Aspirin and lung cancer

A review with meta-analysis

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EXECUTIVE SUMMARY

Twelve epidemiological studies have been identified which relate use of aspirin (or total use of non specific anti-inflammatory drugs) to risk of lung cancer. Using sex-specific estimates where available, there is some evidence of a negative relationship with both "ever exposure" and "regular exposure" to aspirin.

Exposure	Estimates combined	Meta-analysis relative risk (95% CI) Fixed-effects	Random-effects
Ever[a]	17	0.94 (0.89-0.99)	0.84 (0.72-0.97)
Regular[b]	16	0.96 (0.90-1.03)	0.81 (0.67-0.99)

[a] "Ever exposure is the most inclusive definition of exposure available for the study.

[b] "Regular exposure" restricts attention to results for the group having the highest frequency of use or the longest duration of use reported.

However, the individual study estimates are highly heterogeneous due to extremely low risk estimates in one case-control study (0.43, 0.34-0.56 for ever exposure and 0.32, 0.23-0.44 for regular exposure) which seems open to a number of criticisms. Omitting this study removes the statistical significance of the association, with random-effects estimates 0.91 (0.81-1.02) for ever exposure and 0.90 (0.77-1.04) for regular exposure.

Other points to note about the data are as follows:

(i) The negative association is not evident in those studies that recorded aspirin use before the diagnosis of lung cancer was known (one intervention study, five prospective studies and one nested case-control study), but can only be seen in the five (non nested) case-control studies;

(ii) There is some evidence of a negative association when attention is restricted to those studies that have controlled for smoking adequately;

(iii) There is little clear evidence of a dose-response in relationship either to frequency of use or duration of exposure;

(iv) Limited evidence does not suggest the relationship between lung cancer risk and aspirin use varies markedly by histological type of lung cancer;

(v) Many of the studies collected data on aspirin use relating to one time point, though evidence from one of the studies demonstrates considerable variability in use over time;

(vi) Interpretation of any differences in lung cancer risk relating to aspirin use is not straightforward. In some case-control studies, control groups may include individuals with diseases for which aspirin use may be indicated (or contra-indicated), while data collected on aspirin use at a time close to diagnosis may reflect the effect of the disease (or conditions leading up to it) on usage.

Although some of the meta-analyses of aspirin use and lung cancer risk do show a statistically significant negative relationship, the relationship is quite weak and the individual risk estimates heterogeneous. In view of the lack of clear dose-response and the various difficulties in interpreting the data, it cannot be concluded from the present evidence that aspirin definitely reduces risk of lung cancer. Though an effect is not implausible and may exist, it seems unlikely to be a strong one.

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1. Introduction

According to the 1997 IARC Handbook of Cancer Prevention on Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (International Agency for Research on Cancer, 1997), "Aspirin and its salicylate metabolite have analgesic, anti-inflammatory and antipyretic properties. Aspirin was first marketed in 1899 (Vane *et al*., 1990). It is used for the relief of mild-to-moderate pain such as headache, dysmenorrhoea, myalgia and dental pain. It is also used in acute and chronic inflammatory disorders such as rheumatoid arthritis and osteoarthritis. Aspirin inhibits platelet aggregation and is used in the prevention of arterial and venous thrombosis." IARC's evaluation of the evidence on aspirin (p90) concluded that there was "limited evidence" in humans and "sufficient evidence" in animals for its cancer-preventive activity, but this related to effects on colorectal cancer, with no mention made of lung cancer. Earlier in the aspirin chapter, in a section on "studies of cancer other than in the digestive tract" (pp62-63) summaries were made of a number of epidemiological studies of possible relevance to the association of aspirin with lung cancer (Friedman & Siegelaub, 1980; Friedman & Ury, 1983; Paganini-Hill et al., 1989; Selby et al., 1989; Thun et al., 1993; Schreinemachers & Everson, 1994). Although one of these studies (Schreinemachers & Everson, 1994) did report a statistically significant reduction in risk of lung cancer associated with aspirin use, others did not and no clear evidence of protection was apparent from the overall data, though IARC did not draw any conclusions. Although the IARC Handbook also contains chapters on sulindac, piroxicam and indomethacin, no reference is made to epidemiological studies relating lung cancer risk to any of these NSAIDs.

More recently other studies have reported a significantly reduced risk of lung cancer associated with aspirin or NSAID use (Akhmedkhanov et al., 2002; Harris et al., 2002; Moysich et al., 2002). The purpose of this document is to review the totality of the available epidemiological data relating risk of lung cancer to aspirin or to total NSAID use, including appropriate meta-analyses. No attempt has been made to consider evidence from studies of the incidence of lung cancer among groups of individuals with diseases such as

rheumatoid arthritis, likely to have very high aspirin use, as the findings would be difficult to interpret specifically in terms of effects of aspirin.

2. Methods

Relevant papers were identified by a combination of MEDLINE searches, search within our in-house reference database and inspection of references cited in papers obtained.

For each study identified, the key features of it were summarized (in sections 3-5 of this report), and relevant relative risks (RRs) or odds ratios (ORs), together with their 95% confidence interval (CI) presented. Where necessary these RRs, ORs and CIs were calculated or estimated from data given in the source papers using standard statistical techniques (e.g. Fleiss & Gross, 1991; Fry & Lee, 2000). RRs, ORs and CIs were entered into an EXCEL database to carry out fixed-effects and random-effects meta-analyses (Fleiss & Gross, 1991).

3. Intervention trials

There are three randomized intervention trials of aspirin, as described in the sections below. Only the trial in male British doctors (section 3.1) has so far reported results for lung cancer.

3.1 Randomized trial of aspirin in British male doctors (Peto et al., 1988)

In 1978 an invitation to participate in a randomized trial of aspirin was sent to all male doctors resident in the UK who were born from 1900 onwards, who had replied to a questionnaire about their smoking habits sent to them in 1951 (as part of the well known British Doctors Study, e.g. Doll et al., 2004) and who were still listed in the 1977 *Medical Directory*. A follow-up invitation to non-respondents was sent in 1979. 5139 of the doctors, almost half of them under 60 in 1978, were eligible to join the study (not already taking aspirin, being unable to take it, or having a history of peptic ulcer, stroke or definite myocardial infarction) and agreed to do so, and were randomly allocated 2:1 to either:

(A) take daily aspirin (500 mg ordinary, soluble or effervescent aspirin as desired or, if subsequently requested, 300 mg enteric coated aspirin) unless some contraindication was thought to have developed, or

(B) avoid aspirin and products containing aspirin unless some specific indication for aspirin was thought to have developed (it being suggested paracetamol be used initially if an analgesic were required).

Placebo tablets were not used, so treatment was not blind.

Treatment was scheduled to continue from November 1978 (or, for the 762 doctors joining later, from November 1979) to November 1984, and the principal analysis of death (or other outcomes) related to events occurring in this period. All the doctors were asked to complete a brief questionnaire every six months about their health and use of aspirin or other antiplatelet agents over the preceding period. Deaths were sought by correspondence with relatives, from the records of the General Medical Council, and from National Health Service records.

During the first year after randomization 670 (19.5%) of the 3429 doctors allocated to take aspirin stopped doing so, and a further 678 (24.8%) stopped in the following five years. In the 1710 doctors allocated to avoid aspirin, the numbers starting to do so in the same two periods were, respectively, 30 (1.8%) and 154 (9.2%). As the authors state, "Effectively, therefore, the study assessed the effects of about two thirds more of the treated than control group taking aspirin regularly". The main findings of the study as regards lung cancer, as shown below, are a non-significant reduction in risk in the aspirin group.

