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Minireview

Aspirin and cancer: has aspirin been overlooked as an adjuvant therapy?

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Aspirin inhibits the enzyme cyclooxygenase (Cox), and there is a significant body of epidemiological evidence demonstrating that regular aspirin use is associated with a decreased incidence of developing cancer. Interest focussed on selective Cox-2 inhibitors both as cancer prevention agents and as therapeutic agents in patients with proven malignancy until concerns were raised about their toxicity profile. Aspirin has several additional mechanisms of action that may contribute to its anti-cancer effect. It also influences cellular processes such as apoptosis and angiogenesis that are crucial for the development and growth of malignancies. Evidence suggests that these effects can occur through Cox-independent pathways questioning the rationale of focussing on Cox-2 inhibition alone as an anti-cancer strategy. Randomised studies with aspirin primarily designed to prevent cardiovascular disease have demonstrated a reduction in cancer deaths with long-term follow-up. Concerns about toxicity, particularly serious haemorrhage, have limited the use of aspirin as a cancer prevention agent, but recent epidemiological evidence demonstrating regular aspirin use after a diagnosis of cancer improves outcomes suggests that it may have a role in the adjuvant setting where the risk:benefit ratio will be different.

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There is a substantial body of epidemiological evidence indicating that regular use of aspirin or other traditional non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced risk of developing cancer (Bosetti *et al*, 2006; Cuzick *et al*, 2009). Selective cyclooxygenase-2 (Cox-2) inhibitors have a more precise molecular target compared with traditional NSAIDs and were designed to have a better safety profile in terms of gastrointestinal toxicity. Several studies started evaluating Cox-2 inhibitors both as prevention agents and as potential therapeutic agents for patients with established cancer until concerns about cardiovascular system toxicities were raised in 2004 (Bresalier *et al*, 2005) when most of this work was discontinued.

Aspirin inhibits both Cox-1 and Cox-2, although it preferentially inhibits Cox-1 (Simmons *et al*, 2004). The first indication of a possible role for aspirin in cancer therapy came in 1968 when Gasic *et al* (1968) showed that platelet reduction was associated with a 50% reduction in metastases in mice. This was followed by the demonstration that aspirin administration produced a significant reduction in metastases in mice (Gasic *et al*, 1972) and that it prevented osteolysis produced by bony metastases from carcinosarcoma cells in rats (Powles *et al*, 1973). These findings were not followed up in human clinical trials. After a 15-year interval, there were a number of epidemiological studies of cancer prevention but almost no work assessing aspirin as a potential therapeutic agent against cancer. Two recent epidemiological studies demonstrating that regular aspirin use *after* a cancer diagnosis improves outcomes suggest that aspirin could have a role as an adjuvant therapy in cancer (Chan *et al*, 2009; Holmes *et al*, 2010).

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ASPIRIN AS AN ANTI-CANCER AGENT: MECHANISMS OF ACTION

Cox inhibition

Aspirin inhibits the enzyme Cox; two isoforms Cox-1 and Cox-2 are well characterised (Simmons *et al*, 2004). Cox converts arachidonic acid to prostaglandin H2, which in turn produces biologically active prostaglandins that influence pathophysiological processes in a range of tissues including angiogenesis, apoptosis, cell proliferation and migration, inflammatory response and thrombosis (Simmons *et al*, 2004; Ulrich *et al*, 2006). Inhibition of prostaglandin synthesis is considered the predominant mechanism by which NSAIDs act as anti-inflammatory agents, but it is unclear whether the anti-cancer properties of these agents can be solely attributed to Cox inhibition.

Support for the hypothesis that the anti-cancer effects of NSAIDs result from prostaglandin inhibition include the observation that higher concentrations of prostaglandins are found in cancers compared with the surrounding normal tissues and led to the hypothesis that prostaglandins might accelerate the growth and invasion of cancer (Easty and Easty, 1976). Growth factors and oncogenes also induce prostaglandin synthesis (Levine, 1981). More recently, Cox-2 overexpression has been identified in a number of different malignancies and it has been hypothesised that Cox-2 prostaglandins promote tumourigenesis by inhibiting apoptosis, modulating the immune system and regulating tumour-associated angiogenesis (Cha and DuBois, 2007). Understanding the relative roles of Cox-1 and Cox-2 in tumour progression is complicated as the enzymes function both in the tumour and in the peri-tumour stromal environment. For example, in a mouse model using stromal fibroblasts, Cox-1 was required for a polyp to develop to 1 mm, and after that, Cox-2 induction and microsomal

prostaglandin E2 were required for further growth (Takeda *et al*, 2003).

