Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study

J Sudbø, J J Lee, S M Lippman, J Mork, S Sagen, N Flatner, A Ristimäki, A Sudbø, L Mao, X Zhou, W Kildal, J F Evensen, A Reith, A J Dannenberg

Summary

Background Non-steroidal anti-inflammatory drugs (NSAIDs) seem to prevent several types of cancer, but could increase the risk of cardiovascular complications. We investigated whether use of NSAIDs was associated with a change in the incidence of oral cancer or overall or cardiovascular mortality.

Methods We undertook a nested case-control study to analyse data from a population-based database (Cohort of Norway; CONOR), which consisted of prospectively obtained health data from all regions of Norway. People with oral cancer were identified from the 9241 individuals in CONOR who were at increased risk of oral cancer because of heavy smoking (≥15 pack-years), and matched controls were selected from the remaining heavy smokers (who did not have cancer).

Findings We identified and analysed 454 (5%) people with oral cancer (279 men, 175 women; mean [SD] age at diagnosis 63·3 [13·2] years) and 454 matched controls (n=908); 263 (29%) had used NSAIDs, 83 (9%) had used paracetamol (for a minimum of 6 months), and 562 (62%) had used neither drug. NSAID use (but not paracetamol use) was associated with a reduced risk of oral cancer (including in active smokers; hazard ratio 0·47, 95% CI 0·37–0·60, $p<0·0001$). Smoking cessation also lowered the risk of oral cancer (0·41, 0·32–0·52, $p<0·0001$). Additionally, long-term use of NSAIDs (but not paracetamol) was associated with an increased risk of cardiovascular-disease-related death (2·06, 1·34–3·18, p=0·001). NSAID use did not significantly reduce overall mortality (p=0·17).

Interpretation Long-term use of NSAIDs is associated with a reduced incidence of oral cancer (including in active smokers), but also with an increased risk of death due to cardiovascular disease. These findings highlight the need for a careful risk-benefit analysis when the long-term use of NSAIDs is considered.

Lancet 2005; 366: 1359–66

Published online October [illegible] 2005
DOI:10.1016/S0140-6736(05)67488-0

Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway (J Sudbø MD); **Department of Biostatistics and Applied Mathematics, University of Texas, MD Anderson Cancer Center, Houston, TX, USA** (Prof J J Lee PhD, X Zhou MSc); **Department of Thoracic/Head and Neck Medical Oncology** (Prof S M Lippman MD, Prof L Mao MD) **and Department of Clinical Cancer Prevention** (Prof S M Lippman), **University of Texas, MD Anderson Cancer Center, Houston, TX, USA; The National Hospital and The Norwegian Cancer Registry, Oslo, Norway** (J Mork MD); **Research Foundation of The Norwegian Radium Hospital, Montebello, Norway** (S Sagen MPH); **Division of Cytology, Department of Pathology, The Norwegian Radium Hospital, Montebello, Norway** (Prof A Reith MD, N Flatner DDS); **Department of Medical Informatics, The Norwegian Radium Hospital, Montebello, Oslo, Norway** (W Kildal MSc); **Department of Pathology, Helsinki University Central Hospital, and Molecular and Cancer Biology Research Programme, Biomedicum Helsinki, University of Helsinki, Helsinki, Finland** (A Ristimäki MD); **Department of Physics, Norwegian University of Science and Technology, Trondheim, Norway** (Prof A Sudbø PhD); **Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, Montebello, Norway** (J F Evensen MD); **and Department of Medicine, Weill Medical College of Cornell University, New York, NY, USA** (Prof A J Dannenberg MD)

Correspondence to:
Dr Jon Sudbø
jon.sudbo@rh.uio.no

See http://www.fhi.no

Introduction

Squamous cell carcinoma of the oral cavity is associated with severe disease-related and treatment-related morbidity and a poor prognosis that has not improved greatly over the past three decades.[1,2] Tobacco smoking is the major cause of this disease.[3] Patients who have oral leucoplakia with the genetic instability marker aneuploidy have an 80% risk of developing oral cancer[4] with a high relapse rate and a 70% risk of death in 5 years.[5,6] Complete surgical excision does not reduce the high risk of aggressive, lethal oral cancer associated with aneuploid oral leucoplakia.[6] Smoking cessation could offer some protection in this setting, but is often difficult to achieve or sustain.[7,8] Therefore, there is an unmet medical need for new treatment strategies, such as chemoprevention with non-steroidal anti-inflammatory drugs (NSAIDs), to reduce the risks of cancer in patients with aneuploid oral leucoplakia.[9–11]