Group	Man years	Deaths[b]	Rate[a]	Relative rate (95% CI)[b]
Controls	9470	11	11.6	1.00
Allocated aspirin	18820	14	7.4	0.64 (0.29-1.41)

[a] per 10,000 man years [b] Data are calculated

Mortality follow-up was thought to be complete, and more elaborate analyses based on time to death and with adjustment minor baseline differences between the two groups produced almost identical results. Numbers of lung cancers in this study were too low to detect other than a substantial effect of aspirin. The study was actually aimed at detecting reductions in vascular disease, and comments by the authors on non-vascular death rates are limited. They noted "a slight shortfall in deaths from cancer" (rates 39.8 vs 48.6) but this was not statistically significant (relative rate 0.82, 95% CI 0.57-1.18), an "unanticipated" difference which "may well represent data-derived fluctuations due to chance". Lung cancer was not mentioned in the text.

3.2 Physicians' Health Study (Physicians' Health Study Research Group, 1989)

The Physicians' Health Study was a randomized, double-blind, placebo-controlled trial designed to determine whether low-dose aspirin (325 mg every other day) decreases cardiovascular mortality and whether beta carotene reduces the incidence of cancer. 22,071 male US physicians, aged 40 to 84 in 1982, who had no history of cancer (except nonmelanoma skin

cancer), myocardial infarction, stroke, or transient cerebral ischaemia were randomly assigned, according to a two-by-two factorial design, to one of four treatment groups: aspirin and beta carotene, aspirin and beta carotene placebo, aspirin placebo and beta carotene, or aspirin placebo and beta carotene placebo. Altogether 11,037 physicians were assigned to receive aspirin and 11,034 to receive aspirin placebo.

In January 1988 the aspirin component of the study was terminated because there was a highly significant ($p<0.001$) and substantial (44%) reduction in the risk of myocardial infarction in the aspirin group. The beta carotene component of the study continued uninterrupted until its scheduled termination at the end of 1995.

In July 1989 the "Final Report" on the aspirin component was published (Physicians' Health Study Research Group, 1989). Although quite detailed results were presented for cardiovascular disease, little information was given for non-cardiovascular deaths. For total non-cardiovascular disease deaths, a non-significant reduction in risk was seen in the aspirin group (124 deaths on aspirin vs 133 deaths on placebo, relative risk 0.93, 95% CI 0.72-1.20), but no results for lung cancer were cited. Nor, as far as I can detect, have any relevant results been published subsequently.

3.3 Women's Health Study (Buring & Hennekens, 1992)

The Women's Health Study (Buring & Hennekens, 1992) was planned as a randomized, double-blind, placebo-controlled 2x2x2 factorial trial involving 40,000 post-menopausal female nurses with no history of cardiovascular disease or cancer (except nonmelanoma skin cancer). Nurses who were eligible, willing to participate in the trial, and satisfactorily underwent a three month run in phase to ascertain their ability to comply with the study regimen went forward to randomization to one of eight groups formed by each combination of 100 mg aspirin or aspirin placebo every other day x 50 mg beta carotene or beta carotene placebo every other day x 400 IU vitamin E or vitamin E placebo every other day.

Enrolment of participants started in 1992, and by 1994 letters of invitation and baseline questionnaires had been mailed to over 1.3 million nurses as well as to over 500,000 female physicians, dentists and other health professionals. In response to the beta carotene results of other trials, the beta carotene arm of the Women's Health Study was terminated in January 1996.

The information above was drawn from a review of intervention trials published in 1999 (Young & Lee, 1999). At that time no information could be ascertained as to when the study was to continue to, and no results had been published of the effects of any intervention. As far as I can detect, no relevant results relating to the effects of aspirin have yet appeared.

4. Prospective studies

Five prospective studies, all conducted in the USA, have studied the relationship of aspirin use to lung cancer risk. All of these have provided quantitative data that can be used in meta-analyses.

4.1 Kaiser-Permanente Medical Center Study (Friedman & Ury, 2004,Friedman & Ury, 1983,Selby et al., 1989)

Between July 1969 and August 1973 the outpatient pharmacy at the Kaiser-Permanente Medical Center in San Francisco was connected to a computer system for recording all prescriptions dispensed. Subscribers to this prepaid medical care programme are socioeconomically and clinically diverse. A cohort of 143,574 pharmacy users was identified and cancer development was followed up until 1978 based on medical records available in California.

Results have been presented of analyses linking more commonly used drugs to risk of cancers based on follow-up to 1976 (Friedman & Ury, 2004), 1978 (Friedman & Ury, 1983) and 1984 (Selby et al., 1989). A drug was screened for an association with each cancer site and with all sites combined by a comparison of the number of new cases developing among the users of that drug (i.e. persons to whom it was dispensed at least once) with the number expected among the same group on the basis of the age- and sex-specific incidence rates for all pharmacy users. Analyses were also carried out with a lag period, i.e. comparing the numbers of observed and expected cases with follow-up starting both one year and two years after the drug was first given. Results are only presented for drugs where a significant association was seen for one or more cancer sites, results then being given for those cancers and for total cancer risk.

The authors noted that their findings concerning aspirin were limited because the usual over-the-counter purchases of this drug were not recorded in their computer-stored prescription data (Friedman & Ury, 1983). The analyses concern five groups of individuals taking aspirin: 381 taking plain aspirin, 21158 taking aspirin with codeine, 2393 taking the combination of aspirin,

phenacetin, caffeine and butalbital, 393 taking enteric coated aspirin and 718 taking the combination of aspirin, phenacetin and caffeine.

For four of the five groups of aspirin users no statistically significant relationships with lung cancer risk were noted in any of the three papers. The only results reported for lung cancer were for the largest group, aspirin and codeine users, who form 84.5% of the total for all five groups. As shown below, there was in the final follow-up (Selby et al., 1989) a significant ($p<0.01$) increase in risk of lung cancer. The authors comment that these results, taken in conjunction with evidence of an increase in cancer of the floor of the mouth for users of aspirin and codeine (13 cases vs 5.2 expected, SMR = 2.49, $p<0.01$) and increases in both lung cancer (25 cases vs 13.3 expected, SMR = 1.89, $p<0.01$) and pharyngeal cancer (3 cases vs 0.1 expected, SMR = 35.73, $p<0.002$) among recipients of pentozocine "suggests that users of narcotic analgesics may more frequently be cigarette smokers, and at increased risk for a variety of cancers because of this behaviour".

		Lung cancer cases		
Use	Subjects	Observed	Expected[a]	SMR (95% CI[b])
Aspirin and codeine	21158	176	141.8	1.24 (1.06-1.44)

[a] On the basis of the age- and sex-specific incidence rates for all pharmacy users
[b] CI are calculated

4.2 California Retirement Community Study (Paganini-Hill et al., 1989)

In 1981 a detailed health questionnaire, which included questions on medical history and the use of drugs, was posted to all residents of a retirement community near Los Angeles. New residents moving into the community later were sent a questionnaire in 1982, 1983 or 1985. 13,987 out of 22,781 (61%) of this white, affluent and well educated community responded, and mortality was followed up to the end of 1987. Only 13 of the respondents (of median age 73) were lost to follow-up but "seemed not to have died".

The results of the study relating to lung cancer, which show no statistically significant relationships, are summarized below.

Sex	Aspirin use	Subjects	Lung cancer deaths	Relative risk (95% CI)[a]
Male	None	3490	46	1.00
	< Daily	685	8	0.87 (0.41-1.84)
	Daily	876	15	1.35 (0.76-2.41)
	Any	1561	23	1.14 (0.69-1.87)
Female	None	6021	32	1.00
	< Daily	1417	8	1.00 (0.46-2.17)
	Daily	1380	2	0.29 (0.07-1.21)
	Any	2797	10	0.67 (0.33-1.36)
Combined	None	9511	78	1.00
	< Daily	2102	16	0.93 (0.54-1.60)
	Daily	2256	17	1.09 (0.64-1.86)
	Any	4358	33	0.96 (0.64-1.44)

[a] Relative risks are adjusted for age (<75, 75-79, 80-84, 85-89, 90+). The authors presented data on numbers of subjects and deaths and relative risks for males and females for none, < daily and daily. Other data are calculated.