Mice modified genetically to be deficient in either Cox-1 or Cox-2 provide insights into the normal physiological functions of these enzymes and their possible role in carcinogenesis (Langenbach *et al*, 1999). Inducing a mutation in the *Apc* gene normally results in 100% of mice having intestinal neoplasia. In Cox-1 or Cox-2 deficient mice, the effect of this mutation is decreased by 80% indicating that inhibition of either Cox-1 or Cox-2 could be an effective anti-cancer strategy (Chulada *et al*, 2000). Similarly, in mouse skin cancer models, genetic or pharmacological inactivation of either Cox-1 or Cox-2 results in reduced tumourigenesis (Tiano *et al*, 2002). The half-life of aspirin in the human body is only 15–20 min; therefore, the clinical observations (Bosetti *et al*, 2006; Chan *et al*, 2009) that once-daily administrations of aspirin appear to have an anti-cancer effect, particularly in tumours that overexpress Cox-2 are intriguing. Patrono *et al* (2001) suggest that the key mechanistic feature is a persistent decrease in platelet Cox-1 activity leading to downregulation of Cox-2 in tumours or the peri-tumoural environment. Aspirin, unlike other NSAIDs, binds irreversibly to Cox, and the anucleate platelet is unable to re-synthesise the enzyme resulting in decreased thromboxane A2 and reduced platelet aggregation. In addition, it is hypothesised that platelets affect the development and spread of metastases through a number of mechanisms, including facilitating the adhesion of cancer cells to circulating leukocytes and endothelial cells, and permitting adhesion to the endothelium and transmigration. They also protect circulating cancer cells from immune-mediated clearance by natural killer cells, and produce growth factors that promote angiogenesis (Honn *et al*, 1992).

Non-Cox-dependent pathways

Several lines of evidence suggest that non-Cox-dependent pathways may also contribute to aspirin's anti-cancer effects (see Figure 1). Sulindac sulphone, an NSAID that inhibits neither Cox-1 nor Cox-2, inhibits tumour formation in mice models (Piazza *et al*, 1997b). In fibroblasts, neither Cox isoform is required for malignant transformation by the oncogene ras or the SV40 virus (Zhang *et al*, 1999). In addition, celecoxib appears a more promising anti-cancer agent than rofecoxib, despite rofecoxib being a more potent inhibitor of Cox-2. Celecoxib has a sulphonamide and 4-methylphenyl moiety that may allow it to interact with other important target proteins, such as the cell-cycle regulator protein kinase B (Grosch *et al*, 2006). A potential Cox-independent intracellular target for aspirin is the transcription factor nuclear factor κb (NFκB). Aspirin inhibits the activation of NFκB (Kopp and Ghosh, 1994); this effect has been demonstrated *in vitro* and *in vivo* and is accompanied by an increase in apoptotic cells in neoplastic epithelial cells but not in normal intestinal mucosa (Stark *et al*, 2007). *In vitro* evidence also demonstrates that aspirin can potentially interact directly with other molecules and pathways implicated in tumourigenesis, including B-catenin and wnt signalling, tumour necrosis factor, polyamine metabolism and the DNA mismatch repair system (Martinez *et al*, 2003; Jankowski and Anderson, 2004; Elwood *et al*, 2009).

Apoptosis and angiogenesis are considered important physiological processes in the growth, development and treatment of cancer. Some *in vitro* studies report that aspirin is relatively inactive as an inducer of cell-cycle arrest and apoptosis and concentrations of 1 mM are required in short-term growth assays. Others found that long-term (25 days) exposure to 100–200 μM of aspirin results in marked growth inhibition and argue that this a more clinically relevant model (Elder and Paraskeva, 1999). Questions as to whether aspirin-induced apoptosis is mediated through Cox inhibition are raised by observations that NSAIDs that inhibit neither Cox-1 or Cox-2 induce apoptosis and, that low-dose salicylates inhibit apoptosis *in vitro* possibly by direct effects on apoptosis-regulating genes such as *Bcl2* and *Bax* (Elwood *et al*, 2009). In addition, 2,5-dimethyl celecoxib, a structural analogue of celecoxib that does not inhibit Cox-2, induces apoptosis both *in vitro* and *in vivo*. This has been attributed to downregulation of survivin, an anti-apoptotic protein that inhibits caspase activity and increases apoptosis (Pyrko *et al*, 2006).

