RES MEDICA
Journal of the Royal Medical Society

REVIEW ARTICLE

A Review on the Use of Aspirin as Chemoprevention in Colorectal Cancer

Sadiq Shanaz[1]

[1]Medical Student, Peninsula College of Medicine & Dentistry
Correspondence email: sadiq.shanaz@students.pcmd.ac.uk

Abstract

Background: Colorectal cancer (CRC) is the second most common cancer worldwide. Estimated lifetime risk of CRC is 5%, with an incidence of 1 million new cases and 600 000 deaths worldwide every year. Lifestyle, dietary, and genetic factors play a crucial part in the development of colorectal cancer. Chemoprevention is a method of CRC prevention.

Aim: This review aims to identify the effectiveness of aspirin in preventing CRC in high-, moderate- and low-risk patients.

Method: Electronic databases were used to search for randomized controlled trials (RCTs) from 1989 to 2012 in MEDLINE, EMBASE, CINAHL, the Cochrane Database of Systemic Reviews, and Cochrane Central Register of Controlled Trials. The search terms employed were "hereditary colorectal cancer", "Lynch syndrome", "colorectal cancer", "aspirin", and "colorectal cancer".

Results: Aspirin reduces the incidence and recurrence of adenoma in patients with high to moderate risk of developing CRC.

Conclusion: There is evidence which supports the use of aspirin in reducing the risk of colorectal cancer in genetically predisposed patients and moderate-risk groups. Higher doses of aspirin appear to reduce the incidence of CRC. It is unclear what the optimum dose to start is, and the duration of administration that will provide effective chemoprevention. Further research is needed to answer these questions.

A Review on the Use of Aspirin as Chemoprevention in Colorectal Cancer

Introduction

Colorectal cancer (CRC) is the second most common cancer worldwide. Its estimated life time risk of 5%, with an incidence of 1 million new cases and 600 000 deaths worldwide per year.[1] The incidence of CRC is higher in developed economies.[2] The reasons behind this variability in CRC incidence cannot be clearly attributed but lifestyle, dietary, and genetic factors have been identified to play a crucial part in the development of colorectal cancer. The effects of putative carcinogenic factors involved have been studied extensively in observational, clinical, and experimental studies.

CRC incidence is dramatically increasing in many developing countries. The rates in the former Eastern European Communist Bloc, that recently underwent a major economic transition, have already reached or exceeded those of the industrial countries of the former Western bloc.[3] The increase in CRC incidence in developing countries, which are often equipped with fewer resources, is paralleled by an increase in the mortality rates, as indicated by studies from South America and Eastern Europe.[4] The uptrend in CRC rates cannot be explained by the effect of screening programmes, as such programmes are either limited, or only newly implemented in these regions.[5] Furthermore, the rise in CRC is usually more prominent in younger populations, who are not subjected to screening programs.[5]

Emphasis is placed on CRC screening to detect early or give information on precancerous colonic polyps. This may maximize survival outcomes. Screening provides an opportunity to educate the public on possible preventative factors. Treating CRC has significant cost implications for the NHS. Performing a colonoscopy to detect CRC costs approximately £500. Preventing CRC through screening also has a cost. Chemoprevention is one potential method for CRC prevention.

This review aims to identify the effectiveness of aspirin in preventing CRC in high-, moderate- and low-risk patients. This paper defines high-risk cancer patients as those who have familial adenomatuous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome. Moderate-risk patients are those with a family history or personal history of adenomas or CRC. The low-risk patients are the general population with no increased risk for CRC.

Pathogenesis of CRC

CRC pathogenesis varies according to genetic, epigenetic, and tumour–host interactions (immune and inflammatory reactions) in the tumour microenvironment.[6,7] These are in turn related to each another in varying degrees. As hypothesized by Fearon and Vogelstein, CRC occurs in a series of stages.[8] The first step in this sequence is directly initiated by a range of genetic, epigenetic, immune, and inflammatory changes, which contribute to the transformation of normal gut epithelium into neoplastic cells.[6,7] The multiple stages towards CRC development is typified by various methods of genetic instability, succeeding clinical manifestations and pathological behaviour characteristics.[6,8] The pathological and biological features of CRC differ according to tumour molecular characteristics, while aetiological factors influence cancer development and progression according to disease subtype.[9] We can further our understanding of the molecular pathogenesis of colorectal neoplasia through the mechanisms by which aspirin exerts its antineoplastic effects through trials and observational studies. This new field of research is known as molecular pathological epidemiology.[9]

What is FAP and HNPCC?