No attempt was made to adjust for any factors associated with use of aspirin, and the paper, which is concerned with chronic diseases in general, and noted an increase in kidney cancer and ischaemic heart disease related to aspirin use, did not discuss results for lung cancer at all.

4.3 American Cancer Society Cancer Prevention Study II (Thun et al., 1993)

In the well known American Cancer Society Cancer Prevention Study II (CPS II) study, 635,031 men and women who did not report having cancer provided information on the frequency and duration of aspirin use at baseline in 1982. Results of analyses relating aspirin use to death from cancer by 1988 were reported in 1993 (Thun et al., 1993). More detailed analyses were presented for cancers of the oesophagus, stomach, colon and rectum, with data for cancer of the respiratory system (which would have included 95% or more cancer of the lung) only expressed as age-adjusted relative risks. These results, reproduced below, show no significant association between aspirin use and risk of respiratory system cancer.

	Men		Women	
Aspirin use per month	Person years at risk	Relative risk 95% CI	Person years at risk	Relative risk 95% CI
Never	644145	1.00	681677	1.00
Occasionally	478969	0.94 (0.83-1.07)	641060	0.83 (0.68-1.03)
1-15	381890	1.00 (0.88-1.13)	485067	0.73 (0.56-0.97)
16+	183867	1.11 (0.98-1.25)	227321	1.07 (0.88-1.30)
Any[a]	1688871	1.02 (0.93-1.12)	2035125	0.91 (0.77-1.08)

[a] Data are calculated approximately

4.4 NHANES I Epidemiologic Follow-up Studies (Schreinemachers & Everson, 1994)

Between 1971 and 1975 the National Health and Examination Survey I (NHANES I) collected data from a probability sample of the civilian, non-institutionalized US population between the ages of 1 and 74 years. The NHANES I Epidemiologic Follow-up Studies (NHEFS) obtained follow-up data on subjects who had undergone a medical examination and were 25-74 years of age at the time of NHANES I. Characterization of aspirin use was based on questions in the baseline interview asking whether subjects used aspirin during the previous 30 days. Data were available from 12,668 subjects followed for an average of 12.4 years, of which 1257 were diagnosed with cancer more than two years after their NHANES I examination.

Results for lung cancer incidence in relation to aspirin use, as reported by the authors, were as follows:

Line	Sex	Age	Cases		Adjustment factors	Relative risk (95% CI)
			Aspirin	No aspirin		
1	Both	All	72	91	Sex, age	0.68 (0.49-0.94)
2	Men	<65	22	30	Age	0.60 (0.35-1.04)
3	Men	65+	18	47	Age	0.51 (0.30-0.88)
4	Men	All	40	77	Age	0.55 (0.38-0.81)
5	Women	<65	25	8	Age	1.70 (0.77-3.76)
6	Women	65+	7	6	Age	0.94 (0.31-2.81)
7	Women	All	32	14	Age	1.40 (0.74-2.66)
8	Men	All	40	77	Age	0.57 (0.39-0.84)
9	Men	All	-	-	Age, race, alcohol, education, smoking	0.54 (0.37-0.80)

Note: The first seven relative risks were calculated using the Mantel-Haenszel methods, whereas the last two were calculated using the Cox proportional hazards model. This accounts for the slight difference between the results for relative risk 4 and 8. Numbers of cases for relative risk 9 are not given, but can be presumed to be similar to those for relative risk 8.

Although the overall data for the sexes combined show a significant reduction in lung cancer risk associated with aspirin use, it is clear that the negative relationship was seen only in males. The relative risks for men and women shown in lines 4 and 7 of the table are in fact significantly ($p<0.05$) heterogeneous.

The paper contains results of a number of additional investigations. First, analysis for various cancer site/sex combinations, including lung cancer in men, showed that additional adjustment for the potential confounders race, education, smoking and alcohol had little effect on relative risk estimates, once age had been adjusted for (see lines 8 and 9 of the table).

Second, for overall cancer risk, where a negative association with aspirin had also been seen (RR = 0.83, 95% CI 0.74-0.93 for sexes combined), there was no indication of a dose-response effect in terms of when subjects took their aspirin last – in the last 0-2 days or in days 3-30 before interview.

Third, although the main analyses had been based on aspirin use at baseline in 1971-75, information had also been collected during the 1982-84 follow-up about "regular" aspirin use at that time, defined as at least once a week. The authors noted that "Among subjects interviewed personally in both studies, 30% of the subjects who reported aspirin use at the baseline interview

also reported a history of regular use at follow-up, whereas 15% who denied use at baseline reported a history of regular use at follow-up". They also noted that if analysis was conducted linking answers to the 1982-84 question, no association of overall cancer risk with aspirin use would have been seen (RR = 1.16, 95% CI 0.96-1.42), but results were not reported specifically for lung cancer.

4.5 Health Professionals Follow-up Study (Holick et al., 2003)

In 2003 results were reported from a prospective study of 49383 male Health Professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists and veterinarians) aged 40-75 and with no history of cancer (other than nonmelanoma skin cancer) at baseline in 1986. These men completed biennial self-administered questionnaires that assessed aspirin use and were followed up until the end of the year 2000. The earlier questionnaires asked about regular use of aspirin, with questions on frequency of aspirin use starting in 1992. Deaths in the cohort were ascertained through family members and the National Death Index.

The main results of the study reported by the authors, which showed no evidence of a relationship of overall lung cancer risk with aspirin use, were as follows:

Years of Relative risk (95% CI)

questionnaire considered	Aspirin use[a]	Deaths	Person Years	adjusted for Age	Multiple factors[b]
1986	No	204	428688	1.00	1.00
	Yes	124	172765	1.19(0.95-1.49)	1.13(0.89-1.43)
1986,1988	No	96	202457	1.00	1.00
	Yes	64	93431	1.11(0.80-1.53)	0.98(0.70-1.36)
1986,1988, 1990	No	66	126065	1.00	1.00
	Yes	41	52730	1.07(0.72-1.60)	0.88(0.58-1.34)
1986,1988, 1990,1992	No	22	44436	1.00	1.00
	Yes	28	37478	1.18(0.66-2.10)	0.89(0.47-1.67)

[a] "Yes" implies aspirin use two or more times a week reported consistently at all years considered, "No" implies aspirin use two or more times a week not reported at any of the years considered.
[b] Current age, age started to smoke regularly, cigarettes per day and time since quitting.

The authors noted that aspirin users tended to be slightly older, to be more likely to have smoked and to have started smoking at an earlier age. Dietary patterns were very similar and users and non-users, except for multivitamin and supplement use. Family history of lung cancer was similar among users and non-users.

Results in a format similar to those above were also reported for non-small cell carcinoma. No significant associations were seen, with the multivariate relative risks 1.16 (0.88-1.54), 1.02 (0.69-1.49), 0.98 (0.61-1.58) and 1.10 (0.52-2.35) for consistent reporting of aspirin use at 1986; 1986 and 1988; 1986, 1988 and 1990; and all four time points. One could also infer from these findings that no significant associations were seen for small cell lung cancer, which formed about a quarter of the cases.

Additional analyses reported in the text by the authors showed:

(i) No significant association of total lung cancer risk with baseline use of either acetaminophen (multivariate adjusted RR 1.26, 0.81-1.96) or other NSAIDs (1.07, 0.69-1.66).

(ii) No significant dose-response of total lung cancer risk with increasing frequency of aspirin use, with RRs 1.00, 0.62 and 1.21 for 0-4, 5-21 and 22+ days per months (trend p = 0.64). Nor was there any dose-response for non-small-cell lung cancer (trend p = 0.40).

(iii) No evidence of an interaction between baseline aspirin and smoking status on lung cancer risk.

