure to NSAIDs across the studies.

Chapter 6: Conclusion

In conclusion, it was found that use of NSAIDs (especially aspirin) could reduce the risk of melanoma and non-melanoma skin cancer. However, there is insufficient understanding of effective periods and dosing of NSAIDs as chemopreventive agents. Pharmacogenetic investigations may help to establish the individual NSAIDs risk-benefit ratio for specific subtypes of skin cancer and therefore allow tailoring of chemoprevention. Future research should be directed towards finding subcellular targets of NSAIDs action in skin cancer subtypes before venturing into large clinical studies.

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Appendix A: Supplementary Tables

Supplementary Table 1

Search strategy used to search in database, Medline (via Ovid) to assess risk of melanoma in NSAIDs users

S.No.	Search terms	Hits
1	Exp *MELANOMA/ or melanoma.mp.	116,569
2	(Malignant melanoma or malignant melanomas or melanoma or melanoma, malignant or melanomas or melanomas, malignant).mp.	118,121
3	Hutchinson's Melanotic Freckle.mp. or exp *Hutchinson's Melanotic Freckle/	608
4	Melanoma, Amelanotic.mp. or exp *Melanoma, Amelanotic/	550
5	1 or 2 or 3 or 4	118,282
6	(Adapalene or Adapalene, Benzoyl Peroxide Drug Combination or Ampyrone or Antipyrine or Apazone or Aspirin or Bufexamac or Clonixin or Diclofenac or Diflunisal or Dipyrone or Epirizole or Etanercept or Feprazone or Flurbiprofen or Ibuprofen or Indomethacin or Ketoprofen or Ketorolac or KetorolacTromethamine or MeclofenamicAcid or MefenamicAcid or Mesalamine or Naproxen or Niflumic Acid or Olopatadine Hydrochloride or Oxyphenbutazone or Phenylbutazone or Piroxicam or Salicylates or SodiumSalicylate or Sulfasalazine or Sulindac or Suprofen or Tolmetin).mp.	172,153
7	(Analgesics, anti-inflammatory or anti-inflammatory agents, nonsteroidal or anti-inflammatory agents, non-steroidal or anti-inflammatory analgesics or anti-inflammatory agents, nonsteroidal or anti-inflammatory agents, nonsteroidal or aspirin-like agents or aspirin-like agents or nsaids or nonsteroidalanti-inflammatory agents or nonsteroidal anti-inflammatory agents or nonsteroidal anti-inflammatory agents or nonsteroidal anti-inflammatory agents or nonsteroidal anti-inflammatory agents).mp.	69,237
8	exp *Anti-Inflammatory Agents, Non-Steroidal/	108,995
9	6 or 7 or 8	222,211
10	5 and 9	536

Supplementary Table 2

Search strategy used to search in database, Embase (via Embase.com) to assess risk of melanoma in NSAIDs users

S.No.	Search terms	Hits
#1	'amelanotic melanoma'/exp or 'choroid melanoma'/exp or 'cutaneous melanoma'/exp or 'desmoplastic melanoma'/exp or 'experimental melanoma'/exp or 'eye melanoma'/exp or 'malignant lentigo'/exp or 'metastatic melanoma'/exp or 'mucosal melanoma'/exp or 'superficial spreading melanoma'/exp	27,889
#2	'amelanotic melanoma' or 'choroid melanoma' or 'cutaneous melanoma' or 'desmoplastic melanoma' or 'experimental melanoma' or 'eye melanoma' or 'malignant lentigo' or 'metastatic melanoma' or 'mucosal melanoma' or 'superficial spreading melanoma'	33,018
#3	'melanoma'/exp OR melanoma	177,571
#4	#1 or #2 or #3	177,578
#5	'adapalene' or 'adapalene, benzoyl peroxide drug combination' or 'ampyrone' or 'antipyrine' or 'apazone' or 'aspirin' or 'bufexamac' or 'clonixin' or 'diclofenac' or 'diflunisal' or 'dipyrone' or 'epirizole' or 'etanercept' or 'feprazone' or 'flurbiprofen' or 'ibuprofen' or 'indomethacin' or 'ketoprofen' or 'ketorolac' or 'ketorolac tromethamine' or 'meclofenamic acid' or 'mefenamic acid' or 'mesalamine' or 'naproxen' or 'niflumic acid' or 'olopatadine hydrochloride' or 'oxyphenbutazone' or 'phenylbutazone' or 'piroxicam' or 'salicylates' or 'sodium salicylate' or 'sulfasalazine' or 'sulindac' or 'suprofen' or 'tolmetin'	307,417
#6	'nonsteroid anti-inflammatory agent'/exp or 'nonsteroid anti-inflammatory agent'	671,901
#7	'non-steroidal anti-inflammatory agent'	429
#8	#5 or #6 or #7	711,889
#9	#4 and #8	4,696

