Critical Reviews in Oncology/Hematology 104 (2016) 87–90

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

The role of aspirin in colorectal cancer chemoprevention

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Contents

ARTICLE INFO

Article history:
Received 16 January 2016
Received in revised form 3 March 2016
Accepted 25 May 2016

Keywords:
Aspirin
Colorectal cancer
Chemoprevention
Cyclooxygenase-1
Cyclooxygenase-2
Prostaglandins

ABSTRACT

Considerable interest has emerged over the last decade regarding the role of aspirin in prevention of colorectal cancer. This disease is one of the commonest cancers in the Western World, therefore, the existence of a simple "everyday" agent, which could have the ability to prevent the disease, represents an invaluable opportunity clinicians may be able to exploit.

Evidence from case-control and cohort studies, and recent updates of randomised controlled trials have been very encouraging—indicating benefit from long term use of aspirin at low dose. Possible mechanisms of chemoprevention include inhibition of the cyclooxygenase (COX) pathway, or COX-independent mechanisms, for example, the PIK3CA pathway, or therapy-induced senescence of cancer cells.

The most serious side effect of prolonged aspirin treatment is haemorrhage, especially from the GI tract. This is likely to be less of a problem with chemoprevention at lower doses. One also needs to consider the impact if aspirin resistance, an increasingly recognised clinical entity.

1. Introduction

The incidence of colorectal cancer is increasing in most countries. Around 1 million new cases occur per year, with nearly 600 000 deaths, globally, with a lifetime risk of about 5 percent (Jemal et al., 2010).

It is accepted most colorectal cancers develop from adenomatous polyps over a number of years (Chell et al., 2005), although some cancers, especially right-sided, may develop independent of a polyp stage, or at least have a much shorter period before becoming a cancer. Whatever the route to malignancy, it is now increasingly clear abnormal prostaglandin generation plays a role in the evolution of most epithelial cancers from precursor lesions (Singh-Ranger and Mokbel, 2002a; Mokbel and Singh-Ranger, 2002; Singh-Ranger et al., 2008); this includes breast, colorectal and prostate cancer.

With regards to the colon, both benign polyps and invasive colorectal cancers contain increased levels of prostaglandins compared to normal tissue (Kettunen et al., 2003; Pugh and Thomas, 1994; Earnest et al., 1992; Giardiello et al., 2004).

Prostaglandin synthesis is catalysed by action of the cyclooxygenase (COX) group of enzymes on cell membrane phospholipids (Picot et al., 1994; Hla et al., 1999; Singh-Ranger and Mokbel, 2002b). Of the iso-enzymes, COX-2 is considered to be the culpable party in cancer promotion – it is inducible, generally expressed after stimulation by growth factors and tumour promoters (Herschman, 1996; Appleby et al., 1994; Yamagata et al., 1993; Simmons et al., 1991; Walenga et al., 1996; Harris et al., 1994; Adegboyega and Ololade, 2004). COX-2 then probably drives

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http://dx.doi.org/10.1016/j.critrevonc.2016.05.011
1040-8428/

uncontrolled expression of prostaglandins, with key effects in cancer promotion (Ranger et al., 2004; Tsujii et al., 1998; Gately, 2001; Marnett, 1992; Prescott and Fitzpatrick, 2000; Wiese et al., 2001).

It has long been known that aspirin can suppress COX-activity (Singh Ranger and Mokbel, 2003). There has been ongoing interest in manipulating this activity to prevent development of colorectal, breast and other types of epithelial cancer where abnormal prostaglandin expression is known to occur. In colorectal cancer, the extensive period of sometimes years before polyp transformation lends itself particularly well to manipulation by prophylaxis.

2. Randomised controlled trials and observational studies

The Physicians Health Study (pH S), and Women's Health Study (WHS) examined the role of low dose aspirin in colorectal cancer prevention, but did not find a significant reduction in incidence or mortality on short-term follow-up (Gann et al., 1993; Cook et al., 2005). Longer follow-up was recently been published by the WHS, and reported a reduction in cancer incidence after 10 years of study, in the aspirin group, primarily with proximal colon cancers (Cook et al., 2013).

Rothwell et al., published a 20 year follow-up of 5 RCTs in 2010 which supported the role of low dose aspirin in reducing colorectal cancer incidence and mortality, with most benefit for proximal colon cancers (Rothwell et al., 2010). Allocation to aspirin for 5 years or longer reduced risk of right sided cancer by 70%, and also reduced risk of rectal cancer. There was no increase in benefit for doses above 75 mg per day.

The results of observational studies were published long before these updates, and were the first to indicate statistically significant reductions in colorectal cancer mortality, and incidence, with non-significant trends in favour of aspirin use (Table 1, (Thun et al., 1991; Suh et al., 1993; Kune et al., 1988; Slattery et al., 2004; Chan et al., 2005; Giovannucci et al., 1994; Garcia-Rodriguez and Huerta-Alvarez, 2001; La Vecchia et al., 1997; Juarranz et al., 2002).