One interesting feature of the study is the extent of inconsistency of response related to aspirin use (defined as two or more times a week). Thus, as shown in the table above, the numbers of lung cancer cases and person years of risk approximately halves for the analysis of consistent use in 1986 and 1988 as compared to the analysis based on use in 1986. This suggests that analyses based on a single assessment of aspirin use at baseline may result in comparison of groups where the "no aspirin" group contains many subjects who later use aspirin and the "aspirin" group contains many subjects who later stop using it.

5. Case-control studies

Six case-control studies have reported relevant results. Three give results only for total NSAID use (sections 5.1, 5.2 and 5.4). Of the other three, one gives results only for aspirin use (section 5.5), one gives results for aspirin use and for NSAID use (section 5.6), and one gives results for aspirin use and for use of any drugs containing acetylsalicylic acid (section 5.3).

5.1 Boston University Medical Centre Surveillance Study (Rosenberg, 1995)

Since 1976 Boston University Medical Centre has been developing and implementing a system of evaluating ambulatory drug effects (Slone et al., 1977), in which patients aged under 70 years of age with any of a number of cancers and other disorders are interviewed for information on previous drug use, medical history and other factors. In 1986 analyses of NSAID use were conducted in relation to the risk of several cancers, including lung cancer (Rosenberg, 1995). The analyses were confined to persons whose cancers had been diagnosed within the previous six months and who had no previous cancer. Controls were patients whose admission to hospital was judged obligatory and was unrelated to NSAID use, split into two groups – cancer controls (persons with sites other than those of the cases) and non-cancer controls (persons admitted for traumatic injuries and acute infections).

Multivariate relative risk estimates were adjusted for age, sex, interview year, geographic area, religion, race, cigarette smoking, coffee consumption, years of education and numbers of previous hospitalisations. As shown below, regular NSAID use initiated at least 1½ years before admission was not significantly related to risk of lung cancer.

Type of controls	Number of subjects by regular NSAID use				Relative risk (95% CI)
	Cases		Controls		
	Yes	No	Yes	No	
Cancer	72	1038	79	1102	0.8 (0.6-1.2)
Non cancer	72	1038	287	4619	1.0 (0.7-1.4)
Both[a]	72	1038	366	5721	0.90 (0.65-1.24)

[a] Data are calculated

5.2 UK General Practice Study (Langman et al., 2000)

Based on a database of general practices throughout the UK, 12,174 patients were identified who had a first diagnosis of one of five gastrointestinal cancers or four non-gastrointestinal cancers in 1993-95 and who had prescription data available for at least the previous 36 months. Each case was matched for age, sex and general practice with three controls without a diagnosis of the case's type of cancer at the time the case was diagnosed. Information was also reported on current smoking habits. Overall there were 1653 male and 907 female cases with lung cancer, matched to 4925 male and 2718 female controls. The authors (Langman et al., 2000) presented numbers of cases and controls and odds ratios adjusted for age and smoking status (and conditional on the matching) by number of prescriptions for aspirin and other NSAIDs in three periods: 13-24, 25-36 and 13-36 months before diagnosis. The results, summarized in the table below, did not show any significant association between lung cancer risk and numbers of prescriptions.

Numbers of prescriptions	Months 13-24 OR (95% CI)	Months 25-36 OR (95% CI)	Months 13-36 Cases	Months 13-36 OR (95% CI)
0	1.00	1.00	1903	1.00
1	0.90 (0.74-1.09)	1.03 (0.86-1.25)	235	0.85 (0.72-1.01)
2-6	0.95 (0.79-1.15)	0.87 (0.71-1.05)	250	1.05 (0.89-1.24)
7+	0.87 (0.68-1.11)	0.86 (0.67-1.11)	172	0.84 (0.69-1.02)
Trend p	0.16	0.10		0.17
Any[a]	0.91 (0.81-1.03)	0.93 (0.82-1.05)	657	0.92 (0.82-1.02)

[a] Data are calculated

The authors note that their data "may be criticised on the grounds that the drug prescription periods examined were relatively close to the time of diagnosis of cancer" and that they were "limited" in their ability to allow for smoking habits.

5.3 New York University Women's Health Study (Akhmedkhanov et al., 2002)

The New York University Women's Health Study is a long-term prospective study in which in 1985-1991 14,275 mostly Caucasian women between the ages of 31 and 70 years were enrolled in a mammography

screening clinic in New York City. Women who, in the preceding six months, had neither used hormonal medications nor been pregnant were eligible for enrolment. Study subjects answered questionnaires at baseline and at approximately every two years afterwards. Subjects who reported use of any drug containing acetylsalicylic acid at baseline were classified as exposed to aspirin. In the 1994-1996 follow-up questionnaire, subjects were asked "Have you taken Aspirin three or more times per week for a period of 6 months or longer?", with positive responders answering questions about the age when aspirin use started and stopped and the total duration of the treatment.

The study relating lung cancer risk to aspirin use (Akhmedkhanov et al., 2002) was a nested case-control study including 81 women with incident lung cancer identified by 2000 who had provided information about aspirin use at enrolment and in 1994-1996. Ten controls per case, matched to the cases on age, menopausal status, and dates of enrolment and follow-up, were randomly selected from the study participants.

Analyses were presented relating lung cancer risk (total and non-small cell) to ever use of aspirin (as defined by the question in the 1994-96 follow-up) and by duration of use. Odds ratios (summarized in the table below) were calculated in two ways: (a) conditional only on the matching factors, and (b) with additional adjustment for smoking (never, past, current) and educational status. 95% CI were only presented for analysis (b).

Lung cancer type	Aspirin use	Cases	Controls	OR_a	OR_b (95% CI)
All	None	66	656	1.00	1.00
	<5 years	6	61	0.98	0.60 (0.21-1.76)
	5+ years	9	91	0.99	0.68 (0.31-1.51)
	Ever	15	152	0.98	0.66 (0.34-1.28)
Non-small cell	None	53	506	1.00	1.00
	<5 years	5	45	1.05	0.48 (0.14-1.66)
	5+ years	4	67	0.57	0.33 (0.10-1.11)
	Ever	9	112	0.76	0.39 (0.16-0.96)

The matched analyses (a) show no evidence of an association for all lung cancer, but some indication of a reduction for non-small cell lung cancer, though this is clearly not statistically significant (I estimate 95% CI of about 0.35-1.60 for the estimate of 0.76). Nor is the implied increase in small cell lung cancer significant.

The matched and adjusted analyses (b) show more evidence of a negative relationship, particularly for non-small cell lung cancer where it is marginally statistically significant.

In the text of the paper the authors also note results relating to exposure to aspirin in the four weeks preceding the baseline enrolment. Here odds ratios were 1.02 (0.69-1.50) based on a matched analysis, and 0.93 (0.56-1.53) with additional adjustment for smoking and education.

The analyses based on the 1994-1996 follow-up questionnaire included 30 cases who reported on their long-term aspirin use after having been diagnosed with lung cancer. Excluding these cases and their matched controls, regular aspirin use was associated with a reduced incidence of all lung cancer (OR = 0.54, 95% CI 0.23-1.24) and of non-small cell lung cancer (0.23, 0.07-0.81) after adjustment for smoking and education.

5.4 James Cancer Hospital Study (Harris et al., 2002)

This case-control study was conducted based on interviews conducted in 1996-1999. The 489 lung cancer patients included in the study were diagnosed and treated at the James Cancer Hospital and Research Institute in Columbus, Ohio, with the diagnosis verified from the pathology report. The patients answered questions which included those on use of medications including NSAIDs and on smoking history. The 978 controls came from subjects without cancer of any kind interviewed in the Ohio State University Comprehensive Cancer Center health screening clinics. Data on use of NSAIDs and smoking history were also collected and the controls were frequency matched to the cases on gender, age, and pack-years of smoking. It was noted by the authors (Harris et al., 2002) that because "among the 489

lung cancer patients, only 17 (3.4%) reported no history of cigarette smoking … we therefore elected to utilize only heavy smokers in the control group". It is not explained, and is not apparent, how the cases and controls could be frequency matched on pack-years of cigarette smoking if the cases but not the controls included never smokers and light smokers. Nor is the term "heavy smokers" defined.

