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REVIEW ARTICLE

Non-steroidal anti-inflammatory drug and aspirin use and the risk of head and neck cancer: a systematic review

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Abstract
Background Use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with a reduced risk of several cancers. This is thought to be through the inhibitory action on the cyclooxygenase (COX) enzyme, COX-2. Evidence for NSAIDs preventing head and neck cancer (HNC) is conflicting. We conducted a systematic literature review to investigate the association between NSAID/aspirin use and risk of head and neck cancer (HNC).
Methodology MEDLINE, EMBASE, PubMed, Cochrane Library, and Web of Science were systematically searched using terms for NSAIDs/aspirin, HNC, and observational/intervention study designs to identify studies published by December 2009.
Results Of 9,268 articles identified, two population-based prescribing database studies and three case–control studies met the selection criteria. The studies investigated different HNC sites. Only one study found a significant protective association of aspirin use with HNC risk (OR 0.75, 95% CI 0.58–0.96), and one showed a significantly increased risk of oral/oropharyngeal cancer with non-low-dose aspirin NSAID use (OR 3.5, 95% CI 1.8–6.7). Many of the studies identified lacked information on important confounding factors.
Conclusion No definitive conclusion on the effect of NSAIDs/aspirin on HNC risk was possible. Aspirin may protect against HNC, although further robust large-scale studies are required to clarify any possible association.

Keywords Head and neck cancer · Non-steroidal anti-inflammatory drugs · Aspirin · Systematic review · COX-2

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Introduction

Each year, over 600,000 individuals worldwide are diagnosed with head and neck cancer (HNC) [1]. There are two predominant independent risk factors for HNC, namely tobacco use and excessive alcohol consumption [1–3]. These have a synergistic effect [3]. Other potential risk factors include genetic susceptibility, poor oral health, low intake of fruit and vegetables, environmental carcinogens, and infection with human papilloma virus [3–6]. HNC is accompanied by high levels of morbidity and mortality, with 5-year survival rates generally low (approximately 30–50%) [3]. The identification of factors that may reduce HNC risk is therefore important.

Experimental tumor model studies show that non-steroidal anti-inflammatory drugs (NSAIDs) impair the growth and development of head and neck SCC, indicating potential as a chemopreventive agent [7–11]. Furthermore, regular use of NSAIDs and aspirin has been shown to reduce the risk of other cancers, particularly colorectal cancer [12–14]. Biologically, NSAIDs act as non-specific inhibitors for the pro-inflammatory cyclooxygenase enzymes (COX-1 and COX-2), which are involved in the synthesis of arachidonic acid (AA) to prostaglandins (PG). COX-1 is present in most tissues and is involved in the production of PGs required for many normal physiological functions, while

COX-2 is found only in a limited number of cell types and is induced by stimulatory factors implicated with inflammation and many cancers [15]. Over-expression of COX-2 and PGs have been reported in a variety of cancer sites, including head and neck squamous cell carcinoma (SCC) [16–19], with increased levels reported in both tumor tissue and adjacent epithelial in HNSCC but not normal epithelium [17]. Studies also suggest a correlation between COX-2 expression and head and neck tumor size and prognosis, with higher expression correlating with poorer outcome [16, 20]. The downstream actions of PGs, such as increased cell proliferation, cell mobility and invasion, neo-angiogenesis, and the inhibition of apoptosis, are known to play important roles in cancer development [7, 15, 18]. The mechanism by which NSAIDs inhibit tumor development is not clearly understood, although it is thought that they may act through the inhibition of COX-2 and consequently the synthesis of PGs and their pro-cancerous downstream effects [7].

Existing epidemiological studies investigating the association between NSAIDs and HNC are sparse and conflicting. This systematic review identifies and assesses the relevant studies investigating the effect of aspirin and non-aspirin NSAIDs on HNC risk.