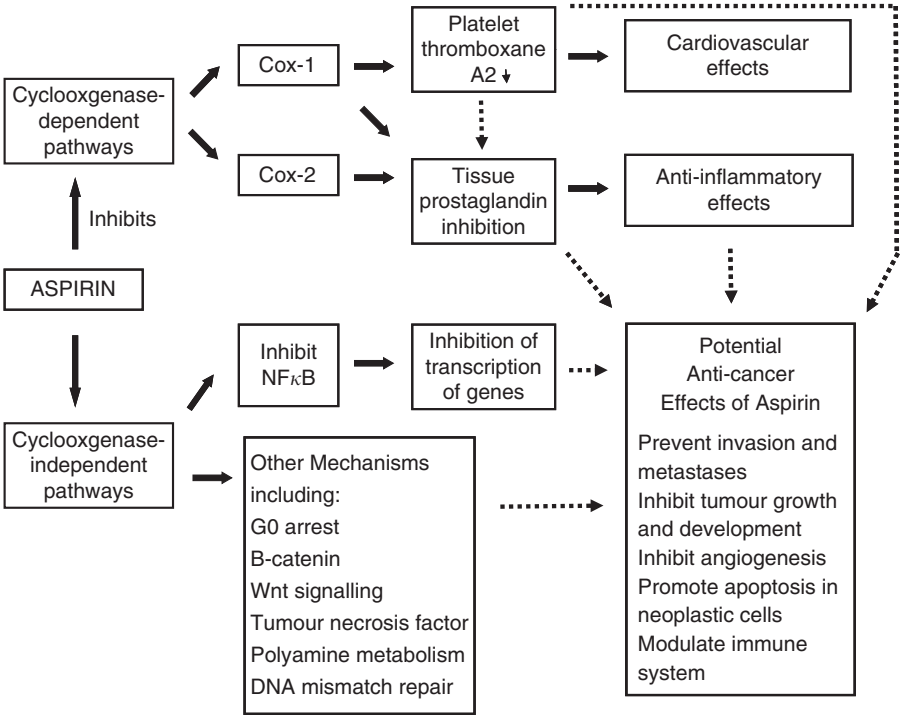

Figure 1 Aspirin mechanisms of action and pathophysiological effects. Black block arrows indicate known mechanisms. Dotted black arrows indicate potential mechanisms that could contribute to anti-cancer effects. Cox = cyclooxygenase; NFκB = nuclear factor-κB.

As early as 1983, aspirin was shown to inhibit tumour growth and vascularisation in tumours transplanted in rats (Peterson, 1983). More recently, it has been shown that aspirin at a therapeutic dose (0.5 mM) inhibits endothelial cell tubule formation, which is essential for vessel remodelling during angiogenesis. Selective inhibitors of Cox-1 and Cox-2 did not inhibit angiogenesis in this assay, suggesting that aspirin may directly inhibit angiogenesis through a Cox-independent pathway (Borthwick *et al*, 2006).

ASPIRIN AS AN ANTI-CANCER AGENT: CLINICAL EVIDENCE

Case–control and cohort studies: primary prevention

The first epidemiological evidence that aspirin could act as a chemoprevention agent was the report by Kune *et al* (1988) of a case–control study, in which aspirin use was associated with a significantly lower risk of colorectal cancer even after adjustment for other risk factors. In 2005, Bosetti *et al* reviewed all case–control and cohort studies up to that date, ~100 studies, in which the use of aspirin and cancer risk was examined. The pooled relative risk (RR) for developing colorectal cancer was 0.71 (95% CI: 0.67–0.75), although there was significant heterogeneity between trials and study designs. There was more limited evidence that aspirin prevented cancers of the oesophagus (RR 0.72, 95% CI: 0.62–0.84), stomach (RR 0.84, 95% CI: 0.76–0.93), breast (RR 0.91, 95% CI: 0.88–0.95) and lung (RR 0.94, 95% CI: 0.89–1.00) (Bosetti *et al*, 2006). Two recent large cohorts have highlighted that response appeared dependent on both the duration of aspirin use and dose, with the maximum reduction in colorectal cancer incidence seen when more than fourteen 325 mg tablets were taken per week for 6–10 years (Chan *et al*, 2005, 2008).