NSAIDs inhibit cyclo-oxygenase (COX) activity and thereby suppress the synthesis of prostaglandin E_2. Raised concentrations of prostaglandin E_2 have been detected in both premalignant and malignant lesions, including squamous cell carcinoma of the oral cavity.[12,13] This increase results from the overexpression of COX-2, the inducible form of COX.[14,15] Several lines of evidence, beyond the finding of raised amounts of prostaglandin E_2 in tumours, suggest that COX enzymes contribute to the development of oral cancer. COX can convert polycyclic aromatic hydrocarbons in tobacco smoke to reactive metabolites, which form mutagenic DNA adducts.[16,17] Prostaglandin E_2 can stimulate cell proliferation and angiogenesis and inhibit apoptosis and immune surveillance.[18,19] NSAIDs protect against the development of oral cancer in animals.[20,21] Observational data have indicated that NSAIDs are associated with the reduced risk of several types of cancers,[22–25] but we know of only two previously published reports of epidemiological studies of NSAIDs with respect to head and neck cancer.[26,27] These reports only included aspirin and showed conflicting results. Before undertaking a trial to investigate NSAIDs in reducing the risk of oral cancer in the very high-risk group of patients with aneuploid leucoplakia, we did a population-based study to examine the potential association between long-term NSAID use and the risk of oral cancer in current and previously heavy smokers. We also examined the potential associations of overall and cardiovascular mortality with NSAID use.

Methods

Risk identification in population-based health-survey database

We did a nested case-control study within the population-based Cohort of Norway (CONOR), which prospectively obtains data for the Norwegian Health Survey from three longitudinal health surveys covering all geographical regions of Norway (Health Surveys of

Tromsø, Oslo, and Nord Trøndelag 1). These surveys include regular clinic visits every 5 years, during which participants have a physical examination and answer standardised interview-administered questionnaires modelled on Framingham study questionnaires. The databases generated from these surveys contain prospectively obtained standardised information on health and risk exposures, including a person's complete medical history, detailed information on treatment drug use, and exposure to disease risk factors such as tobacco, alcohol, and other life-style factors. Norwegian Health Survey and CONOR data are suitable for both cohort and nested case-control studies.[28]

About 300 000 people entered the Norwegian Health Survey between 1975 and 1995 by submitting a preliminary survey questionnaire. A cohort of 123 234 individuals proceeded to participate actively in the survey by having a formal interview and physical examination and were included in our study (8034 from Tromsø, 46 068 from Oslo, and 69 132 from Nord Trøndelag 1). Data from these health surveys can be cross-linked to quality-assured population-based disease registries, such as the Norwegian Cancer Registry, which is estimated to have a 99% completeness rate.[29] This completeness is based on the finding that 99% of cases recorded in hospital-based registries are also recorded in the Cancer Registry.[29]

Participants and data from CONOR

Of the 123 234 active Norwegian Health Survey participants, 88 072 (71%) were non-smokers and 35 162 (29%) were smokers. Of the smokers, 9241 (26%) smoked heavily (≥15 pack years, according to criteria of the Directorate for Health and Social Affairs) and 25 921 (74%) were moderate-to-light smokers (<15 pack years). Total tobacco exposure was obtained during the entire follow-up. The definition of a heavy smoker was based on known smoking history and was not affected by whether the person had quit smoking or not. The 9241 heavy smokers were assumed to be at a high risk of oral cancer, and so we identified individuals who developed oral cancer from these heavy smokers; we identified our matched controls from the remaining cohort of heavy smokers without oral cancer or any other type of cancer. 1035 heavy smokers were identified from the Health Survey of Tromsø, 3233 from Oslo, and 4973 from Nord Trøndelag 1. The cohort of heavy smokers had complete information on age, sex, risk factors (tobacco, alcohol) for head and neck cancer, and treatment drug use.

Norwegian Health Survey participants have an 11-digit personal identification number, which we used to link all heavy smokers to the Norwegian Cancer Registry and thus identify our cases, who were diagnosed with oral squamous cell cancer between 1975 and 2004. Oral cavity sites were defined according to the codes of the International Classification of Diseases, seventh revision (ICD):[30] cancers with topographical ICD codes 141 (tongue), 143 (floor of mouth), and 144 (oral cavity, not otherwise specified) were included. We used a one-to-one case-control design because of logistical limitations imposed by obtaining the detailed treatment drug information. Matching of controls (ie, heavy smokers without cancer) to these cases was complete with respect to sex and was within 5 years (before or after) of the date of birth.

Standardised interview-administered questionnaires were undertaken every 5 years. The standardised survey questionnaires allowed us to gather data for the type and duration of NSAID use. Information about drugs, including NSAIDs, was obtained at the first visit within every survey and updated on subsequent visits (people who died during follow-up were included in the analysis). NSAIDs are prescription drugs in Norway; patients' prescriptions for this study were retrieved from a central registry that covered the entire study period.

The data for patients' prescriptions were systematically gathered and entered into a digital registry. We used the number of prescriptions given to every person, as well as the number of pills and amount of active substance in every pill and prescription to calculate the cumulative exposure to NSAIDs per person. Data for the use of drugs were further available from the medical history given by patients at every visit in the survey. Long-term use was defined as the cumulative use of NSAIDs at least once a day for 6 or more months.

For this nested case-control study, we obtained exposure information with respect to the type of NSAID used and duration of use as well as date of oral cancer, date and cause of death for deceased patients, and last follow-up date for patients who were still alive at the end of follow-up. It is mandatory to report data for mortality, which were gathered from a national death certificate registry. In this registry, the cause or probable cause of death is always reported. Paracetamol was included as a reference because it has analgesic properties but does not inhibit COX enzyme activity or reduce inflammation. All information obtained from the surveys was treated according to the guidelines of the Data Inspectorate of Norway.