Supplementary Table 3

Search strategy used to search in database, Cochrane Library to assess risk of melanoma in NSAIDs users

S.No.	Search terms	Hits
#1	MeSH descriptor: [Melanoma] explode all trees	1,329
#2	'amelanotic melanoma' or 'choroid melanoma' or 'cutaneous melanoma' or 'desmoplastic melanoma' or 'experimental melanoma' or 'eye melanoma' or 'malignant lentigo' or 'metastatic melanoma' or 'mucosal melanoma' or 'superficial spreading melanoma' or 'malignant melanoma'	2,388
#3	#1 or #2	2,892
#4	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees	7,503
#5	‘adapalene or 'adapalene, benzoyl peroxide drug combination' or ampyrone or antipyrine or apazone or aspirin or bufexamac or clonixin or diclofenac or diflunisal or dipyrone or epirizole or etanercept or feprazone or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or 'ketorolac tromethamine' or 'meclofenamic acid' or 'mefenamic acid' or mesalamine or naproxen or 'niflumic acid' or 'olopatadine hydrochloride' or oxyphenbutazone or phenylbutazone or piroxicam or salicylates or 'sodium salicylate' or sulfasalazine or sulindac or suprofen or tolmetin	30,882
#6	'nonsteroidal anti-inflammatory agent' or 'nonsteroid anti-inflammatory agent'	3,834
#7	#4 or #5 or #6	34,905
#8	#3 and #7	86

Supplementary Table 4

Search strategy used to search in database, Medline (via Ovid) to assess risk of non-melanoma skin cancer in NSAIDs users

S.No.	Search terms	Hits
1	(non-melanoma skin cancer or non-melanoma skin cancer).mp.	3,230
2	squamous cell carcinoma.mp. or exp *Carcinoma, Squamous Cell/	119,023
3	(Carcinoma, epidermoid or carcinoma, planocellular or carcinoma, squamous or carcinoma, squamous cell or carcinomas, epidermoid or carcinomas, planocellular or carcinomas, squamous or carcinomas, squamous cell or epidermoid carcinoma or epidermoid carcinomas or planocellular carcinoma or planocellular carcinomas or squamous carcinoma or squamous carcinomas or squamous cell carcinoma or squamous cell carcinomas).mp.	148,824
4	Basal cell carcinoma.mp. or exp *Carcinoma, Basal Cell/	16,343
5	(basal cell carcinoma or basal cell carcinomas or basal cell epithelioma or basal cell epitheliomas or carcinoma, basal cell or carcinoma, basal cell, pigmented or carcinomas, basal cell or epithelioma, basal cell or epitheliomas, basal cell).mp.	20,126
6	1 or 2 or 3 or 4 or 5	164,369
7	(Adapalene or Adapalene, Benzoyl Peroxide Drug Combination or Ampyrone or Antipyrine or Apazone or Aspirin or Bufexamac or Clonixin or Diclofenac or Diflunisal or Dipyrone or Epirizole or Etanercept or Feprazone or Flurbiprofen or Ibuprofen or Indomethacin or Ketoprofen or Ketorolac or Ketorolac Tromethamine or Meclofenamic Acid or Mefenamic Acid or Mesalamine or Naproxen or Niflumic Acid or Olopatadine Hydrochloride or Oxyphenbutazone or Phenylbutazone or Piroxicam or Salicylates or SodiumSalicylate or Sulfasalazine or Sulindac or Suprofen or Tolmetin).mp.	172,153
8	(analgesics, anti-inflammatory or anti-inflammatory agents, nonsteroidal or anti-inflammatory agents, nonsteroidal or anti-inflammatory analgesics or anti-inflammatory agents, nonsteroidal or anti-inflammatory agents, nonsteroidal or aspirin like agents or aspirin-like agents or nsaids or nonsteroidal anti-inflammatory agents or nonsteroidal anti-inflammatory agents or nonsteroidal anti-inflammatory agents or nonsteroidal anti-inflammatory agents or nonsteroidal anti-inflammatory agents).mp.	69,237
9	exp *Anti-Inflammatory Agents, Non-Steroidal/	108,995
10	7 or 8 or 9	222,211
11	6 and 10	751