The authors present results, given below, of analyses unadjusted for any potential confounding variables, which show a dose-related reduction in risk of lung cancer with increasing frequency of NSAID use. The estimates were stated not to be modified by adjustment for matching or potential confounding factors.

NSAID use[a]	Cases	Controls	Relative risk (95% CI)
None	319	466	1.00
<1 PPD	72	185	0.57 (0.40-0.82)
1+ PPD	55	252	0.32 (0.23-0.44)
Trend p			<0.01
Any[b]	127	427	0.43 (0.34-0.56)

[a] Pills per day (PPD) for at least two years duration
[b] Data are calculated

The authors also noted that relative risk estimates were similar for the daily use of individual compounds such as aspirin (RR = 0.25) and ibuprofen (RR = 0.39) and for men (RR = 0.41) and women (RR = 0.22), with confidence limits not given. Use of the related analgesic acetaminophen was stated to show no association with lung cancer risk (RR 0.87, 95% CI 0.57-1.29).

Apart from the concerns noted above concerning the matching for smoking, it is also unclear from the paper whether the questions asked about use of NSAIDs were actually the same for the cases and the controls. It is also not clear whether adjustment in analysis was only attempted for age, gender and smoking or whether other factors were considered as potential confounding variables. Hospital patients with lung cancer and men and

women attending screening clinics may differ in respect of other factors which may affect aspirin use. Another possible weakness of the study lies in its use of NSAID data right up to the time of diagnosis, when the illness might have affected choice of analgesic.

The authors make little reference to other literature or any attempt to discuss biases that might have affected the findings.

5.5 Roswell Park Cancer Institute Study (Moysich et al., 2002)

This study included individuals who received medical services at the Roswell Park Cancer Institute (RPCI) in Buffalo, New York between 1982 and 1998 who completed a comprehensive questionnaire. The cases were 868 patients with primary, incident lung cancer, while the controls were 935 individuals with non-neoplastic conditions (though they had originally attended RPCI with a suspicion of neoplastic disease). Controls were frequency matched to cases on sex and five year age intervals. Cases and controls answered questions about aspirin use relevant to the period prior to the onset of disease, and provided information on frequency and duration of use.

The authors (Moysich et al., 2002) presented a variety of odds ratios adjusted for age, education and pack-years of cigarettes where appropriate. For regular use of aspirin (as defined as self-reported use at least once a week for at least one year) a reduced incidence of lung cancer was evident overall, and in various subsets of the population by sex, smoking and histological type of lung cancer. The negative association appears quite consistent.

Sex	Smoking[a]	Cell type	Cases		Controls		Adjusted OR (95% CI)
			User	Non User	User	Non User	
All	All	All	121	747	167	768	0.57 (0.41-0.78)
Males	All	All	85	448	115	462	0.62 (0.43-0.90)
Females	All	All	36	299	52	306	0.52 (0.29-0.95)
All	Low	All	13	149	50	238	0.43 (0.22-0.83)
All	Middle	All	43	264	30	127	0.70 (0.41-1.18)
All	High	All	58	278	22	68	0.66 (0.37-1.16)
All	All	Adeno	46	247	167	768	0.70 (0.46-1.06)
All	All	Squamous	43	264	167	768	0.70 (0.41-1.18)
All	All	Large	14	108	167	768	0.52 (0.27-1.00)
All	All	Small	12	142	167	768	0.32 (0.16-0.63)

[a] Low, middle and high based on pack-year distribution among current and former smokers

As shown in the table below, there was no very clear evidence of a dose-response relationship. The authors refer to "risk reductions associated with greater frequency of use", and with "prolonged duration of use and increasing table years", but the odds ratios do not actually appear to vary significantly, or even in a systematic direction, with frequency, duration or tablet years.

Dose-response index	Odds ratios (95% CI) Sexes combined	Males	Females
Frequency (tablets/wk)			
1-6	0.53 (0.28-0.99)	1.01 (0.46-2.59)	0.17 (0.05-0.50)
7+	0.58 (0.41-0.82)	0.56 (0.37-0.83)	0.88 (0.43-1.79)
Years of use			
1-10	0.56 (0.39-0.79)	0.65 (0.43-0.98)	0.42 (0.21-0.86)
11+	0.61 (0.34-1.09)	0.53 (0.26-1.10)	0.88 (0.30-2.55)
Tablet years[a]			
1-10	0.63 (0.44-0.92)	0.73 (0.48-1.12)	0.47 (0.22-0.99)
11+	0.45 (0.27-0.77)	0.40 (0.21-0.78)	0.61 (0.24-1.54)

[a] Tablets per day x years of use

In discussion, the authors present a summary of published studies and claim that their results are "largely consistent with the existing body of evidence on the association between regular aspirin use and lung cancer risk", although they note differences between findings of the various studies. In commenting on possible biases, they note that aspirin use was similar among the most common diagnostic categories forming the controls, tending to argue

against a bias due to inclusion of patients with specific conditions that would make them more likely to use aspirin.

5.6 American Health Foundation Study (Muscat et al., 2003)

This case-control study was conducted in 1992-2000 in several large hospitals in New York and Washington. The cases were patients with confirmed lung cancer The controls were patients without cancer from the same hospital matched to the cases by month of interview, gender and age. Controls with conditions related to regular aspirin use were excluded from the analyses – these conditions included rheumatoid arthritis, osteoarthritis and joint problems as well as peptic ulcer and bleeding disorders. At interview subjects provided information on use of over-the-counter and prescription medications, including brand, frequency and duration of use, as well as detailed data on smoking and other lifestyle and demographic characteristics.

Usage of NSAIDs varied little by diagnostic group of the controls or, among the controls, by gender, age education and smoking. As shown in the table below, regular use of NSAIDs and of aspirin, as compared to no or infrequent use, was associated with a reduced risk of lung cancer in most of the analyses.

			Odds ratio (95% CI)[a]	
Sex	Smoking	Cell type	NSAID	Aspirin
All	All	All	0.68 (0.53-0.89)	0.84 (0.62-1.14)
Male	All	All	0.61 (0.42-0.87)	0.70 (0.47-1.04)
Female	All	All	0.82 (0.56-1.20)	1.11 (0.69-1.80)
All	Never	All	1.28 (0.73-2.25)	2.03 (1.08-3.81)
All	Ever	All	0.60 (0.45-0.80)	0.68 (0.45-0.96)
All	Current	All	0.71 (0.41-1.22)	0.72 (0.38-1.36)
All	Former	All	0.58 (0.41-0.83)	0.69 (0.46-1.04)
All	All	Adenocarcinoma	0.66 (0.47-0.91)	0.82 (0.56-1.20)
All	All	Small cell	0.64 (0.35-1.15)	0.68 (0.34-1.35)
All	All	Squamous/other	0.70 (0.51-0.96)	0.80 (0.55-1.17)

[a] Adjusted for age, gender, years of education and pack-years of smoking

However, the negative relationship was only significant in some analyses (more so for NSAIDs than for aspirin), was not evident in never smokers, and (for aspirin) was not evident in women. The odds ratios did not actually vary significantly by sex though.

For the total data, analyses were also presented by duration and frequency of use. No dose response was evident within the patients who regularly used aspirin or NSAIDs.

	Odds ratio (95% CI)[a]	
	NSAID	Aspirin
Duration of use (months)		
No/infrequent use	1.00	1.00
12-59	0.62 (0.44-0.89)	0.72 (0.47-1.11)
60+	0.75 (0.53-1.06)	0.96 (0.64-1.43)
Frequency of use (tablets/day)		
<1	1.00	1.00
1-5	0.61 (0.45-0.83)	0.65 (0.45-0.93)
5+[b]	0.58 (0.43-0.78)	0.73 (0.51-1.05)

[a] Adjusted for age, gender, years of education and pack-years of smoking
[b] Categories as reported by the authors. It is unclear where 5 tablets/day fits in.