Statistical analysis

Mean and SD values for continuous variables and frequency tabulation for discrete variables were calculated to characterise our study population. The association between discrete variables was assessed by cross-tabulation and the χ^2 test. We used the Kaplan-Meier method to calculate the event probabilities for censored time-to-event data in the sample. Although these curves compare subgroups in the sample, event rates cannot be extrapolated to the entire population because of the case-control design. NSAID use depends on time; the longer the follow-up, the more likely a participant is to have used NSAIDs. Recensoring was applied for every matched case-control pair to avoid any bias introduced by unequal follow-up time. Our study had a predefined cohort in

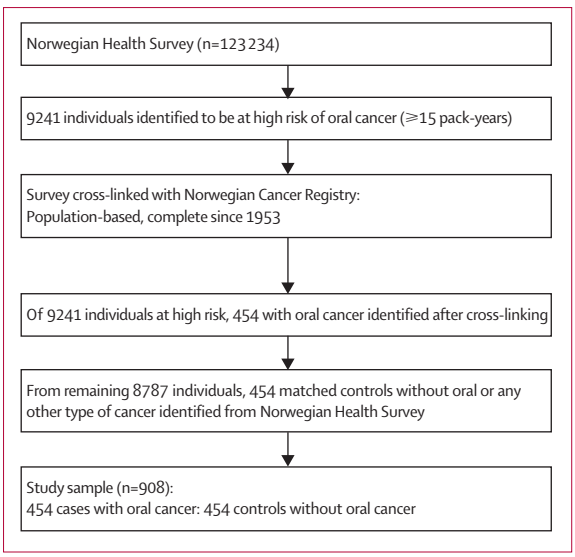

Figure 1: **Identification process of study cohorts**

which the time-to-cancer development was available for all participants because of the mandatory reporting to cancer registry. The time to last follow-up for all controls was available from the longitudinally followed Cohort of Norway study. Therefore, our study could be regarded as a retrospective cohort study with complete follow-up data. Both matched and unmatched Cox regression analyses were done to determine the effect of NSAID and other covariates on oral cancer risk and survival. Unmatched analysis was reported because the result is conservative and more robust if positive correlation exists between cases and controls within the same pair. Additionally, overall mortality and cardiovascular-disease-related death were analysed by the log-rank test and Cox model. Because of the potential effect of smoking on both oral cancer risk and survival, multivariate Cox-model analysis was used to examine the effect of NSAID, paracetamol, smoking pack-years, and quit smoking status on both risk to oral cancer and overall survival.

We calculated the hazard ratio (HR) and its 95% CI to estimate the effect of covariates on time to oral cancer or death. Crude or unadjusted HR estimates were reported unless otherwise specified. Generally, odds ratios are suitable for a case-control or nested case-control study, whereas HRs can only be calculated for a cohort or case-cohort study; however, our study was a population-based nested case-control study. Because of the cancer registry and the longitudinally conducted health survey, the event data (time of oral cancer, death, or last follow-up) were prospectively recorded. Unlike a typical case-control study, in which only the status of event is known, we had accurate data for time to the event. Therefore, the HR estimate was valid in this setting.[31] All p values were two-sided, and we regarded p values of 0·05 or less as significant.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 454 cases (with oral cancer) and 454 matched controls from our high-risk cohort of heavy smokers (figure 1). The topographical distribution of cancers was as follows: tongue (n=149), floor of mouth (n=149), and oral cavity site not otherwise specified (n=148).

Of the 908 cases and controls, 29% of individuals had used NSAIDs and 9% had used paracetamol for 6 or more months; 63% did not have a history of long-term NSAID or paracetamol use (table 1). The NSAIDs used included aspirin (all used less than 100 mg per day), ibuprofen, naproxen, indometacin, piroxicam, and ketoprofen (table 1). The indication for use of aspirin

	Cases (n=454)	Controls (n=454)*	Total (n=908)
Age (years)†			
At time of oral cancer or last follow-up	63·3 (13·2)	63·3 (13·2), 73·6 (10·1)‡	63·3 (13·2), 68·4 (12·8)‡
At death or last follow-up	70·4 (10·7), 71·9 (10·9)‡	70·4 (10·7), 73·6 (10·1)‡	70·4 (10·7), 72·8 (10·5)‡
Sex			
Male	279 (61%)	279 (61%)	558 (61%)
Female	175 (39%)	175 (39%)	350 (39%)
Tobacco smoking			
Number of cigarettes			
15–20 cigarettes/day	186 (41%)	189 (42%)	375 (41%)
21–30 cigarettes/day	166 (37%)	153 (34%)	319 (35%)
31–40 cigarettes/day	76 (17%)	81 (18%)	157 (17%)
>40 cigarettes/day	26 (6%)	31 (7%)	57 (6%)
Pack-years	43·0 (14·6)	39·0 (14·7)	41·0 (14·8)
Alcohol			
Never	24 (5%)	30 (7%)	54 (6%)
1–5 units/week	164 (36%)	165 (36%)	329 (36%)
>5 units/week	194 (43%)	199 (44%)	393 (43%)
No information	72 (16%)	60 (13%)	132 (15%)
Drug type used			
NSAID	77 (17%)	186 (41%)	263 (29%)
Aspirin	5	9	14
Ibuprofen	13	39	52
Naproxen	16	39	55
Indometacin	15	47	62
Piroxicam	17	35	52
Ketoprofen	11	17	28
Paracetamol	48 (11%)	35 (8%)	83 (9%)
Length of NSAID use (years)			
<5	10	21	31 (12%)
5–10	22	25	47 (18%)
10–15	26	61	87 (33%)
≥15–26	19	79	98 (37%)