Supplementary Table 5

Search strategy used to search in database, Cochrane Library to assess risk of non-melanoma skin cancer in NSAIDs users

S.No.	Search terms	Hits
#1	‘squamous cell skin carcinoma’/exp	3,977
#2	‘Bowen disease’/exp	3,503
#3	‘squamous cell skin carcinoma’ or ‘Bowen disease’	4,047
#4	‘basal cell carcinoma’/exp	25,878
#5	‘nodular basal cell carcinoma’/exp	107
#6	‘superficial basal cell carcinoma’/exp	86
#7	‘basal cell carcinoma’ or ‘nodular basal cell carcinoma’ or ‘superficial basal cell carcinoma’	28,140
#8	‘skin squamous cell carcinoma’ or ‘basal cell epithelioma’ or ‘basal cell tumor’ or ‘basal cell tumour’ or ‘basal squamous carcinoma’ or ‘basalioma’ or ‘basaloid tumor’ or ‘basaloid tumour’ or ‘basaloma’ or ‘basalomaterebrans’ or ‘basocellular carcinoma’ or ‘basocellular epithelioma’ or ‘basosquamous carcinoma’ or ‘carcinoma, basal cell’ or ‘carcinoma, basosquamous’ or ‘carcinoma, basal cell’ or ‘epithelioma, basal cell’ or ‘neoplasms, basal cell’ or ‘skin carcinoma, basal cell type’	2,280
#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	31,355
#10	'adapalene' or 'adapalene, benzoyl peroxide drug combination' or 'ampyrone' or 'antipyrine' or 'apazone' or 'aspirin' or 'bufexamac' or 'clonixin' or 'diclofenac' or 'diflunisal' or 'dipyrone' or 'epirizole' or 'etanercept' or 'feprazone' or 'flurbiprofen' or 'ibuprofen' or 'indomethacin' or 'ketoprofen' or 'ketorolac' or 'ketorolac tromethamine' or 'meclofenamic acid' or 'mefenamic acid' or 'mesalamine' or 'naproxen' or 'niflumic acid' or 'olopatadine hydrochloride' or 'oxyphenbutazone' or 'phenylbutazone' or 'piroxicam' or 'salicylates' or 'sodium salicylate' or 'sulfasalazine' or 'sulindac' or 'suprofen' or 'tolmetin'	307,417
#11	'nonsteroid anti-inflammatory agent'/exp OR 'nonsteroid anti-inflammatory agent'	671,901
#12	'non-steroidal anti-inflammatory agent'	429
#13	#10 or #11 or #12	711,889
#14	#9 and #13	1,287

Supplementary Table 6

Search strategy used to search in database, Cochrane Library to assess risk of non-melanoma skin cancer in NSAIDs users

S.No.	Search terms	Hits
#1	MeSH descriptor: [Carcinoma, Basal Cell] explode all trees	263
#2	MeSH descriptor: [Carcinoma, Squamous Cell] explode all trees	2,532
#3	'non-melanoma skin cancer' or 'non-melanoma skin cancer'	782
#4	#1 or #2 or #3	3,439
#5	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees	7,503
#6	‘adapalene or 'adapalene, benzoyl peroxide drug combination' or ampyrone or antipyrine or apazone or aspirin or bufexamac or clonixin or diclofenac or diflunisal or dipyrone or epirizole or etanercept or feprazone or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or 'ketorolac tromethamine' or 'meclofenamic acid' or 'mefenamic acid' or mesalamine or naproxen or 'niflumic acid' or 'olopatadine hydrochloride' or oxyphenbutazone or phenylbutazone or piroxicam or salicylates or 'sodium salicylate' or sulfasalazine or sulindac or suprofen or tolmetin	30,882
#7	'non-steroidal anti-inflammatory agent' or 'nonsteroid anti-inflammatory agent'	3,834
#8	#5 or #6 or #7	34,905
#9	#3 and #8	89