6. Summary of data and meta-analyses

Table 1 summarizes some characteristics of the 12 studies that have reported results (in terms of risk estimates with 95% CI) relating lung cancer risk to use of aspirin or NSAIDs. It can be seen that much of the relevant material has been published recently, with three studies published in the late 1980s, three in the mid 1990s and six published since the year 2000. Of these 12 studies, one is a randomised controlled trial, five are prospective studies and six are case-control studies (one nested in a prospective study). Of the five non-nested case-control studies, two attempted to remove patients suffering from NSAID-related conditions from the control group.

Ten of the studies were conducted in the USA (seven in specific areas and three nationwide) and two were conducted in the UK (both nationwide). As described in sections 3 to 5, two of the 12 studies (Peto et al., 1988; Holick et al., 2003) were conducted in doctors or other groups of health professionals and one was conducted in a retirement community (Paganini-Hill et al., 1989). Only two of the studies (Schreinemachers & Everson, 1994; Langman et al., 2000) can be considered nationally representative of the general population.

Two studies were of males and one of females. Of the other nine, five presented results separately for males and females. Only one study presented results for separate age groups. Three studies presented results by separate smoking groups. All the studies presented results for total lung cancer. Two studies also presented results for non small cell lung cancer, while two presented results by more detailed histological type.

Table 2 presents information on control of potential confounding by other factors in the 12 studies. Of the six case-control studies, all but one match for age and, where relevant, gender. Some adjusted for additional factors, including general practice month of interview and date of enrolment and follow-up. Only one matched for smoking though, as described in section 5.4, there must be doubts about the appropriateness of the matching procedure.

Of the 12 studies, all but two adjusted for age in analysis (in some cases by using methods appropriate for matched studies). The other two studies both made statements to the effect that matching made no difference and one of these was in any case a randomised trial. All the studies presenting results for males and females combined also adjusted for gender (or used matched methods) except for one study which said this made no difference to the results. Seven of the 12 studies adjusted for smoking in analysis. Of the other five, two were the studies that stated such adjustment made no difference. Six studies adjusted for one or more other factors, including race, education, alcohol consumption, area of study, religion and coffee consumption.

Table 3 presents information relating to exposure. Of the 12 studies, three present results according to NSAID use, seven present results according to aspirin use (one also in relation to any drug containing acetylsalicylic acid), one presents results according to both NSAID use and aspirin use, and one reports results relating to use of an aspirin and codeine mixture (which formed 84.5% of the prescriptions for aspirin in the Kaiser-Permanente pharmacies on which the study was based). Table 3 also includes details of the types of dose-response information available. Four give no such data, while eight give data according to one or more of some aspects of frequency of use, duration of use or consistency of use at different time points.

For the purposes of the meta-analyses, two definitions of exposure to aspirin or NSAIDs have been used. The "ever exposure" variable is the most inclusive, containing the widest definition of exposure. Thus, if data are available for aspirin use never, <1, 1-15 or 16+ times per month, the results for any exposure including all three exposed groups combined would be used. The "regular exposure" restricts attention to results for the group having the highest frequency of use or the longest duration of use reported. If results are given for both high frequency and long duration, those for high frequency have been selected. For both "ever exposure" and "regular exposure", the denominator of the relative risk is always the non-exposed group. Where dose response data are not available, the definitions of "ever exposure" and "regular

exposure" are the same. Studies vary in how they present the results, in some cases ignoring exposure unless it occurs with some minimum frequency or duration. As a result, low or infrequent exposure may appear in the numerator of the relative risk in some studies and as the denominator in others. This inconsistency cannot be avoided.

Table 3 includes the actual definitions of "ever exposure" and "regular exposure" used for the 12 studies. Table 4 gives the corresponding relative risks and meta-analyses, using data that are adjusted for most variables where there is a choice of estimates.

For "ever exposure" there are 17 relative risk estimates, 6 greater than 1.00 and 11 less than 1.00. The only statistically significant relative risks are the increase for the Selby study, the decrease for the Harris study, the decrease for males in the Schreinemachers study, and the two decreases (one for each sex) in the Moysich study. The estimates with the largest weight are the two for the Thun study (combined weight 578.8 of a total of 1385.5) and those for the Langman study (322.6) and the Selby study (163.7). Although the fixed-effects relative risk of 0.94 (95% CI 0.89-0.99) is statistically significant ($p<0.001$), there is also highly significant ($p<0.001$) heterogeneity. This is mainly due to the Harris study whose upper 95% confidence limit of 0.56 is below 14 of the estimates and below the lower 95% confidence limit of nine of them. The random-effects estimate, 0.84, is lower than the fixed-effects estimate. Though it has wider variation (95% CI 0.72-0.97), it remains statistically significant.

In view of the substantial contribution to the heterogeneity caused by the Harris study (and the doubts expressed in section 5.4 about its study design), estimates were also calculated omitting this study. The heterogeneity was reduced, but still remained statistically significant ($p<0.001$). Both the fixed-effects and the random-effects estimates increased, and became non-significant, being respectively 0.97 (95% CI 0.92-1.03) and 0.91 (95% CI 0.81-1.02).

The results for "regular exposure" are quite similar to those for "ever exposure". Again, there is highly significant ($p<0.001$) heterogeneity, with the Harris study a major contributor to it. With the Harris study included, the random-effects estimate (0.81, 0.67-0.99), but not the fixed-effects estimate (0.96, 0.90-1.03) is significant. When it is excluded, neither the fixed-effects estimate (1.01, 0.94-1.08) nor the random-effects estimate (0.90, 0.77-1.04) is significant.

Table 5 gives the results of some further meta-analyses, with estimates separated according to type of study, gender or whether the estimate related to aspirin or NSAID. As regards type of study, significant negative associations with aspirin are not evident in studies where the exposure data had been collected before disease (the intervention, prospective and nested case-control studies), and indeed a marginally significant ($p<0.05$) positive association is seen in the fixed-effects analysis for regular exposure. However a significant negative association is seen in the other case-control studies. However, the case-control estimates, which include that from the Harris study, are highly significantly ($p<0.001$) heterogeneous.

Combined estimates for males, for females or for sexes combined are not significant, although they tend to be less than 1.00.

When the exposure is based on aspirin use, no significant reduction in risk is seen. Estimates are lower and consistently significant when based on NSAID use, as they include results from the Harris study.

That the results for "ever exposure" and "regular exposure" are quite similar is not surprising, since the dose-response data given in detail in sections 4 and 5 and summarized in Table 6 often show no tendency for risk to reduce with increasing frequency or duration within users of aspirin or NSAID.

Of the 12 studies, three (Paganini-Hill et al., 1989; Selby et al., 1989; Thun et al., 1993) did not take account of smoking at all in their analysis and

one (Harris et al., 2002) seems not to have adequately controlled for smoking (see section 5.4). The other eight studies appear to have adequately controlled for smoking in analysis or by randomization. Restricting attention to these studies there is significant evidence of a negative association with lung cancer risk, and only limited evidence of heterogeneity. Thus, for ever exposure, fixed-effects estimates are 0.88 (0.81-0.96) and random-effects estimates are 0.82 (0.69-0.97) while, for regular exposure, the fixed-effects estimates are 0.78 (0.69-0.88) and random-effects estimates are 0.77 (0.66-0.89).

Formal meta-analyses have not been attempted by type of lung cancer, as type of lung cancer has only been considered in four studies. One prospective study (Holick et al., 2003) reported quite similar findings of a lack of association with aspirin use for both all lung cancer and non-small cell carcinoma, while a nested case-control study (Akhmedkhanov et al., 2002) reported a stronger negative association with aspirin use for non-small cell carcinoma than for all lung cancer. Two case-control studies (Moysich et al., 2002; Muscat et al., 2003) reported results by more detailed lung cancer type, but there was no tendency for risk estimates for a specific type to vary significantly from that reported for overall lung cancer risk.