Data are mean (SD) for continuous variables or number of individuals (%) for discrete variables. *Follow-up times of matched controls were recensored to be precisely equal to the time of oral cancer for the corresponding case. †Age at time of oral cancer development or death or follow-up for the matched case-control pairs were recensored to ensure similar length of follow-up between cases and controls. ‡Summary statistics for the raw data before recensoring.

Table 1: **Clinical characteristics of study population**

	Cases (n=454)	Cases and controls (n=908)	HR (95% CI)	p
Univariate analysis				
NSAID or paracetamol use				
None	329	562	1	..
NSAID use	77	263	0·47 (0·37–0·60)	<0·0001
Paracetamol use	48	83	0·79 (0·59–1·08)	0·14
NSAID use duration				
<5 years	10	31	0·53 (0·28–0·98)	0·044
5–10 years	22	47	0·68 (0·44–1·04)	0·075
10–15 years	26	87	0·61 (0·41–0·91)	0·015
⩾15–26 years	19	98	0·30 (0·19–0·47)	<0·0001
Type of NSAID				
Aspirin	5	14	0·38 (0·16–0·93)	0·034
Ibuprofen	13	52	0·37 (0·21–0·64)	0·0004
Naproxen	16	55	0·50 (0·30–0·82)	0·007
Indometacin	15	62	0·41 (0·25–0·69)	0·0007
Piroxicam	17	52	0·56 (0·34–0·91)	0·020
Ketoprofen	11	28	0·68 (0·37–1·25)	0·21
Smoking pack-years				
As continuous variable	..	..	1·011 (1·005, 1·017)	0·007
As binary variable				
<40 pack-years	205	475	1	..
⩾40 pack-years	249	433	1·45 (1·20–1·76)	<0·0001
Quit smoking years				
As continuous variable	..	..	0·79 (0·75–0·85)	<0·0001
As binary variable				
Active smokers	367	692	1	..
Quitters	87	216	0·41 (0·32–0·52)	<0·0001
Multi-covariate analysis				
NSAID use	..	..	0·49 (0·38–0·63)	<0·0001
Paracetamol use	..	..	0·86 (0·63–1·16)	0·31
Smoking pack-years (<40 or ⩾40)	..	..	1·31 (1·10–1·62)	0·004
Quit smoking (yes or no)	..	..	0·44 (0·34–0·56)	<0·0001

Both univariate and multi-covariate analyses were reported. Univariate analyses included the ... analysed one at a time. Multiple-covariate analyses contained all specified variables in ... model.

Table 2: **Univariate and multi-covariate analysis of ... and paracetamol use, smoking status, and oral cancer risk**

was prevention of coronary heart disease in all cases. The remaining 249 individuals took NSAIDs to treat pain related to various musculoskeletal conditions (193, 7... rheumatoid arthritis (56, 21%). 12% of NSAID users had taken the drug for less than 5 years, 18% for 5–10 years, 39% for 10–15 years, and 37% for 15–26 years (table 1).

Ever-used use of NSAIDs and paracetamol were each associated with a reduced risk of oral cancer, although the relation was not significant for paracetamol (table 2, figure 2, A). The HRs for various durations of NSAID use were: 0·53 for less than 5 years, 0·68 for 5–10 years, 0·61 for 10–15 years, and 0·30 for 15 or more years (table 2, figure 2, B). NSAID use for 15 or more years had the lowest and most highly significant HR for oral cancer. The inverse association with risk of oral cancer was significant for all NSAIDs apart from ketoprofen, presumably because of the small sample size of ketoprofen users (table 2). No significant difference between different types of NSAIDs was noted.

Smoking was a strong risk factor for oral cancer, and we quantified its effect on oral cancer risk in our study. The number of pack-years of smoking as a continuous variable was associated with an increased risk of oral cancer. When pack-years were dichotomised at their median (40 pack-years), HRs were greatly increased for 40 or more pack-years compared with less than 40 pack-years; however, years of smoking cessation (or since last smoking) were associated with a reduced risk of oral cancer. The overall HR of oral cancer in former smokers was 0·41 (95% CI 0·32–0·52; table 2). Of the 562 people who had never used NSAIDs or paracetamol, smoking cessation was also associated with a significantly reduced risk of oral cancer (HR 0·43, 95% CI 0·32–0·58; figure 2, ...