Randomised studies: primary prevention

Two large placebo-controlled trials designed to evaluate low-dose aspirin (100 or 325 mg on alternate days) as a primary prevention strategy against cancer, with a mean follow-up of ~10 years, did not show a reduction in the risk of developing colorectal cancer (Sturmer *et al*, 1998; Cook *et al*, 2005) (Table 1 and Figure 2A). Potential reasons why these trials were negative include lack of efficacy, ineffective dose and scheduling, poor compliance and the need for even longer follow-up. Two smaller randomised trials with longer-term (median 23 years) follow-up evaluating whether higher doses of aspirin (300–1200 mg) decreased the incidence of vascular events (Flossmann and Rothwell, 2007) did show a reduction in colorectal cancer incidence (HR 0.73, 95% CI: 0.56–0.96, $P=0.02$) (Table 1 and Figure 2A), and a recent pooled analysis of individual patient data (IPD) from these trials and two others primarily assessing the cardiovascular benefits of daily aspirin has shown an overall reduction in long-term incidence of colorectal cancer (HR 0.76, 95% CI: 0.6–0.96, $P=0.02$) (Rothwell *et al*, 2010). Analysing all the randomised data of aspirin *vs* no aspirin in which colorectal cancer incidence data are available (Figure 2B) results in an HR of 0.92 (95% CI: 0.8–1.05, $P=0.20$).

A subsequent IPD meta-analysis with death from cancer as the primary outcome measure that included seven randomised trials of aspirin for primary or secondary prevention of vascular disease (Table 1) with an average treatment period of at least 4 years (Rothwell *et al*, 2011) showed a reduction in deaths from all cancers after 5 years of follow-up (HR 0.66, 95% CI: 0.50–0.87, $P=0.003$). The latent period before an effect on deaths from oesophageal, pancreatic, brain, and lung cancers was ~5 years, but later for stomach and prostate cancers and also colorectal cancer consistent with our current understanding of the genetic events that underlie the development and progression from adenoma to colorectal carcinoma. Benefit was seen with doses as low as 75 mg daily and the absolute reduction in 20-year risk of cancer death was 7.08% (2.42–11.74) for those aged >65 years.

Randomised studies: secondary prevention

Four randomised trials (Table 1 and Cole *et al*, 2009) have evaluated aspirin and the development of colorectal adenomas in patients previously diagnosed with colorectal cancer or adenoma. In one study, a reduction in the risk of developing further adenomas was seen counter-intuitively with low-dose aspirin (81 mg daily) (RR 0.81, 95% CI: 0.69–0.96) but not with higher doses (325 mg daily) (RR 0.96, 95% CI: 0.81–1.13, $P=0.06$) (Baron *et al*, 2003). Combining results of the secondary prevention trials in a meta-analysis (Figure 2C and Cole *et al*, 2009), suggests that aspirin reduces the RR of further adenomas by 18% (RR 0.82, 95% CI: 0.74–0.91, $P=0.0002$), with similar estimates for doses <300 mg (RR 0.82, 95% CI: 0.70–0.95, $P=0.007$) or >300 mg (RR 0.84, 95% CI: 0.74–0.94, $P=0.004$) of aspirin daily.