Supplementary Table 7

Melanoma Dataset Used for Analysis

study	studydesign	studylocation	exposureassessment	qualityassessment	ee_asa	ll_asa	ul_asa	ee_nonasa	ll_nonasa	ul_nonasa	ee_any	ll_any	ul_any
Schreinemachers, 1994	Cohort	North America	Self-reported	Low	0.91	0.56	1.49				0.91	0.56	1.49
Harris, 2001	Case-control	North America	Database	Low							0.518	0.207	0.829
Friis, 2003	Cohort	Europe	Database	Medium	1.2	0.9	1.6				1.2	0.9	1.6
Sorensen, 2003	Cohort	Europe	Database	Medium				1	0.8	1.1	1	0.8	1.1
Jacobs, 2007	Cohort	North America	Self-reported	Medium	1.037	0.908	1.166				1.037	0.908	1.166
Asgari, 2008	Cohort	North America	Self-reported	Medium	1.1	0.76	1.58	1.22	0.75	1.99	1.12	0.84	1.48
Joosse, 2009	Case-control	Europe	Database	Medium	0.92	0.76	1.12	1.1	0.97	1.24	1.035	0.927	1.143
Jeter, 2011	Case-control	North America	Self-reported	Medium	0.584	0.308	1.107	0.854	0.431	1.693	0.661	0.324	0.999
Curiel-Lewandrowski, 2011	Case-control	North America	Database	Medium	0.72	0.55	0.94	0.92	0.7	1.19	0.73	0.56	0.96
Jeter, 2012	Cohort	North America	Self-reported	Low				0.936	0.777	1.095	1.045	0.911	1.178
Johannesdottir, 2012	Case-control	Europe	Database	Medium	0.89	0.76	1.03				0.87	0.8	0.95
Gamba, 2013	Cohort	North America	Self-reported	Medium	0.79	0.63	0.98	1.05	0.83	1.34	0.873	0.729	1.018
Shebl, 2014	Cohort	North America	Self-reported	Medium				0.8	0.69	0.93	0.8	0.69	0.93
Brasky, 2014	Cohort	North America	Self-reported	Medium	0.689	0.529	0.848	1.224	0.903	1.546	0.899	0.728	1.07
Cook, 2005	RCT	North America	Self-reported	Medium	0.97	0.7	1.36				0.97	0.7	1.36

Supplementary Table 8

Squamous Cell Carcinoma Dataset Used for Analysis

study	studydesign	studylocation	exposureassessment	qualityassessment	ee_asa_scc	ll_asa_scc	ul_asa_scc	ee_nonasa_scc	ll_nonasa_scc	ul_nonasa_scc	ee_any_scc	ll_any_scc	ul_any_scc
Grau, 2006	Case-control	North America	Self-reported	Medium							0.79	0.52	1.21
Clouser, 2009	Cohort	North America	Self-reported	High	0.71	0.41	1.22	0.8	0.45	1.42	0.7	0.46	1.06
Asgari, 2010	Case-control	North America	Self-reported	Medium	1.38	0.96	1.97	0.84	0.56	1.26	1.32	0.92	1.89
Elmets, 2010	RCT	North America	Self-reported	High							0.42	0.19	0.93
Torti, 2011	Case-control	North America	Self-reported	Medium	0.75	0.55	1.02				0.78	0.59	1.03
Johannesdottir, 2012	Case-control	Europe	Database	Medium	0.86	0.76	0.99				0.85	0.76	0.94
Jeter, 2012	Cohort	North America	Self-reported	Low	0.99	0.85	1.12	0.98	0.87	1.08	0.98	0.9	1.06
Nunes, 2011	Cohort	North America	Database	Medium	0.7	0.55	0.88	0.82	0.64	1.04	0.75	0.62	0.88
Reinau, 2014	Case-control	Europe	Database	Medium	0.94	0.87	1.01	0.98	0.91	1.05	0.98	0.91	1.04
de Vries, 2012	Case-control	Europe	Self-reported	Medium							0.88	0.62	1.25
Butler, 2005	Case-control	Australia	Self-reported	Medium							0.55	0.25	0.84