Materials and methods

Study selection

Literature searches were conducted using Ovid MEDLINE (US National Library of Medicine, Bethesda, MD, USA), EMBASE (Reed Elsevier PLC, Amsterdam, The Netherlands), Cochrane Library (Wiley InterScience, John Wiley & Sons, Inc.), PubMed (US National Library of Medicine and the National Institutes of Health, Bethesda, MD, USA), and the Web of Science (Thomson Reuters). The searches were limited to human studies published by December 2009 and excluded review articles. No language restriction was imposed. The searches covered three discrete dimensions:

1. Cancer terms (including an 'overarching' cancer term and terms for HNC) and specific head and neck cancer sites taken from the corresponding ICD codes (C00–C14).
2. NSAID terms, including specific NSAID types.
3. Observational and interventional study designs.

Two independent reviewers screened articles on title and abstract and then on full text. Articles were included if they met all the inclusion criteria: (1) study design was an observational study (a case–control or cohort study) or an interventional study (randomized controlled trial (RCT)); (2) the study evaluated exposure to any NSAID or aspirin or combination of NSAIDs/aspirin; (3) incidence of HNC was reported; and (4) a relative risk or odds ratios (ORs) with 95% confidence intervals (CI), or sufficient data to permit their calculation, was reported. Reference lists of included articles were examined to identify other relevant studies. Final identified papers were independently screened by three reviewers (JCW, CH, and LM) to ensure that all criteria were met. Discrepancies were resolved by discussion.

Data extraction

Information regarding study design, year, population, case numbers, comparison group, study duration, exposure, duration and frequency of use, dose, classification of NSAID/aspirin use (e.g., never/ever use), exposure ascertainment, HNC site, ascertainment of diagnosis, risk measurement, and confounders adjusted for was extracted from the articles.

Unadjusted ORs were calculated for studies only reporting adjusted results to examine whether the adjustment for confounders significantly altered the observed OR.

Results

Included studies

After omitting duplicates, 9,268 articles were identified, as shown in Fig. 1. Six papers met all criteria (one after communication with the author to obtain 95% CI). Papers by