Therapeutic studies

Two recent non-randomised studies have examined the use of aspirin after a diagnosis of cancer. Chan *et al* reported that compared with non-users, regular users of aspirin after a diagnosis of colorectal cancer had reduced colorectal cancer-specific mortality (HR 0.71, 95% CI: 0.53–0.95) and overall mortality (HR 0.79, 95% CI: 0.65–0.97) in a multivariate analysis. Importantly, participants whose primary tumours overexpressed Cox-2 had most benefit with an HR of 0.39 (95% CI: 0.20–0.76) for colorectal cancer-specific mortality compared with an HR of 1.22 (95% CI: 0.36–4.18) for those whose primary tumours had weak or absent Cox-2 expression. In addition, those who had taken aspirin before diagnosis did not seem to benefit (HR 0.89, 95% CI: 0.59–1.35) compared with those with no previous use (HR 0.53, 95% CI: 0.51–0.92) (Chan *et al*, 2009). Similar results have been seen for breast cancer, with aspirin use after breast cancer diagnosis associated with decreased distant recurrence and breast cancer mortality (Holmes *et al*, 2010). The adjusted RRs for 2–5 or 6–7 days of aspirin use on breast cancer mortality compared with no use were 0.29 (95% CI: 0.16–0.52) and 0.36 (95% CI: 0.24–0.65), respectively.

Three small randomised-controlled trials have assessed the effects of aspirin in combination with traditional anti-cancer therapies (Table 1 and Figure 2D). Three hundred small cell lung cancer patients were assigned to aspirin 1 g per day for 18 months or no aspirin in addition to their chemotherapy (Lebeau *et al*, 1993). There was no evidence that survival was different (HR 1.01, 95% CI: 0.81–1.27, $P=0.09$) and aspirin appeared to be well tolerated. Another trial found no evidence of a survival benefit (HR 0.91, 95% CI: 0.63–1.31, $P=0.60$) when 176 patients with advanced renal cell cancer received interferon-α with or without aspirin 2400 mg daily (Creagan *et al*, 1991). A small trial of only 66 patients evaluated 1200 mg of aspirin daily compared with placebo as adjuvant treatment for Duke's B2 and C colorectal cancer (HR for survival 0.65, 95% CI: 0.02–18.06, $P=0.90$) (Lipton *et al*, 1982).

DISCUSSION

Current drug development work recognises that the growth of tumours involves cross-talk between different signalling pathways, and that resistance develops to agents that have a single target. Aspirin affects multiple intracellular pathways and influences physiological processes such as apoptosis and angiogenesis that are important in the growth and development of malignancies (Figure 1). Publicly funded researchers have a responsibility to

Table 1 Randomised trials of aspirin *vs* no aspirin/placebo assessing cancer outcomes