Supplementary Table 9

Basal Cell Carcinoma Dataset Used for Analysis

study	studydesign	studylocation	exposureassessment	qualityassessment	ee_asa_bcc	ll_asa_bcc	ul_asa_bcc	ee_nonasa_bcc	ll_nonasa_bcc	ul_nonasa_bcc	ee_any_bcc	ll_any_bcc	ul_any_bcc
Milan, 2003	Case-control	Europe	Self-reported	Medium							1.12	0.68	1.56
Grau, 2006	Case-control	North America	Self-reported	Medium							0.91	0.74	1.12
Vogel, 2007	Case-control	Europe	Self-reported	Medium							0.85	0.66	1.1
Clouser, 2009	Cohort	North America	Self-reported	High	0.64	0.38	1.06	0.6	0.34	1.06	0.64	0.38	1.06
Elmets, 2010	RCT	North America	Self-reported	High							0.4	0.18	0.93
Nunes, 2011	Cohort	North America	Database	Medium	0.73	0.61	0.88	0.66	0.54	0.8	0.73	0.61	0.88
Torti, 2011	Case-control	North America	Self-reported	Medium	0.81	0.59	1.12				0.91	0.69	1.21
Cahoon, 2011	Cohort	North America	Self-reported	Medium	0.97	0.9	1.04	1.03	0.96	1.1	0.91	0.8	1.02
Johannesdottir, 2012	Case-control	Europe	Database	Medium	0.97	0.91	1.02				0.97	0.93	1.01
Jeter, 2012	Cohort	North America	Self-reported	Low	0.99	0.95	1.02	1.02	0.99	1.06	0.98	0.95	1.02
de Vries, 2012	Case-control	Europe	Self-reported	Medium							0.72	0.53	0.97
Reinau, 2014	Case-control	North America	Database	Medium	0.99	0.95	1.02	0.96	0.92	1	1	0.98	1.03

Appendix B: STATA commands used for analysis

STATA commands used to assess NSAID and risk of melanoma

Main analysis

metan ee_any ll_any ul_any, random label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1)

Subgroup analysis

metafunnel ee_any se_any

metabias ee_any se_any, egger

metabias ee_any se_any, begg

Oneway sensitivity analysis

metaninf ee_any ll_any ul_any, random label (namevar=study)

Subgroup analysis

metan ee_any ll_any ul_any, random by (study design) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

metan ee_any ll_any ul_any, random by (studylocation) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

metan ee_any ll_any ul_any, random by (exposureassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

metan ee_any ll_any ul_any, random by (qualityassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

STATA commands used to assess aspirin and risk of melanoma

Main analysis

metan ee_asa ll_asa ul_asa, random label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1)

Subgroup analysis

metafunnel ee_asa se_asa

metabias ee_asa se_asa, egger

metabias ee_asa se_asa, begg

Oneway sensitivity analysis

metaninf ee_asa ll_asa ul_asa, random label (namevar=study)

Subgroup analysis

metan ee_asa ll_asa ul_asa, random by (studydesign) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

metan ee_asa ll_asa ul_asa, random by (studylocation) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

metan ee_asa ll_asa ul_asa, random by (exposureassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

metan ee_asa ll_asa ul_asa, random by (qualityassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

STATA commands used to assess non-aspirin NSAID and risk of melanoma

Main analysis

metan ee_nonasa ll_nonasa ul_nonasa, random label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1)

Subgroup analysis

metafunnel ee_nonasa se_nonasa

metabias ee_nonasa se_nonasa, egger

metabias ee_nonasa se_nonasa, begg

Oneway sensitivity analysis

metaninf ee_nonasa ll_nonasa ul_nonasa, random label (namevar=study)

Subgroup analysis

metan ee_nonasa ll_nonasa ul_nonasa, random by (studydesign) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall

metan ee_nonasa ll_nonasa ul_nonasa, random by (studylocation) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall

metan ee_nonasa ll_nonasa ul_nonasa, random by (exposureassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall

metan ee_nonasa ll_nonasa ul_nonasa, random by (qualityassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall

STATA commands used to assess NSAID and risk of BCC

Main analysis

metan ee_any_bcc ll_any_bcc ul_any_bcc, random label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1)

Subgroup analysis

metafunnel ee_any_bcc se_any_bcc

metabias ee_any_bcc se_any_bcc, egger

metabias ee_any_bcc se_any_bcc, begg

Oneway sensitivity analysis

metaninf ee_any_bcc ll_any_bcc ul_any_bcc, random label (namevar=study)

Subgroup analysis

metan ee_any_bcc ll_any_bcc ul_any_bcc, random by (studydesign) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

metan ee_any_bcc ll_any_bcc ul_any_bcc, random by (studylocation) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

metan ee_any_bcc ll_any_bcc ul_any_bcc, random by (exposureassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

metan ee_any_bcc ll_any_bcc ul_any_bcc, random by (qualityassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

STATA commands used to assess aspirin and risk of BCC

Main analysis

metan ee_asa_bcc ll_asa_bcc ul_asa_bcc, random label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1)

Subgroup analysis

metafunnel ee_asa_bcc se_asa_bcc

metabias ee_asa_bcc se_asa_bcc, egger

metabias ee_asa_bcc se_asa_bcc, begg

Oneway sensitivity analysis

metaninf ee_asa_bcc ll_asa_bcc ul_asa_bcc, random label (namevar=study)