Because of the importance of tobacco habits, pack-years of smoking and years since quitting smoking were added to the multiple-covariate analysis. After adjustment for tobacco habits, NSAIDs (but not paracetamol) use was still associated with a decreased risk of oral cancer (table 2). This inverse association was similar when we analysed pack-years and years since quitting smoking as continuous variables. In both the univariate and multiple-covariate analyses, the results consistently showed that long-term NSAID use was associated with an approximately 50% reduction of oral cancer risk in this high-risk group.

The association between NSAID use and reduced risk of oral cancer was seen in all smokers, but the effect was greater in heavy smokers (figure 3, A and 3, B). The oral cancer rates were 21% for NSAID users versus 56% for non-users with fewer than 40 pack-years (figure 3, A) and were 43% for NSAID users versus 66% for non-users with 40 or more pack-years (figure 3, B). In individuals with a smoking history of less than 40 pack-years who had quit smoking, NSAIDs users were associated with a lower cancer risk than non-users (25% *vs* 40%), although this relation was not significant (figure 3, C). NSAIDs were associated with a reduced risk of oral cancer in people with a smoking history of 40 or more pack-years who had quit smoking. Oral cancer rates were 13% for NSAID users versus 69% for non-users (figure 3, D).

Although use of NSAIDs was associated with a reduced risk of oral cancer, it was not associated with increased overall survival (figure 2, D), which led us to investigate potential adverse effects of NSAIDs. 42 (16%) NSAID users died of cardiovascular events (15 myocardial infarction, 27 stroke) compared with 41 (7%) non-users (15 myocardial infarction, 26 stroke) and four (5%) paracetamol users (two myocardial infarction, two stroke; table 3). Aspirin did not seem to increase the risk of cardiovascular-disease-related death. By contrast, naproxen, piroxicam, ketoprofen, indometacin, and ibuprofen had HRs ranging from 1·70 to 2·86, of which indometacin and ibuprofen were associated with a significant increase in the risk of cardiovascular-disease-related death (table 3). The HRs of these substances had wide 95% CIs because of the small sample sizes and number of events in every