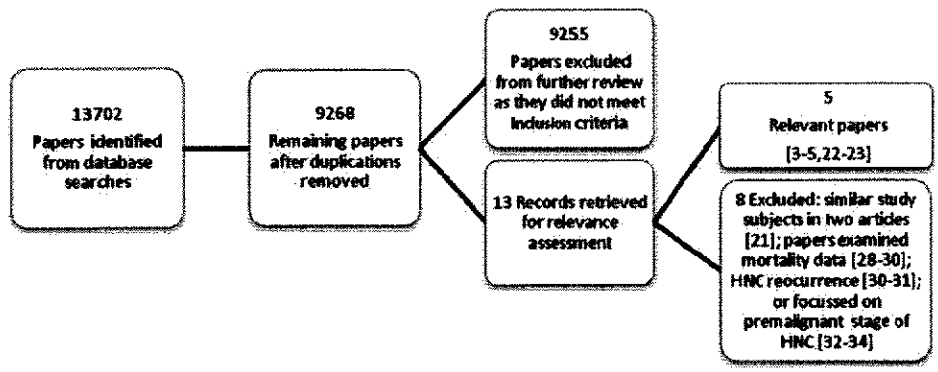

Fig. 1 Flow diagram describing the process of paper selection

Table 1 Design characteristics of the 5 studies meeting the inclusion criteria

Author (Year)	Design	Study period	Study population	Exposure source	Source of cancer diagnosis	Classification of use	Dose	Duration of drug use/ frequency of use
Friis (2006)	Population-based prescribing database studies	1991–2002	North Jutland County, Denmark	Prescription database	Danish Cancer Registry	Prescriptions/No prescriptions during study period	N/A	Prescriptions
Friis (2003)	Population-based prescribing database studies	1989–1995	North Jutland County, Denmark	Prescription database	Danish Cancer Registry	Prescriptions/No prescriptions during study period	Low-dose aspirin (70, 100, 150 mg)	Prescriptions
Jayaprakash (2006)	Hospital-based Case –control	1982–1998	Roswell Park Cancer Institute (RPCI), Buffalo, NY	Self administered questionnaire	RPCI tumor registry and diagnostic index	Ever/Never used	N/A	Number of aspirin/wk and duration of use.
Bosetti (2003)	3 Hospital-Based Case–control	1992–2000	3 Populations in Italy	Interview administered questionnaire	Does not mention	Regular users/Never users	N/A	Regular use (1/weeks–6 months)/Duration of use/Time since first use
Rosenquist (2005)	Case–control	2000–2004	Southern Health care region of Sweden	Standardized Interview; Same interviewer	Hospital diagnosis	Ever/Never use	Low-dose aspirin-75–150 mg/Day N/A for NSAID	N/A

Sørensen et al. [21] and Friis et al. [22] showed similar study populations, methodologies, exposure variables, and apparent overlap of outcome measures. Only the Friis et al.'s [22] study was included as it provided a better measurement of risk, stating standardized rate ratios (SRR).

The study characteristics reported in Table 1 included two large-scale prescribing database studies [4, 22] and three smaller case–control studies [3, 5, 23]. No RCTs were identified. Aside from the North American study by Jayaprakash et al. [3], all were European based (Denmark, Italy, and Sweden). Given the limited number and heterogeneity of the studies identified, no meta-analysis was conducted.

Study design

Prescribing database studies

Both Friis et al.'s studies [4, 22] used drug-dispensing information from the Pharmaco-Epidemiological Prescription Database, North Jutland County, Denmark. Information on prescription medications dispensed since 1991 was linked to the Danish Cancer Registry. Friis et al. [4] calculated the standardized incidence ratio (SIR) of HNC according to first-dispensed low-dose aspirin prescription, compared with the number of expected HNC cases within the North Jutland County population. Friis et al. [22] calculated the standardized rate ratio (SRR) for HNC of non-aspirin NSAID users (defined as having obtained $\geq$2 prescriptions) compared with non-users (no NSAID prescriptions) within the identified study population. Average follow-up was 4.1 and 5.8 years for Friis et al. [4, 22], respectively.

Case–control studies

The remaining studies utilized a case–control study design. The studies by Jayaprakash et al. [3] and Bosetti et al. [5] were hospital based, utilizing hospital controls with various non-malignant/benign diagnoses. Rosenquist et al. [23] conducted a population-based study in Sweden using incident cases of oral and oropharyngeal squamous cell carcinoma and controls (individuals with no previous history of cancer, identified by stratified randomized sampling of the Swedish Population Registry).

Questionnaires and standardized interviews were used to obtain information on NSAID/non-aspirin NSAID exposure. Rosenquist et al. [23] and Bosetti et al. [5] employed interviewer-standardized interviews. Jayaprakash et al. [3] used a self-administered questionnaire. Response rates for both cases and controls were high in the Bosetti et al.'s [5] and Rosenquist et al.'s [23] studies (>95 and 80%, respectively). The Jayaprakash et al.'s [3] study had approximately a 50% response rate; information regarding response rates within cases and controls was not reported.

Drug use

Of the prescribing database studies, Friis et al. [4] examined low-dose aspirin use (defined as 70, 100, 150 mg) and Friis et al. [22] investigated non-aspirin NSAID use; no dosage or information on NSAID type was provided.

All three case–control studies examined aspirin use [3, 5, 23]. Bosetti et al. [5] noted that regular use was primarily for cardiovascular prevention (72%); stratification by indication of use was not conducted. Rosenquist et al. [23] separately investigated low-dose aspirin (75–150 mg/day use) and other aspirin NSAID use. Information on non-low-dose aspirin NSAID dose or specific NSAID type use was not stated. Jayaprakash et al. [3] did not state dosage.

Reported results

There was heterogeneity in the HNC sites reported by the five studies, as shown in Table 2. The risk ratios are displayed in a forest plot, as shown in Fig. 2. Bosetti et al. [5] reported adjusted results for oral, pharyngeal, esophageal, and laryngeal cancer sites combined. After communication with the author, unadjusted results for oral, pharyngeal, and laryngeal cancer sites combined were provided, as reported.