Trial	Accrual period	Participants randomised	Type of participants/main aim	Aspirin comparison	Aspirin duration	Follow-up
Primary prevention of cancer						
Physicians' Health Study (PHS) (Sturmer *et al*, 1998)	1982–1988	22 071	Male physicians 40–84 years Primary prevention of cancer	Aspirin 325 mg alternate days *vs* placebo	7–11 years	Mean = 12 years
Women's Health Study (WHS) (Cook *et al*, 2005)	1993–1996	39 876	Female health-care professionals ⩾45 years Primary prevention of cancer	Aspirin 100 mg alternate days *vs* placebo	5 years	Mean = 10 years
British Doctors Aspirin Trial (BDAT) (Flossmann and Rothwell, 2007)	1978–1984	5139	UK resident male doctors <80 years Primary prevention of cardiovascular (CV) events	Aspirin 500 mg *vs* no aspirin	5–6 years	Median = 23 years
UK Transient Ischaemic Attack trial (UK-TIA) (Flossmann and Rothwell, 2007)	1979–1985	2449	TIA or minor ischaemic stroke within 3 months, >40years Secondary prevention of CV events	Aspirin 300 or 1200 mg daily *vs* placebo	Median 4 years, range 1–7 years	Median = 23 years
Swedish Aspirin Low-dose Trial (SALT) (Rothwell *et al*, 2010)	1984–1989	1360	Patients 50–79 years, with recent CV event or retinal artery occlusion Secondary prevention of CV events	Aspirin 75 mg daily *vs* placebo	Median 2.7 years	Until 2007 – ~20 years from randomisation
Swedish Angina Pectoris Aspirin Trial (SAPAT) (Rothwell *et al*, 2011)	1985–1989	2035	Patients with chronic stable angina Primary prevention of myocardial infarction	Aspirin 75 mg daily *vs* placebo	Median 4.2 years, range 1.9–6.3 years	Until 1991
Thrombosis Prevention Trial (TPT) (Rothwell *et al*, 2010)	1989–1992	5085	Males 45–69 years, at high risk of CV disease Primary prevention of CV events	Aspirin 75 mg daily *vs* placebo	Median 6.9 years, range 4.3–8.6 years	Until 2009 – ~20 years from randomisation
Early Treatment Diabetic Retinopathic Study (ETDRS) (Rothwell *et al*, 2011)	1980–1985	3771	Patients, 18–70 years, with diabetic retinopathy Primary prevention of death, CV events and kidney disease	Aspirin 650 mg daily *vs* placebo	Median 5 years, range 4–9 years	Mean = 5 years
Prevention of Progression of Arterial Disease and Diabetes Trial (POPADAD) (Rothwell *et al*, 2011)	1997–2001	1276	Patients ⩾40 years, with type I/II diabetes and asymptomatic peripheral arterial disease Primary prevention of CV events	Aspirin 100 mg daily *vs* placebo	Median 6.7 years, range 4.5–8.6 years	Until 2006
Japanese Primary Prevention of Atherosclerosis Trial (JPAD) (Rothwell *et al*, 2011)	2002–2005	2539	Patients 30–85 years, with type II diabetes mellitus Primary prevention of CV events	Aspirin 81 or 100 mg *vs* placebo	Median 4.4 years, range 3.0–5.4 years	Until 2008
Aspirin for Asymptomatic Atherosclerosis Trial (AAA) (Rothwell *et al*, 2011)	1998–2008	3350	Patients 50–75 years, with low ankle brachial index and no clinical CV disease Primary prevention of CV events	Aspirin 100 mg *vs* placebo	Median 8.2 years, range 6.7–10.5 years	Mean = 8.2 years
Secondary prevention of cancer						
Colorectal Adenoma Prevention Study (CAP) (Sandler *et al*, 2003)	1993–2000	635	Patients with history of colorectal cancer Secondary prevention of adenoma	Aspirin 325 mg daily *vs* placebo	3–4 years	Median = 2.6 years
Aspirin/Folate Polyp Prevention Study (AFPPS) (Baron *et al*, 2003)	1994–1998	1121	Patients with recent history of histologically verified adenoma Secondary prevention of adenoma	Aspirin 81 or 325 mg daily *vs* placebo	A few years	Mean = 2.8 years
Association por la Prevention par l'Aspirine du Cancer Colorectal (APACC) (Benamouzig *et al*, 2003)	1996–2000	272	Patients with history of histologically verified adenoma Secondary prevention of adenoma	Lysine acetylsalicylate 160 or 300 mg *vs* placebo	1 year	At 1 year
UK Colorectal Adenoma Prevention Study (ukCAP) (Logan *et al*, 2008)	1997–2001	945	Patients with recent history of adenoma Secondary prevention of adenoma	Aspirin 300 mg daily *vs* placebo	3.5–5.5 years	At 3 years
Treatment of cancer						
Lipton *et al* (1982)	Not stated	66	Patients with resected Dukes' B2 or C colorectal cancer Cancer therapy	Aspirin 1200 mg daily *vs* placebo	2 years	Median = 2 years (aspirin) Median = 2.3 years (control)
Lebeau *et al* (1993)	1983–1985	320	Patients with limited or extensive small cell lung cancer Cancer therapy	CCAVP16 chemotherapy+1000 mg aspirin daily *vs* CCAVP16 chemotherapy	18 months	5–7 years
Creagan *et al* (1991)	1988–1990	179	Patients with renal adenocarcinoma Cancer therapy	IFN-α2A+2400 mg aspirin daily *vs* IFN-α2A	Not stated	Not stated

Abbreviation: IFN-α2A = interferon-α2A.