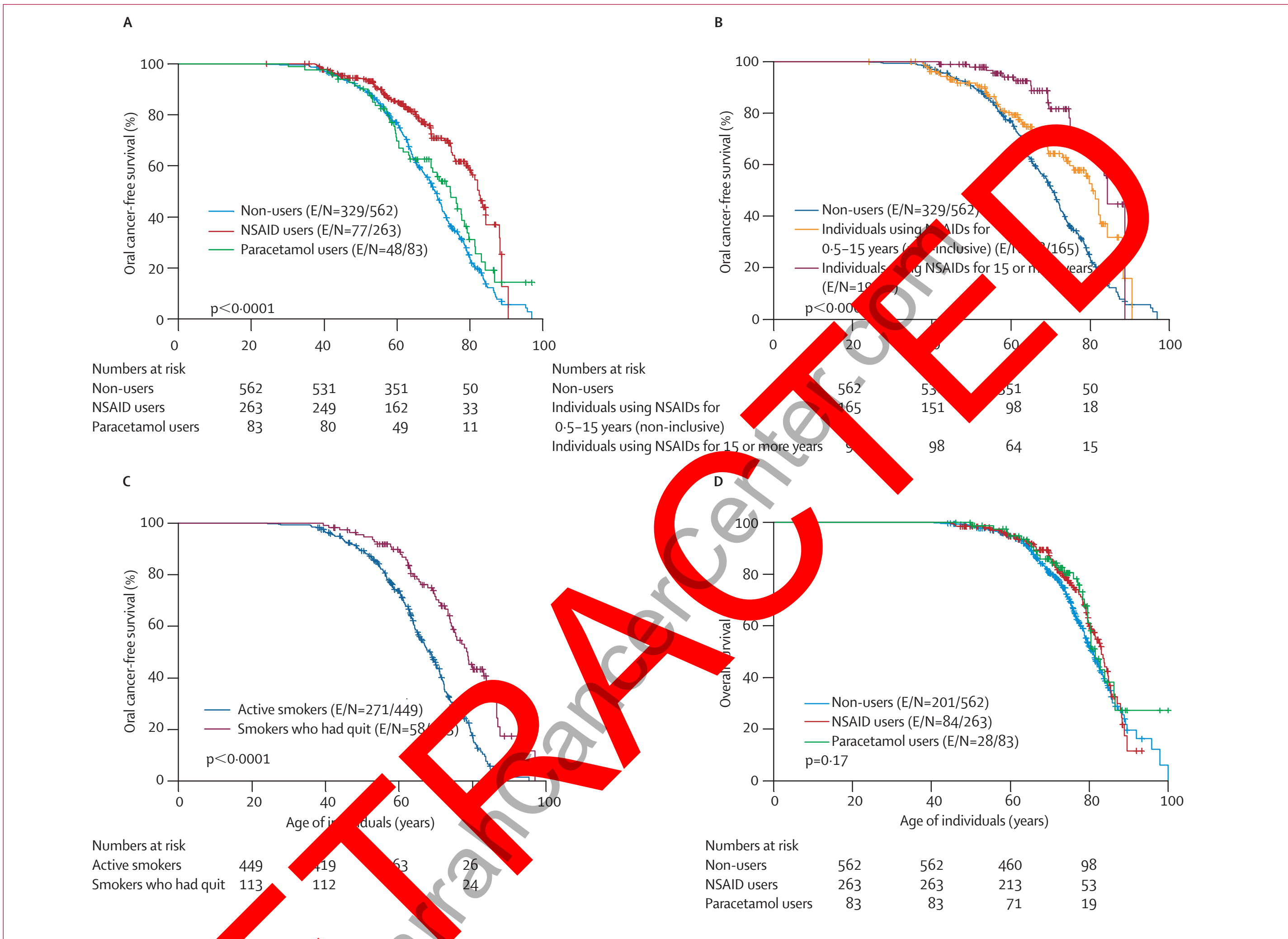

Figure 2: **Cancer-free and overall survival related to NSAID use**
(A) Cancer-free survival. (B) Relationship between cancer-free survival and duration of NSAID use. (C) Cancer-free survival after smoking cessation in people with no history of NSAID or paracetamol use. (D) Overall mortality. Kaplan-Meier curves go to zero because the risk set reduces over time, mainly because of censoring and late events (ie, oral cancer developing at older ages). E/N=number of events/total number of individuals in subgroup. Tick marks on Kaplan-Meier curves=censored data.

NSAID group (table 3). Multi-covariate analysis also showed that NSAID use was associated with increased cardiovascular-disease-related death (HR 2·05, 95% CI 1·33–3·16; p=0·0[illegible]) after adjustment for smoking pack-years and quit smoking status. When including previous history of cardiovascular disease in the analysis, similar risk estimates were recorded (data not shown). Paracetamol use was associated with a non-significant reduction of risk of cardiovascular-disease-related death (table 3). The results of paracetamol were similar in the multi-covariate analysis. NSAID use was not associated with increased risk of death from any other cause.

Discussion

Our nested case-control analysis shows that long-term use of NSAIDs is associated with about a 50% reduction in the risk of oral cancer in a high-risk group of smokers with 15 or more pack-years of smoking history. This finding is consistent with growing evidence that extended use of NSAIDs reduces the risk of cancers of the lower gastrointestinal tract.[26,32–34] Some studies have suggested that NSAIDs also protect against cancer development in the upper gastrointestinal tract.[22,27,35] However, our finding that long-term use of NSAIDs was associated with a reduced the risk of oral cancer, including in active smokers, is novel. The magnitude of the protective effect of NSAIDs against oral cancer was comparable with that of smoking cessation.

The significant inverse association between NSAID use and oral cancer risk could be due to the ability of NSAIDs to inhibit COX-2 activity. COX-2 is nearly