Prescribing database studies

Neither prescribing database study found a protective association with NSAID usage. For low-dose aspirin, Friis et al. [4] reported SIRs of 1.2 (95% CI 0.8–1.7) and 1.4 (95% CI 0.8–2.3) for the 'buccal cavity and pharynx' and 'larynx', respectively. Friis et al. [22] reported a SRR of 1.2 (95% CI 1.0–1.6) for non-aspirin NSAID use and oral cavity cancer risk.

Case–control studies

The updated results from Bosetti et al. [5] found no significant association between aspirin use and HNC, OR 0.86 (95% CI 0.46–1.61). Rosenquist et al. [23] observed no protective association with low-dose aspirin use, OR 1.0 (95% CI 0.6–1.7). However, a significant increased risk of oral and oropharyngeal squamous cell carcinoma associated with NSAID use was observed, OR 3.5 (95% CI 1.8–6.7). Jayaprakash et al. [3] reported a significant protective association of aspirin on overall HNC risk, adjusted odds ratio (OR) 0.75 (95% CI 0.58–0.96). In subsite-specific analyses, although all AORs were below 1.0, none was significant (Table 2).

Frequency/duration of use

Several studies [3, 5, 22] attempted to examine frequency and/or duration of aspirin/NSAID use with respect to HNC risk. Friis et al. [22] reported a significant increased risk of HNC with increased number of NSAID prescriptions dispensed, SRR 1.3 (95% CI 1.0–1.6). Bosetti et al.'s [5] updated results reported a significant reduction in HNC risk with increased duration of use (≥5 years), OR 0.21 (95% CI 0.05–0.85), compared to non-users. Numbers in these subgroup analyses were small. No protective association was observed with <5 years of use in either category. Jayaprakash et al. [3] observed no apparent association between frequency of aspirin use and overall HNC risk. However, a significant trend with duration of use was reported (p_{trend} 0.005); the categorical analyses reported significant risk reductions with >10 years of use.

Confounding/effect modification

All studies adjusted the analyses for age and gender.

Prescribing database studies

The Friis et al.'s [22] study attempted to indirectly control for smoking through the separate analysis of those hospitalized/not hospitalized with chronic obstructive pulmonary disease (COPD), assuming that those with COPD were smokers. No significant associations were observed in the COPD group. Friis et al. [22] tried to control for confounding by indication by excluding person-time between first and second NSAID prescription.

Case–control studies

All retrospective studies adjusted for the two independent risk factors for HNC, alcohol and tobacco use. Jayaprakash et al. [3] attempted to examine whether increasing alcohol and tobacco use altered the effect of aspirin use. They reported a protective association in moderate smokers and drinkers only, AOR 0.67 (95% CI 0.50–0.91). The unadjusted results for Jayaprakash et al. [3], OR 0.76 (95% CI 0.59–0.97), and Rosenquist et al. [23], OR 3.8 (95% CI 2.1–6.9), were similar to the adjusted models, as shown in Table 2.

Unlike Jayaprakash et al. [3] who asked only for information on aspirin usage before the onset of illness, studies by Bosetti et al. [5] and Rosenquist et al. [23] did not account for possible confounding by indication and collected information on NSAID/aspirin usage up to the interview date.

Discussion

To the best of our knowledge, this is the first systematic review to investigate the association between aspirin and/or non-aspirin NSAID use and the risk of HNCs. The review