The heterogeneity of the findings and the lack of control for smoking in some studies makes drawing an overall conclusion difficult. Another problem is determining whether aspirin use is affecting risk of lung cancer, or whether lung cancer (or conditions associated with it) is affecting aspirin use. Some of the studies recognized this problem and used procedures to try to ensure issues of "reverse causation" were minimized. These include the intervention trial (Peto et al., 1988) and the two case-control studies which used controls with conditions unrelated to aspirin use (Rosenberg, 1995; Muscat et al., 2003). However, the issue has certainly not been resolved in many of the studies.

A further problem is in obtaining reliable data on aspirin use. One study (Holick et al., 2003), which collected data on usage at four time points two years apart, found that relatively few people consistently reported aspirin

use (two or more times a week) at all the time points. Although there would be some loss due to death and loss to follow-up, the proportion of subjects reporting aspirin in use at the first questionnaire in 1986 who reported aspirin use consistently in 1988, 1990 and 1992 was quite low (about 22%).

7. Conclusions

Twelve epidemiological studies have been identified which relate use of aspirin (or total use of non specific anti-inflammatory drugs) to risk of lung cancer. Using sex-specific estimates where available, there is some evidence of a negative relationship with both "ever exposure" and "regular exposure" to aspirin.

Exposure	Estimates combined	Meta-analysis relative risk (95% CI) Fixed-effects	Random-effects
Ever[a]	17	0.94 (0.89-0.99)	0.84 (0.72-0.97)
Regular[b]	16	0.96 (0.90-1.03)	0.81 (0.67-0.99)

[a] "Ever exposure is the most inclusive definition of exposure available for the study.

[b] "Regular exposure" restricts attention to results for the group having the highest frequency of use or the longest duration of use reported.

However, the individual study estimates are highly heterogeneous due to extremely low risk estimates in one case-control study (0.43, 0.34-0.56 for ever exposure and 0.32, 0.23-0.44 for regular exposure) which seems open to a number of criticisms. Omitting this study removes the statistical significance of the association, with random-effects estimates 0.91 (0.81-1.02) for ever exposure and 0.90 (0.77-1.04) for regular exposure.

Other points to note about the data are as follows:

(i) The negative association is not evident in those studies that recorded aspirin use before the diagnosis of lung cancer was known (one intervention study, five prospective studies and one nested case-control study), but can only be seen in the five (non-nested) case-control studies;

(ii) There is some evidence of a negative association when attention is restricted to those studies that have controlled for smoking adequately;

(iii) There is little clear evidence of a dose-response in relationship either to frequency of use or duration of exposure;

(iv) Limited evidence does not suggest the relationship between lung cancer risk and aspirin use varies markedly by histological type of lung cancer;

(v) Many of the studies collected data on aspirin use relating to one time point, though evidence from one of the studies demonstrates considerable variability in use over time;

(vi) Interpretation of any differences in lung cancer risk relating to aspirin use is not straightforward. In some case-control studies, control groups may include individuals with diseases for which aspirin use may be indicated (or contra-indicated), while data collected on aspirin use at a time close to diagnosis may reflect the effect of the disease (or conditions leading up to it) on usage.

Although some of the meta-analyses of aspirin use and lung cancer risk do show a statistically significant negative relationship, the relationship is quite weak and the individual risk estimates heterogeneous. In view of the lack of clear dose-response and the various difficulties in interpreting the data, it cannot be concluded from the present evidence that aspirin definitely reduces risk of lung cancer. Though an effect is not implausible and may exist, it seems unlikely to be a strong one.

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TABLE 1 : Some characteristics of the 12 studies reporting results relating lung cancer risk to use of aspirin or NSAIDs

					Results by			
Principal author	Year[a]	Study Design[b]	Control Diseases	Location	Gender	Age	Smoking	Hist. Type[c]
Peto	1988	RCT	Not applicable	UK	M	No	No	No
Selby	1989	P	Not applicable	US, San Francisco	M+F	No	No	No
Paganini-Hill	1989	P	Not applicable	UK, Los Angeles	M,F.M+F	No	No	No
Thun	1993	P	Not applicable	US	M,F	No	No	No
Schreinemachers	1994	P	Not applicable	US	M,F,M+F	Yes	No	No
Holick	2003	P	Not applicable	US	M	No	Yes	NSM
Rosenberg	1995	CCH	Unrelated to NSAID use	US, Boston	M+F	No	No	No
Langman	2000	CCG	Not lung cancer	UK	M+F	No	No	No
Akhmedkhanov	2002	NCC	Not applicable	US, New York	F	No	No	NSM
Harris	2002	CCP	Not cancer	US, Columbus	M+F[d]	No	No	No
Moysich	2002	CCH	Non-neoplastic conditions	US, Buffalo	M,F.M+F	No	Yes	AD,SQ, LG,SM
Muscat	2003	CCH	Not cancer or aspirin related conditions	US, New York and Washington	M,F,M+F	No	Yes	AD,SM, SQ/OTH

[a] Year of publication

[b] RCT = randomised controlled trial, P = prospective study, CCH = case-control study in hospital(s), CCG = case-control study in general practice(s), NCC = case-control study nested in prospective study, CCP = case-control study with population controls

[c] All studies give results for overall lung cancer risk (or all respiratory cancer in Thun study). Some studies presented results additionally for AD = adenocarcinoma, SM = small cell carcinoma, SQ = squamous cell carcinoma, NSM = non small cell carcinoma, LG = large cell carcinoma or SQ/OTH = squamous cell or other carcinoma (not AD or SM)

[d] Results for males and females separately were not given with 95% CI

TABLE 2 : Control of potential confounding by other factors in the 12 studies reporting results relating lung cancer risk to use of aspirin or NSAIDs

Principal author	Matching factors	Factors adjusted for in statistical analysis
Peto	Randomized trial	Man years in study[a]
Selby	Not applicable (prospective study)	Age, gender
Paganini-Hill	Not applicable (prospective study)	Age, gender
Thun	Not applicable (prospective study)	Age
Schreinemachers	Not applicable (prospective study)	Age, gender and in some analyses race, alcohol, education and smoking (ever/never)
Holick	Not applicable (prospective study)	Age and in some analyses smoking (age at start, cigs/day and time since quitting)
Rosenberg	None	Age, gender, interview year, area, religion, race, cigarette smoking, coffee, education and number of previous hospitalizations
Langman	Age, gender and general practice	Age, smoking (ever/never) and matching factors
Akhmedkhanov	Age, menopausal status and dates of enrolment and follow-up	Matching factors and in some analyses smoking (never, past, current) and education
Harris	Age, gender and smoking (pack-years)	None[b]
Moysich	Age, gender	Age, gender, education and smoking (pack-years)
Muscat	Age, gender and month of interview	Age, gender, education and smoking (pack-years)

[a] It was noted that adjustment for minor baseline differences produced almost identical results
[b] It was noted that estimates were not modified by adjustment for matching or potential confounding factors

TABLE 3 : Definitions of exposure and aspects of dose-response studied for the 12 studies relating lung cancer risk to use of aspirin or NSAIDs