Subgroup analysis

metan ee_asa_bcc ll_asa_bcc ul_asa_bcc, random by (studydesign) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

metan ee_asa_bcc ll_asa_bcc ul_asa_bcc, random by (studylocation) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

metan ee_asa_bcc ll_asa_bcc ul_asa_bcc, random by (exposureassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

metan ee_asa_bcc ll_asa_bcc ul_asa_bcc, random by (qualityassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

STATA commands used to assess non-aspirin NSAID and risk of BCC

Main analysis

metan ee_nonasa_bcc ll_nonasa_bcc ul_nonasa_bcc, random label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1)

Subgroup analysis

metafunnel ee_nonasa_bcc se_nonasa_bcc

metabias ee_nonasa_bcc se_nonasa_bcc, egger

metabias ee_nonasa_bcc se_nonasa_bcc, begg

Oneway sensitivity analysis

metaninf ee_nonasa_bcc ll_nonasa_bcc ul_nonasa_bcc, random label (namevar=study)

Subgroup analysis

metan ee_nonasa_bcc ll_nonasa_bcc ul_nonasa_bcc, random by (studydesign) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall

metan ee_nonasa_bcc ll_nonasa_bcc ul_nonasa_bcc, random by (studylocation) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall

metan ee_nonasa_bcc ll_nonasa_bcc ul_nonasa_bcc, random by (exposureassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall

metan ee_nonasa_bcc ll_nonasa_bcc ul_nonasa_bcc, random by (qualityassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall

STATA commands used to assess NSAID and risk of SCC

Main analysis

metan ee_any_scc ll_any_scc ul_any_scc, random label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1)

Subgroup analysis

metafunnel ee_any_scc se_any_scc

metabias ee_any_scc se_any_scc, egger

metabias ee_any_scc se_any_scc, begg

Oneway sensitivity analysis

metaninf ee_any_scc ll_any_scc ul_any_scc, random label (namevar=study)

Subgroup analysis

metan ee_any_scc ll_any_scc ul_any_scc, random by (studydesign) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

metan ee_any_scc ll_any_scc ul_any_scc, random by (studylocation) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

metan ee_any_scc ll_any_scc ul_any_scc, random by (exposureassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

metan ee_any_scc ll_any_scc ul_any_scc, random by (qualityassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. NSAID #Not Fav. NSAID) null (1) nooverall

STATA commands used to assess aspirin and risk of SCC

Main analysis

metan ee_asa_scc ll_asa_scc ul_asa_scc, random label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1)

Subgroup analysis

metafunnel ee_asa_scc se_asa_scc

metabias ee_asa_scc se_asa_scc, egger

metabias ee_asa_scc se_asa_scc, begg

Oneway sensitivity analysis

metaninf ee_asa_scc ll_asa_scc ul_asa_scc, random label (namevar=study)

Subgroup analysis

metan ee_asa_scc ll_asa_scc ul_asa_scc, random by (studydesign) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

metan ee_asa_scc ll_asa_scc ul_asa_scc, random by (studylocation) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

metan ee_asa_scc ll_asa_scc ul_asa_scc, random by (exposureassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

metan ee_asa_scc ll_asa_scc ul_asa_scc, random by (qualityassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. Aspirin #Not Fav. Aspirin) null (1) nooverall

STATA commands used to assess non-aspirin NSAID and risk of SCC

Main analysis

metan ee_nonasa_scc ll_nonasa_scc ul_nonasa_scc, random label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1)

Subgroup analysis

metafunnel ee_nonasa_scc se_nonasa_scc

metabias ee_nonasa_scc se_nonasa_scc, egger

metabias ee_nonasa_scc se_nonasa_scc, begg

Oneway sensitivity analysis

metaninf ee_nonasa_scc ll_nonasa_scc ul_nonasa_scc, random label (namevar=study)

Subgroup analysis

metan ee_nonasa_scc ll_nonasa_scc ul_nonasa_scc, random by (studydesign) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall

metan ee_nonasa_scc ll_nonasa_scc ul_nonasa_scc, random by (studylocation) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall

metan ee_nonasa_scc ll_nonasa_scc ul_nonasa_scc, random by (exposureassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall

metan ee_nonasa_scc ll_nonasa_scc ul_nonasa_scc, random by (qualityassessment) label (namevar=study) xlabel (0.5,1,1.5) favours (Fav. non-ASA NSAID #Not Fav. non-ASA NSAID) null (1) nooverall