Table 2 Results from the 5 studies meeting the inclusion criteria

Author (Year)	Exposure	Comparison group/no. of controls	HNC sites	No. of cases	Overall risk measurement	Confounders included in adjusted estimates
Friis (2006)	NSAIDs	Non-cases	Oral cancer (Month and tongue)	Non-users: 110 Users: 75	SRR = 1.2 (95% CI 1.0–1.6)	Tobacco indirectly, age, sex
Friis (2003)	Aspirin	# Expected cancer cases	Buccal cavity and pharynx	32	SIR = 1.3 (95% CI 0.9–1.7)	Age, sex
			Larynx	16	SIR = 1.5 (95% CI 0.9–2.4)	
Jayaprakash (2006)	Aspirin	Never used: 208;	Combined sites	Never used: 244	AOR = 0.75 (95% CI 0.58–0.96)	Age, sex, packs of cigarettes per day, alcoholic drink per week
		Ever used: 321	Separate sites	Ever used: 285	Separate sites	
			Nasopharynx		AOR = 0.88 (95% CI 0.36–2.15)	
			Hypopharynx		AOR = 0.77 (95% CI 0.35–1.66)	
			Larynx		AOR = 0.89 (95% CI 0.58–1.35)	
			Oropharynx		AOR = 0.68 (95% CI 0.44–1.05)	
			Oral cavity		AOR = 0.73 (95% CI 0.51–1.05)	
Bosetti (2003)	Aspirin	Non-users: 1033; Regular users: 38	Combined Oral, Pharynx, and larynx (esophageal excluded)	Non-users: 716; Regular users: 24	AOR = 0.86* (95% CI 0.46–1.61)	Sex, age, center, education, tobacco smoking and alcohol drinking
Rosenquist (2005)	Low-dose aspirin	Non-users = 260	Oral and oropharyngeal	Non-users: 107	OR = 1.0* (95% CI 0.6–1.7)	Did adjust for potential confounders-mentions tobacco, alcohol
		Users = 60		Users: 25	OR 3.5 (95% CI 1.8–6.7)	
	Non-low-dose aspirin NSAIDs	Non-users: 298		Non-users: 103		
		Users: 22		Users: 29		

NSAIDs non-steroidal anti-inflammatory drugs, *OR* odds ratio, *AOR* Adjusted odds ratio, *SRR* standardized risk ratio, *SIR* standardized incidence rate

* Not reported in article—calculated from figures available or requested from author

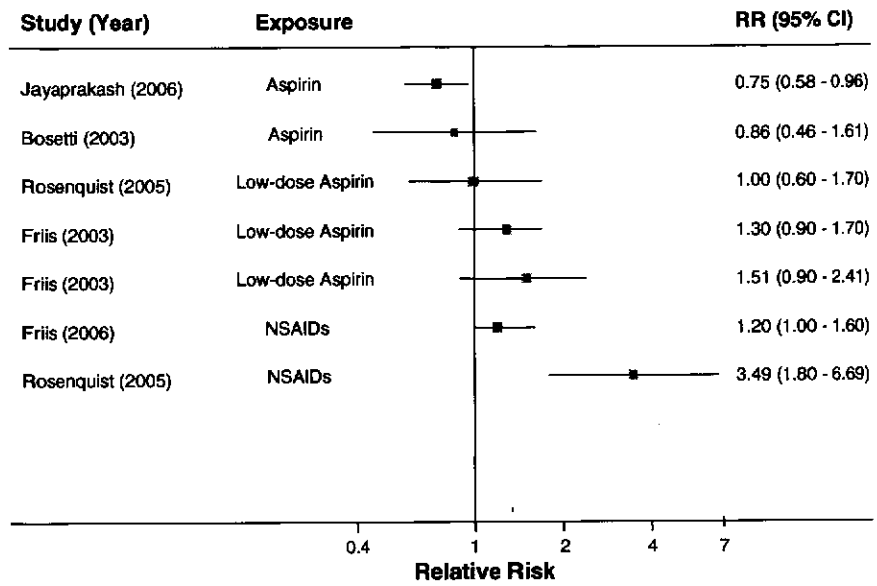

Fig. 2 Forest plot of included studies

confirmed a paucity of studies in the area and heterogeneity among those which exist. No RCTs have been conducted. Of the observational studies identified, two were population-based prescription database studies, Friis et al. [4, 22], and three case–control studies, [3, 5, 23]. Both prescribing database studies [4, 22], and two of the case–control studies [5, 23], found no overall protective association for HNC with aspirin, low-dose aspirin, or other NSAID use. One case–control study [3] found a significant 25% reduced risk of HNC in ever aspirin users compared to non-users, but had poor response rates and utilized hospital controls. A significant reduction in risk with prolonged aspirin use was also observed in two case–control studies [3, 5], suggesting that long-term aspirin use may reduce HNC risk. However, one study did find a significant increased risk of oral and oropharyngeal squamous cell carcinoma with NSAID use [23].