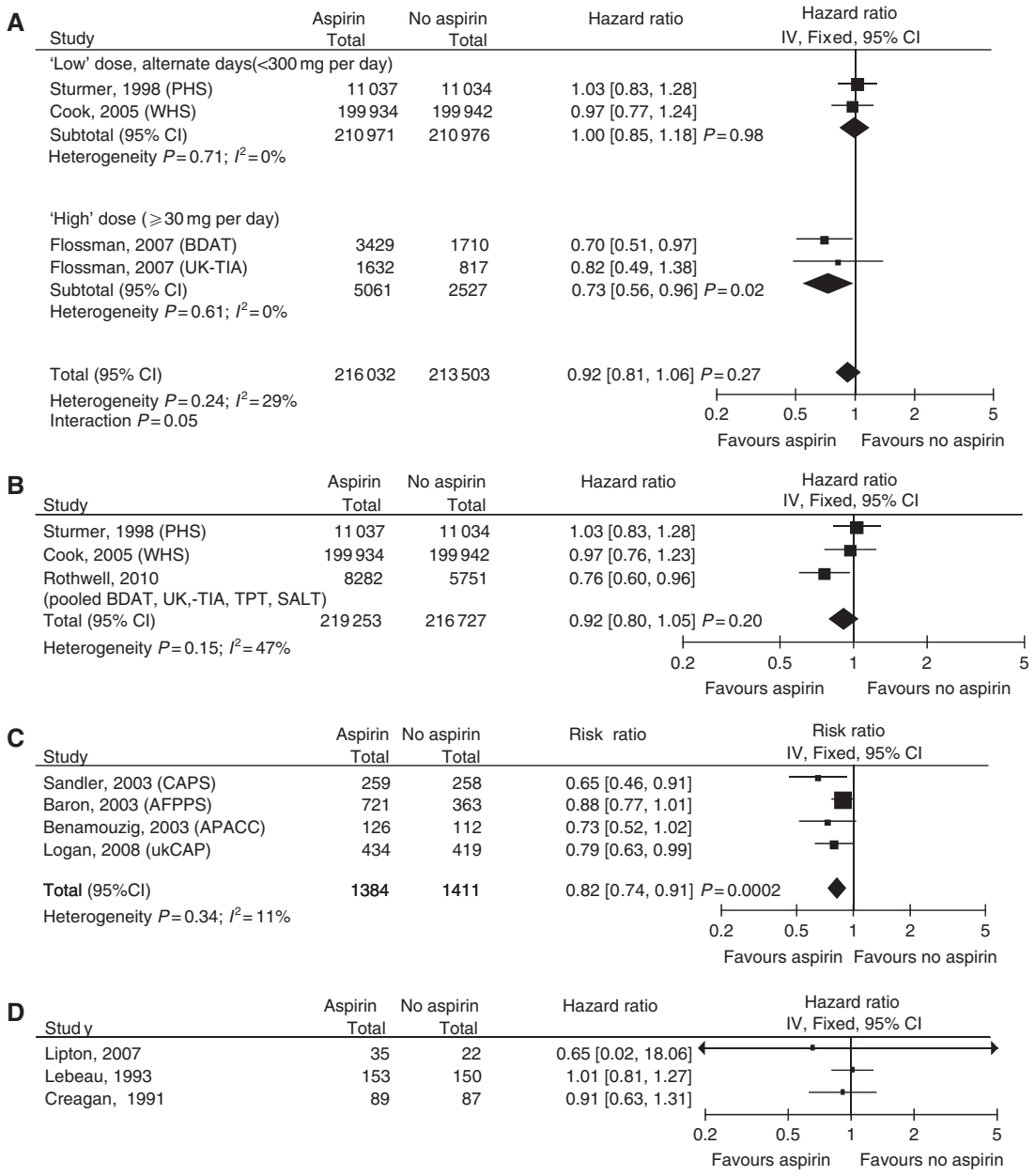

Figure 2 (**A**–**C**) Randomised trials of aspirin *vs* no aspirin/placebo in which colorectal cancer outcomes are available. (**A**) Includes trials designed to assess aspirin as a primary prevention agent against cancer and the first evidence from the long-term follow-up of trials primarily designed to improve cardiovascular outcomes. (**B**) Includes recent data from a meta-analysis of cardiovascular trials from which cancer incidence data were obtained. (**C**) Trials designed as secondary prevention against colorectal cancer. (**D**) Trials in which aspirin was used as a therapeutic agent against cancer with overall survival as the primary outcome measure. Details of the trials are given in Table 1.

ensure that drugs for which there is no longer a financial incentive for pharmaceutical companies to develop further are assessed in light of current knowledge and evolving clinical practice. Aspirin pre-dates current anti-cancer strategies such as the use of adjuvant chemotherapy after a potentially curative operation. Although significant tumour shrinkage is not seen when aspirin is administered for other clinical indications such as cardiovascular disease, epidemiological evidence and pre-clinical data suggest that aspirin is worthy of further investigation particularly in the adjuvant setting, after potentially curative surgery and chemotherapy if appropriate, when disease burden is expected to be minimal.