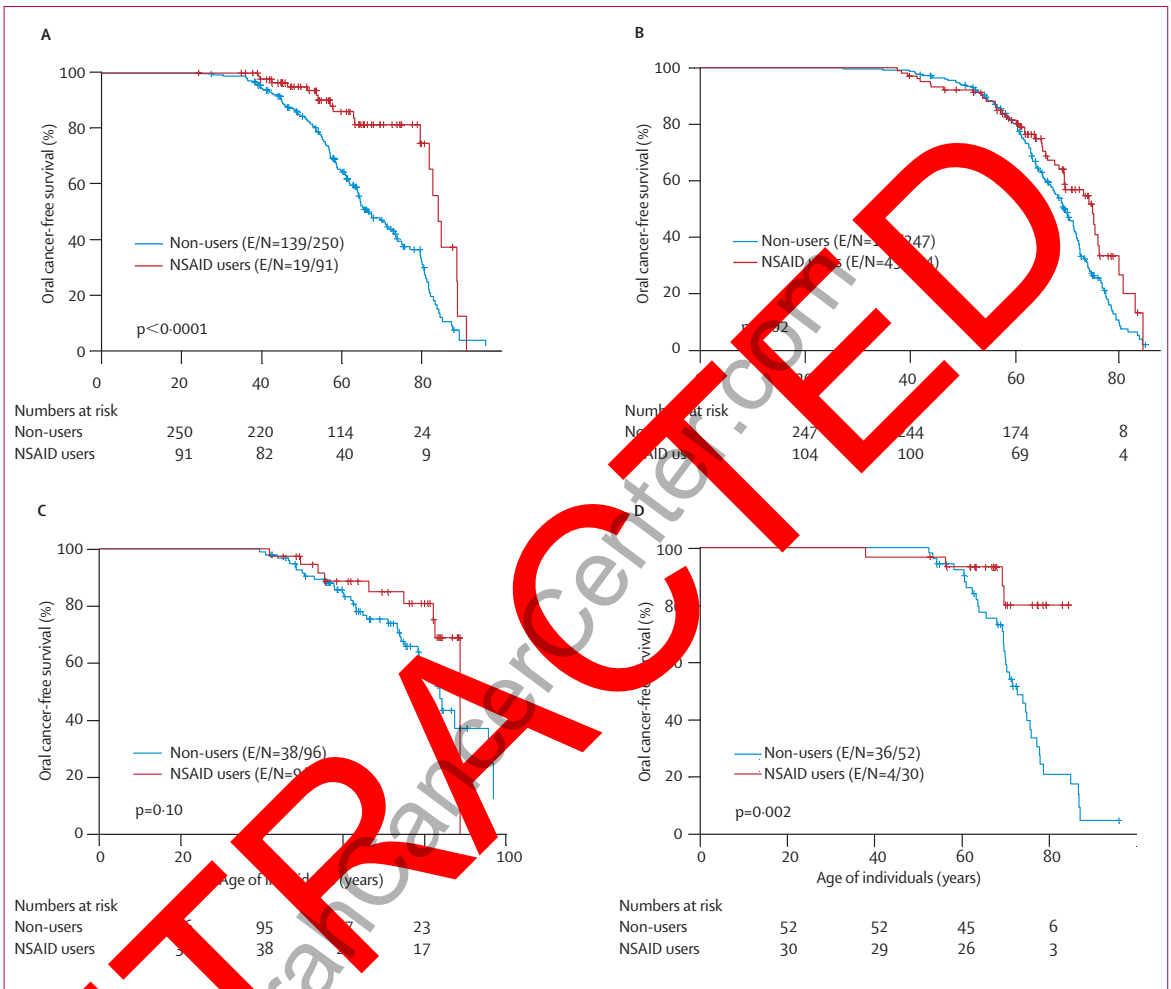

Figure **ancer protective effect NSAID use as related to smoking habits**
Blu eople with no history of NSAID se. Red=people with history of NSAID use. (A) Oral-cancer-free survival in 341 active smokers with smoking history of l than 40 pac ears. (B) Oral-cancer-free survival in 351 active smokers with smoking history of 40 or more pack-years. (C) Oral-cancer-free survival in 1 people w had quit smoking with a smoking history of less than 40 pack-years. (D) Oral-cancer-free survival in 82 people who had quit smoking with a sm tory of 40 o re pack-years. E/N=number of events/total number of individuals in subgroup. Tick marks on Kaplan-Meier curves=censored data.

	Numb cardiovas ular-disease-ted deaths	Total number of people	HR (95% CI)	p
Univariate analys				
Individuals who had ed NSAIDs	41 (7%)	562	..	..
Individuals who had used IDs	42 (16%)	263	2·06 (1·34–3·18)	0·001
Aspirin	2 (14%)	14	1·16 (0·28–4·80)	0·84
Ibuprofen	12 (23%)	52	2·86 (1·50–5·45)	0·001
Naproxen	7 (13%)	55	1·70 (0·76–3·79)	0·20
Indometacin	10 (16%)	62	2·26 (1·13–4·52)	0·02
Piroxicam	7 (13%)	52	1·84 (0·82–4·11)	0·14
Ketoprofen	4 (14%)	28	1·90 (0·68–5·31)	0·22
Individuals who had used paracetamol	4 (5%)	83	0·51 (0·18–1·42)	0·20
Multicovariate analysis				
NSAID use	..	..	2·05 (1·33–3·16)	0·001
Paracetamol use	..	..	0·50 (0·18–1·40)	0·18
Smoking pack-years (<40 or ⩾40)	..	..	1·02 (0·65–1·60)	0·93
Quit smoking (yes or no)	..	..	1·13 (0·72–1·77)	0·60

Table 3: **Risk of cardiovascular-disease-related death in long-term users of NSAIDs and paracetamol**

undetectable in healthy oral mucosa but is induced by mitogenic and pro-inflammatory stimuli.[14,36] We recently showed that COX-2 is upregulated during the transition from healthy to dysplastic to cancerous oral mucosa[15] and that COX-2 seems to be upregulated preferentially in DNA aneuploid oral lesions, which have a high risk of cancer and cancer-related mortality (compared with non-aneuploid lesions).[4,6] Furthermore, exposure to tobacco smoke can activate epidermal-growth-factor receptor (EGFR) signalling, leading to raised concentrations of COX-2 and enhanced synthesis of prostaglandin E_2, which in turn can activate EGFR signalling.[37–39] Therefore, a positive feedback loop is established. These effects could enhance the mutagenicity of tobacco smoke. For example, COX-2 can convert polycyclic aromatic hydrocarbons in tobacco smoke to reactive metabolites that form mutagenic DNA adducts.[16,17,40] Therefore, tobacco-smoke-mediated induction of COX-2

could amplify the effect of a given dose of tobacco smoke on mutagenesis. Furthermore, conversion of DNA adducts to mutations can only occur in proliferating cells,[41,42] and stimulation of COX-2-mediated synthesis of prostaglandin E_2 or EGFR signalling enhances cell proliferation.[38] This event could, in turn, increase the mutagenicity of tobacco smoke. Inhibition of COX-2 has been shown to suppress cell proliferation, reduce chemical mutagenesis, induce apoptosis, and stimulate immune surveillance in experimental models.[18,19,36] These findings suggest that inhibition of COX-2 can explain, at least partly, the reduction in oral cancer risk associated with NSAID use.