In the Jayaprakash et al. [3] study, only controls admitted for acute, non-neoplastic conditions were recruited and may not be representative of the population. However, the characteristics of the case/control groups were reported as comparable to that of the general population [3]. There is an argument also that hospital controls may be more likely to recall past medication use, potentially reducing recall bias between the case and control groups [24]. Overall response rates were low (approximately 50%) and individual response rates for HNC cases and controls were unavailable, potentially introducing bias.

The huge risk reduction observed by Bosetti et al. [5] with increased duration and age since first use is startling and clearly needs further investigation. However, the results should be interpreted with caution as there were limited numbers in the stratified analyses (<10 cases/<25 controls in both groups).

Consistent with previous studies investigating aspirin use and other cancer sites [9, 10, 25, 26], no association was observed with low-dose aspirin [4, 23]. A protective association was reported in two studies with unspecified aspirin dosage [3, 5]. In the original Bosetti et al.'s [5] study, over 70% of cases and 50% of controls regularly took aspirin for cardiovascular disease prevention, which is likely to be low-dose aspirin and could explain the observed overall non-significant risk reduction. However, the percentage of HNC cases taking aspirin for cardiovascular disease prevention only is uncertain as information on indication of use was only available for all cases including cases with esophageal cancer.

All retrospective case–control studies controlled for confounding of the major risk factors, alcohol and smoking. Calculating unadjusted estimates showed little change in the reported OR. Although Friis et al. [22] attempted to indirectly control for smoking in one of the prescription database studies, the method used was not ideal, as it is possible that the non-COPD hospitalized subgroup included smokers. Neither prescription database study [4, 22] collected information on over-the-counter (OTC) use or prescription adherence, both possible confounders.

Rosenquist et al. [23] observed a significant increase in oropharyngeal squamous cell carcinoma with non-low-dose aspirin NSAID use (OR = 3.5). However, the authors thought this likely to be a result of a spurious association from 'self-medication due to early symptoms of oropharyngeal squamous cell carcinoma' [23]. Confounding by indication can be problematic in pharmacoepidemiological studies. Only two studies [3, 22] took account of this in the study design. Bosetti et al. [5] argued that the presence of an inverse association with longer use negates the possibility of this confounding in their study.

The strengths of this review are that no language or place of publishing restrictions were applied, multiple databases were searched thus reducing the possibility of publication bias (confirmed by the identification of studies reporting little and negative effects from aspirin and non-aspirin NSAID use), and study authors were approached to obtain necessary unpublished information. However, the small numbers and heterogeneity of the studies, particularly the differing HNC sites investigated, precluded a meta-analysis of the data.

On the basis of this review, no definitive conclusion can be reached on NSAID/aspirin use and HNC risk. The review found some evidence to suggest an inverse association between aspirin use and HNC risk, particularly with prolonged use. Studies investigating the use of aspirin/NSAIDs and the associated risk of HNC were limited by either potential bias in the study group selection, lack of information on OTC use, from confounding by indication, or a lack of vital information. Nevertheless, experimental studies [15, 27] support a protective association for aspirin and NSAIDs against the development and progression of cancer and further work in regard to HNC risk is needed, bearing in mind higher doses of aspirin can result in gastrointestinal bleeding and ulceration due to the inhibition of COX-1. Future HNC studies in this area require more robust study design, including adequate measures of exposure and outcome. Sufficient information on important confounding factors such as smoking and alcohol use is also essential.

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