Regular aspirin use is not currently recommended as a primary prevention strategy against cancer for those at average risk because of the risk of toxicity, particularly serious gastrointestinal bleeding. It is estimated that regular aspirin use increases the risk of a significant bleed from 1% over 10 years to 2–3% (Cuzick *et al*, 2009) and this outweighs the potential cancer benefits particularly if effective screening is available. For aspirin administered adjuvantly, the benefit:risk ratio will be different, as higher morbidity and mortality from recurrent cancer may outweigh the toxicity associated with regular aspirin use. There is also potential for wider health benefits; colorectal cancer shares similar risk factors, such as smoking and the metabolic syndrome, with coronary artery disease; thus, aspirin could potentially be beneficial from both an oncological and cardiological perspective (Chan *et al*, 2007). In any future trials the challenge will be to identify and exclude those individuals most at risk of toxicity, for

example, those with a previous history of gastric ulceration (Patrono *et al*, 2001) and include those most likely to benefit. Commencing aspirin while conventional adjuvant cytotoxic chemotherapy is being administered could increase toxicity, particularly the risk of bleeding if thrombocytopaenia was present. Waiting until chemotherapy had finished would allow the use of a 'run-in' period, as used in adenoma prevention trials, in which a dose of 300 mg daily appeared to be well tolerated and participants were assessed as to whether they would be able to tolerate aspirin before they were randomised (Baron *et al*, 2003; Sandler *et al*, 2003). This increased compliance and reduced the risk of serious adverse events particularly gastrointestinal haemorrhage.

With the exception of the recent data from the Thrombosis Prevention Trial and the Swedish Aspirin Low Dose Trial presented by Rothwell *et al* (2010), the epidemiological data and the randomised trials assessing primary prevention support the premise that the anti-cancer effects of aspirin are most likely to be seen when higher doses are administered, there is long-term use (many years), longer follow-up (>10 years in some instances) and daily usage rather than alternate day scheduling. At higher doses, aspirin is a more potent inhibitor of Cox-2 providing a potential mechanistic explanation for these findings. The observation that the benefit of aspirin after colorectal diagnosis was greatest in those whose tumours overexpressed Cox-2, and that those who had taken aspirin before diagnosis did not appear to benefit from taking aspirin adjuvantly (Rothwell *et al*, 2010) gives an indication as to who may benefit from aspirin after a cancer diagnosis and emphasises the need for pathological assessment of tumour samples to be built into any randomised trials.

The current limited testing of aspirin (http://clinicaltrials.gov) as a therapeutic agent either in the adjuvant setting (ASCOLT and Big A trial) or in combination with other anti-cancer agents is in marked contrast to the number of studies that were initiated using selective Cox-2 inhibitors before 2004. There were numerous phase II studies and at least 12 randomised phase III trials that were ongoing in 2004, before the concerns about cardiovascular toxicity were raised, with >9000 planned participants including those with breast, colorectal, oesophageal, prostate and lung malignancies. A number of these studies involved rofecoxib and had to be discontinued when the product was withdrawn. Others were stopped early although the investigational agent (usually celecoxib) was not withdrawn.

Conclusions

Aspirin continues to be evaluated *in vitro* and in pre-clinical models to help elucidate mechanisms involved in carcinogenesis and the response of tumours to anti-neoplastic agents. Recent randomised evidence from trials primarily designed to prevent cardiovascular disease show a reduction in cancer incidence with long-term follow-up and epidemiological evidence from colorectal and breast cancer studies evaluating the effects of aspirin use after diagnosis suggests that aspirin may have a role in the adjuvant setting. The clinical management of patients is also continually evolving, with new combinations of agents or strategies being assessed; aspirin should not be overlooked in this process because it is neither new nor expensive.

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