The most recent systematic review by Cuzick et al. indicated the effects of aspirin on cancer really start to be observed around 3 years after the start of use, with benefit for some years even after cessation of long term use. Again, low doses between 75 and 325 mg per day seem to be effective, with more toxicity than benefit for higher doses (Cuzick et al., 2015).

RCTs have also indicated daily low dose aspirin (81–325 mg/d) provides significant risk reduction in adenoma incidence in patients with a previous history of these lesions (Gann et al., 1993; Baron et al., 2003; Benamouzig et al., 2003), and observational studies generally confirm a reduction in the incidence of colorectal adenomas with regular aspirin use for over 5 years (Chan et al., 2005; Giovannucci et al., 1994; Chan et al., 2004; Ladenheim et al., 1995; Tangrea et al., 2003; Logan et al., 1993; Breuer-Katschinski et al., 2000).

Use of aspirin is however, associated with haemorrhage, both cardiovascular and gastrointestinal, with increasing doses and prolonged administration. Recent data from systematic reviews has given good insight into potential harms and rates of inpatient admission and treatment (Hart et al., 2000; He et al., 1998; Weisman and Graham, 2002; Serebruany et al., 2004; Tramer et al., 2000; Roderick et al., 1993).

3. COX-independent mechanisms

Inhibition of COX-2 expression would seem to be the easiest and most simplistic explanation by which aspirin exerts an anti-cancer effect, but the situation is rather more complex – termination of COX-2 function by nucleated cells, requires supranormal doses of aspirin (Patrono et al., 2004) – in fact, aspirin at the low dosages used in the community and in most randomised studies does *not* appreciably suppress COX-2 expression, so there must be other ways in which a low dose of the agent manages to cause a functional blockade of COX-2 activity, or other mechanisms at play.

Interestingly, COX-1 activity in activated platelets may serve as an induction signal for COX-2 expression (Patrono et al., 2001). Permanent inactivation of platelet COX-1 occurs with aspirin at low dose, which may then inhibit COX-2 expression in adjacent cells in the intestinal mucosa.

It is also possible that aspirin might have effects via COX-2 independent pathways, for example, phosphatidylinositol 3-kinase-related pathways (PIK3CA), (Liao et al., 2012). It has also been suggested that patients with mutated PIK3CA may have increased cancer-specific and overall survival if using aspirin regularly after diagnosis compared to non-users (Langley and Rothwell, 2013), mutated PIK3CA could provide a useful biomarker for adjuvant aspirin treatment. Recent work has also suggested that aspirin at low dose may directly initiate "therapy-induced senescence" (TIS) of colorectal cancer cells by manipulation of the sirtuin1 (SIRT1) pathway of cellular metabolism (Jung et al., 2015), or have effects via acetylation of other proteins in blood coagulation (Patrono, 2015).

4. Aspirin resistance

A growing body of evidence is beginning to suggest that regular low dose aspirin is ineffective in some patients. So-called "aspirin resistance" can be defined as persistent platelet activation despite intake of a regular therapeutic dose of aspirin. Clinically this would translate to failure of treatment, initially recognised over the last 20 years by cases of recurrent stroke or ischaemic heart disease symptoms in patients despite therapy (Hankey and Eikelboom, 2004), and could affect between 5 and 23% of patients (Gurn et al., 2001).

The reasons for aspirin resistance are likely to be multifactorial, but could include increased rates of platelet turnover in some patients, decreased bioavailability of aspirin, alternative pathways for production of thromboxane A2 (TXA2), variant COX-1 (Patrono, 2003). There is also some evidence to suggest that tolerance to aspirin occurs over time, which is only partially responsive to escalating dose administration (Pulcinelli et al., 2004). Lifestyle factors such as smoking, inadequate dosing, poor compliance, and concurrent administration of other drugs may also play a role, but the evidence is conflicting – for example, some studies have indicated non-smokers may have higher rates of aspirin resistance, and that aspirin resistance may not be a static phenomenon (Gum et al., 2001).

There remains the potential for this to affect chemoprevention – are higher risk groups more likely to be or become aspirin-resistant over time. Clearly more work is required on this issue.

Table 1
Results of observational studies of aspirin use and colorectal cancer chemoprevention.

Study	Design	Patients	Aspirin	Duration	Relative risk
Cancer Prevention Study II	Cohort	1083, 531	Various	>15 years	0.58–0.61 (mortality)
Nurses' Health Study	Cohort	89, 446	>2/week	10 years	0.62 (incidence)
Slattery et al.	Case-control	3051	>3/week	>5 years	0.7 (incidence)
Health Professionals'Follow-up Study	Cohort	47, 900	>2/week	4 years	0.54 (incidence)