The 5% oral cancer rate that we recorded could seem somewhat high, but is reasonable if we consider the nature of our study population and design. We assessed only heavy smokers (not all smokers), and an estimated 70% of these heavy smokers used hand-rolled unfiltered cigarettes.[43] The risk of oral cancer with any type of unfiltered cigarette is twice that of filtered cigarettes,[3] and hand-rolled unfiltered cigarettes increase the risk of oral cancer even more than do factory-made unfiltered cigarettes.[43]

Long-term NSAID use was not associated with increased overall survival, despite being associated with a reduced risk of oral cancer. The lack of a survival benefit could be due to our finding of an NSAID-associated increase in cardiovascular-disease-related death, which might have neutralised the expected beneficial effect of decreased oral cancer death. The present cardiovascular result is consistent with preliminary evidence that continuous use of NSAIDs (both non-selective and selective COX-2 inhibitors) could raise the risk of serious adverse cardiovascular effects.[44] Data from the randomised clinical Adenomatous Polyp Prevention on Vioxx (APPROVe) trial indicated that the COX-2-selective NSAID rofecoxib taken for 18 months or more caused an increased relative risk of serious cardiovascular events. As a result this drug was voluntarily withdrawn from the world market. The Adenoma Prevention with Celecoxib (APC) trial[46] found an increased risk of cardiovascular complications in individuals treated with the selective COX-2 inhibitor celecoxib. Overall, we found that the use of NSAIDs was associated with a reduced risk of oral cancer and an increased risk of death due to cardiovascular disease. However, the effect of individual NSAIDs needs to be interpreted with caution because of the restricted sample size in our study.

Additionally, we cannot exclude a confounding effect of inflammation or reduced physical activity related to arthritis. For example, arthritis patients treated with NSAIDs could exercise less than those who do not use NSAIDs. Therefore, a reduction in physical activity rather than use of NSAIDs could be responsible for the increased risk of death due to cardiovascular disease in this population. Finally, we note that cause of death was a secondary endpoint in this study. This limitation underscores the need for prospective studies that further investigate the relation between the use of NSAIDs and the risk of cardiovascular disease.

Our study suggests that NSAIDs show promise in reducing the risk of oral cancer in former and active smokers. The magnitude of risk reduction is comparable to quitting smoking. NSAIDs are promising drugs for preventing cancer in high-risk settings,[37,38] such as aneuploid oral leucoplakia. The extremely high rates of cancer and cancer mortality associated with aneuploid oral leucoplakia make prevention in this setting tantamount to cancer therapy, in which adverse effects are more acceptable than would be the case in a low-risk population. Oral cancer prevention trials of NSAIDs are either planned or underway. Researchers of these trials must carefully monitor potential adverse cardiovascular effects in their populations, who are at an increased risk of cardiovascular disease as well as oral cancer, and implement other safety measures such as excluding patients with cardiovascular disease or specific risk factors of cardiovascular disease. Over the next few years these trials will determine whether NSAIDs can reduce the devastating effect of oral cancer on patients, their families, and public health.

Contributors

J Sudbø initiated the investigations leading to these results; wrote the protocol for the study; participated in discussions on the undertaking of the study; conceived, designed, and supervised the study; collected the data; reviewed all iterations of the paper; and wrote the first draft and the final version of the paper. A J Dannenberg suggested the original idea for the study, supervised the study, and reviewed and contributed to the writing of all iterations of the paper, including the final version of the manuscript. J J Lee participated in discussions on the undertaking of the study, supervised and did the statistical analysis, interpreted the data, reviewed the paper for content, and reviewed and contributed to the writing of all iterations of the paper, including the final version of the manuscript. S M Lippman participated in discussions on the undertaking of the study, designed and supervised the study, interpreted the data, reviewed the paper for content, and reviewed and contributed to the writing of all iterations of the paper, including the final version of the manuscript. A Reith together with J Sudbø conceived of the idea to use the Norwegian Health Surveys for investigating lifestyle factors and cancer risk, initiated the study and contracts, and contributed substantially to the discussions and final version of the paper. J Mork, Simone Sagen, N Flatner, A Ristimäki, L Mao, W Kildal, A Sudbø, and J F Evensen contributed substantially to discussions and in writing the paper. X Zhou did statistical analysis. J Sudbø, S M Lippman, A J Dannenberg, and A Sudbø obtained funding for the study. All authors approved the final report.

Conflict of interest statement

A J Dannenberg has consulted for Pfizer, but not in relation to this study. The other authors declare that they have no conflict of interest.

Acknowledgments

JS, JJL, SML, and AJD contributed equally to this paper. This study was supported partly by grants from the Norwegian Cancer Society (E 03010/002, E 03010/003, and HF-51019), the Research Foundation of the Norwegian Radium Hospital (SP 2526, 702525-13 and SE 0207), Astrid and Birger Torsteds Legat (to JS), Research Council of Norway (grant 158518/431 [NANOMAT] to AS), US National Cancer Institute grants P01CA106451 (to SML) and R01 CA082578, and the Center for Cancer Prevention Research (to AJD). We are indebted to the staff of CONOR for their expert technical assistance.

See http://www.vioxx.com/rofecoxib/vioxx/consumer/index.jsp

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