Principal author	Aspirin or NSAID	Definition(s) of "ever exposure"	Definition(s) of "regular exposure"	Dose-response data
Peto	Aspirin	Daily aspirin	Daily aspirin	No
Selby	Aspirin + codeine	Ever dispensed at specified pharmacies	Ever dispensed at specified pharmacies	No
Paganini-Hill	Aspirin	Any use at baseline in last month	Daily use at baseline	By frequency (never, <daily, daily)
Thun	Aspirin	Any use in last month	16+ times per month at baseline	By use per month (0, <1, 1-15, 16+)
Schreinemachers	Aspirin	Any use in last 30 days	Any use in last 30 days	No
Holick	Aspirin	2+ times per week at baseline	2+ times per week at baseline and in 1988, 1990 and 1992	By consistency of use at 4 time points
Rosenberg	NSAID	Regular use started at least 1½ years before admission	Regular use started at least 1½ years before admission	No
Langman	NSAID	Any prescription 13-36 months before diagnosis	7+ prescriptions 13-36 months before diagnosis	By number of prescriptions (0,1,2-6,7+) 13-24, 25-36 or 13-36 months before diagnosis
Akhmedkhanov	Aspirin	Ever 3+ times per week for 6 months in 1994-1996	Ever 3+ times per week for 5+ years in 1994-1996)	By years used 3+ times per week (0,<5,5+)
	(Any drug containing ASA)[a]	(Any use at baseline)	(Any use at baseline)	(No)
Harris	NSAID[b]	Use for at least two years	1+ pack per day for at least two years	By pills per day for at least two years (0,<1,1+)
Moysich	Aspirin	Use at least once a week for at least once a year	Use 7+ tablets a week for at least once a year	By tablets/wk (0,1-6,7+), years of use (0,1-10,11+) and tablet years (0,1-10,11+)
Muscat	Aspirin	Regular use	5+ tablets/day	By months of use (no/infrequent,12-59,60+) and tablets/day (<1,1-5,5+)
	(NSAID)	(Regular use)	(5+ tablets/day)	

[a] Acetylsalicylic acid
[b] RR estimates were given for aspirin use but not with 95% CI
Note: bracketed definitions are not used in the meta-analyses in Table 4

TABLE 4 : Relative risks and meta-analyses for "ever exposure" and "regular exposure"

Principal author	Gender	Ever exposure RR (95% CI)	Weight	Regular exposure RR (95% CI)	Weight
Peto	M	0.64 (0.29-1.41)	6.1	0.64 (0.29-1.41)	6.1
Selby	M+F	1.24 (1.06-1.44)	163.7	1.24 (1.06-1.44)	163.7
Paganini-Hill	M	1.14 (0.64-1.87)	15.5	1.35 (0.76-2.41)	11.5
	F	0.67 (0.33-1.36)	7.7	0.29 (0.07-1.21)	1.9
Thun	M	1.02 (0.93-1.12)	444.6	1.11 (0.98-1.25)	259.5
	F	0.91 (0.77-1.08)	134.2	1.07 (0.88-1.30)	100.9
Schreinemachers	M	0.54 (0.37-0.80)	9.4	0.54 (0.37-0.80)	9.4
	F	1.40 (0.74-2.66)	25.8	1.40 (0.74-2.66)	25.8
Holick	M	1.13 (0.89-1.43)	68.3	0.89 (0.47-1.67)	9.6
Rosenberg	M+F	0.90 (0.65-1.24)	36.8	0.90 (0.65-1.24)	36.8
Langman	M+F	0.92 (0.82-1.02)	322.6	0.84 (0.69-1.02)	100.6
Akhmedhkanov	F	0.66 (0.34-1.28)	8.7	0.68 (0.31-1.51)	6.1
Harris	M+F	0.43 (0.34-0.56)	61.7	0.32 (0.23-0.44)	36.5
Moysich	M	0.62 (0.43-0.90)	28.2	0.56 (0.37-0.83)	23.5
	F	0.52 (0.29-0.95)	10.9	0.88 (0.43-1.79)	7.6
Muscat	M	0.70 (0.47-1.04)	24.4	M+F	
		1.11 (0.69-1.80)	16.7	0.73 (0.51-1.05)	29.5
Total			1385.5		829.1
<u>Include all estimates</u>					
Number of estimates		17		16	
Degrees of freedom		16		15	
Heterogeneity chisquared		80.10		88.24	
Heterogeneity p		<0.001		<0.001	
Fixed-effects estimate		0.94 (0.89-0.99)		0.96 (0.90-1.03)	
Random-effects estimate		0.84 (0.72-0.97)		0.81 (0.67-0.99)	
Main contributor to heterogeneity		Harris M+F = 37.39		Harris M+F = 43.90	
<u>Remove Harris</u>					
Heterogeneity chisquared		40.97		42.32	
Heterogeneity p		<0.001		<0.001	
Fixed-effects estimate		0.97 (0.92-1.03)		1.01 (0.94-1.08)	
Random-effects estimate		0.91 (0.81-1.02)		0.90 (0.77-1.04)	
Other major contributor to heterogeneity		Selby M+F = 9.78		Schreinemachers M = 10.05	

TABLE 5 : Further meta-analyses for “ever exposure” and “regular exposure”

	Ever Exposure				Regular exposure			
	No. of estimates	Fixed effects RR(95% CI)	Random effects RR(95% CI)	Het p	No. of estimates	Fixed effects RR(95% CI)	Random effects RR(95% CI)	Het p
All	17	0.94(0.89-0.99)	0.84(0.72-0.97)	***	16	0.96(0.90-1.03)	0.81(0.67-0.99)	***
All except Harris	16	0.97(0.92-1.03)	0.91(0.81-1.02)	***	15	1.01(0.94-1.08)	0.90(0.77-1.04)	***
Intervention, prospective & nested case-control	10	1.02(0.96-1.09)	0.97(0.83-1.12)	**	10	1.09(1.01-1.18)	0.99(0.83-1.18)	**
Other case-control	7	0.80(0.74-0.88)	0.71(0.54-0.94)	***	6	0.69(0.61-0.79)	0.66(0.47-0.92)	***
Male	7	0.97(0.89-1.05)	0.83(0.66-1.04)	**	6	0.99(0.89-1.10)	0.80(0.56-1.15)	***
Female	6	0.89(0.77-1.03)	0.87(0.69-1.10)	NS	5	1.04(0.87-1.23)	0.98(0.73-1.31)	NS
Combined	4	0.92(0.85-1.00)	0.82(0.57-1.20)	***	5	0.90(0.82-1.01)	0.75(0.49-1.14)	***
Aspirin	14	0.99(0.93-1.06)	0.89(0.77-1.03)	***	13	1.04(0.97-1.13)	0.90(0.75-1.07)	***
NSAID[a]	5	0.81(0.74-0.88)	0.71(0.51-0.99)	***	4	0.67(0.59-0.77)	0.62(0.40-0.95)	***
Control for smoking	11	0.88(0.81-0.96)	0.82(0.69-0.97)	*	10	0.78(0.69-0.88)	0.77(0.66-0.89)	NS
No adequate control	6	0.97(0.91-1.04)	0.87(0.66-1.14)	***	6	1.05(0.97-1.14)	0.86(0.61-1.12)	***

[a] Including estimates from the Muscat study for NSAID shown in section 5.6 and not in Table 4

TABLE 6 : Summary of dose-response relative risks

Principal author	Gender	Levels	Relative risks
Paganini-Hill	M+F	None <Daily Daily	1.00 0.93 1.09
Thun	M	Never Occasionally 1-15 16+ per month	1.00 0.94 1.00 1.11
	F	Never Occasionally 1-15 16+ per month	1.00 0.83 0.73 1.07
Langman	M+F	0 1 2-6 7+ prescriptions in 13-36 months before diagnosis	1.00 0.85 1.05 0.84
Akhmedkhanov	F	None <5 5+ years use	1.00 0.60 0.68
Harris	M+F	None <1 1+ pills per day	1.00 0.57 0.32
Moysich	M	None 1-6 7+ tablets per week	1.00 1.01 0.56
	F	None 1-6 7+ tablets per week	1.00 0.17 0.88
	M	None 1-10 11+ years use	1.00 0.65 0.53
	F	None 1-10 11+ years use	1.00 0.42 0.88
Muscat	M	No/infrequent 12-59 60+ months use	1.00 0.72 0.96
	M	<1 1-5 5+	1.00 0.65 0.73