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).

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 SV-40 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 is 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 (Pyrkko 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 I 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) (Stulmmer 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    | 5,139                   | 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    | 2,449                   | TIA or minor ischaemic stroke within 3 months, > 40 years, secondary prevention of CV events | Aspirin 300 or 1,200 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    | 1,360                   | Patients 50 – 79 years, 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    | 2,035                   | 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    | 5,085                   | 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    | 3,771                   | 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 (POPADADD) (Rothwell et al, 2011)                                         | 1997 – 2001    | 1,276                   | Patients ≥ 40 years, with type III 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 (JAPAD) (Rothwell et al, 2011)                                                   | 2002 – 2005    | 2,539                   | Patients 30 – 85 years, with type II diabetes mellitus, primary prevention of CV events      | Aspirin 81 or 100 mg daily 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    | 3,350                   | Patients 50 – 75 years, with low ankle brachial index and no clinical CV disease, primary prevention of CV events | Aspirin 100 mg daily 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 |
| AspirinFolate Polyp Prevention Study (AFPPS) (Baron et al, 2003)                                                                        | 1994 – 1998    | 1,121                   | 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 pour la Prevention par l’Aspirine du Cancer Colorectal (APACC) (Benhamouz et al, 2003)                                        | 1996 – 2000    | 272                     | Patients with history of histologically verified adenoma, secondary prevention of adenoma   | Lysine acetylsalicylate 160 or 300 mg daily vs placebo | 1 year          | At 1 year |
| UK Colorectal Adenoma Prevention Study (uCAP) (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 1,200 mg daily vs placebo | 2 years         | Median = 2 years (aspirin) |
| Lebeau et al (1993)                                                                                                                     | 1983 – 1985    | 320                     | Patients with limited or extensive small cell lung cancer, cancer therapy                   | CCAVP16 chemotherapy + 1,000 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 + 2,400 mg aspirin daily vs IFN-α2A | Not stated     | Not stated |

**Abbreviation:** IFN-α2A = interferon-α2A.
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 overlooked as an adjuvant therapy?

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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 thrombocytopenia 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 cancer 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 (usual 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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