One-third of the population develops an adenoma by the age of 60.[10] Most of these adenomas are asymptomatic and do not go on to develop cancer. There is indirect evidence that implies that the presence of adenomas for 10 years or more increases the malignancy potential.[11] Individuals with identified polyps are invited for polypectomy and regular endoscopic surveillance. Most CRC cases are sporadic. 5% of CRC is associated with hereditary conditions such as FAP and HNPCC.[11] Those with FAP and HNPCC are more likely to develop colorectal cancer earlier than the general population. There are 2 independent mechanisms by which CRC can occur; these are the chromosomal and microsatellite instability pathways. The majority of CRC occurs as a result of chromosomal instability. Microsatellite instability results in a smaller proportion of CRC, of which many are HNPCC cases. Microsatellite instability is a feature found in 90% of HNPCC patients.[11] HNPCC is characterized by the development of colorectal, endometrial, ovarian, and other cancers. Mutations and inactivation of any of the mismatch repair (MMR) genes – MLH1, MSH2, MSH6, or PMS2 – lead to instability of microsatellites and, in time, lead to CRC.[12] FAP results from a mutation in the

adenomatous polyposis coli (APC) gene in the germ cells of affected individuals.[6] Individuals with FAP tend to develop more than 100 polyps in their colon.[12] The age of onset is variable, being present in only 15% of FAP gene carriers at 10 years of age, 75% by age 20, and 90% by age 30, if untreated.[13] 100% of FAP patients will develop CRC before the age of 50.

Methods

The search strategy was developed in MEDLINE and modified for other databases. The search was limited to English-language reports. The following electronic databases were used to search for randomized controlled trials (RCTs) from 1989 to 2012: MEDLINE, EMBASE, CINAHI, the Cochrane Database of Systemic Reviews, and Cochrane Central Register of Controlled Trials. The search terms employed were "hereditary colorectal cancer", "Lynch syndrome", "colorectal cancer", "aspirin", and "colorectal cancer".

Potentially relevant studies were checked against the inclusion criteria. The quality of RCTs was assessed on the criteria from the Centre for Reviews and Dissemination. The efficacy and effectiveness of aspirin used in RCTs was considered, and included, provided the outcome and population criteria were fulfilled. The population criteria was high-risk cancer patients classed as those having FAP and HNPCC, also known as Lynch syndrome; moderate-risk classed as patients with a family history or personal history of adenomas or CRC; low-risk are the general population with no increased risk for CRC.

Data synthesis and analysis

Synthesis methods employed were systematic reviews and meta-analyses of RCTs. A logical framework was used to group studies, and for the data extracted, in an effort to minimize clinical heterogeneity. Studies were categorized according to the medical condition (colorectal adenoma versus colorectal cancer), study design, sample size, and medication given. The medication given was further subdivided into length of time, medication taken, dose effect, and secondary outcomes.

Limitations

Important clinical and methodological heterogeneity in the definitions of regular use, dose, and duration of use of aspirin necessitated careful grouping for analysis.

Results

One RCT studied FAP patients who were given aspirin 600 mg daily for approximately for 1 year.

Table 1. Results for aspirin's effect on patients with FAP or HNPCC (high risk)

Treatment study	Population and age	Intervention (*n* randomized)	Control (*n* randomized)	Duration	Follow-up duration
Primary prevention (assessing adenoma incidence)					
Burn 2003 (CAPP1 Study)[14]	FAP and polyps	Aspirin 600 mg/day ± resistant starch 30 mg/day (*n* unknown; *n* =133 analysed across both aspirin and placebo groups)	Placebo (*n* unknown; *n* =133 analysed across both aspirin and placebo groups) (some also received starch)	At least 1 year	At least 1 year
Secondary prevention (assessing reduction in adenoma burden)					
Burn 2011 (CAPP2 Study)[15]	HNPCC carriers Age > 25 eligible (mean 46, range 25–79)	Aspirin 600 mg/day (*n* analysed = 427; *n* randomized not reported) (some also received starch)	Placebo (*n* analysed = 510; *n* randomized not reported) (some also received starch)	2.5 years (approximately)	2.5 years (approximately)

Table 2. Aspirin's effect on patients with a history of adenoma or CRC (moderate risk)

Study	Population and age	Intervention (*n* randomized)	Control (*n* randomized)	Treatment duration	Follow-up duration
Logan 2008 (United Kingdom Colorectal Adenoma Prevention (ukCAP) trial)[16]	History of adenomas Age < 75 eligible (mean 58, range 28–75)	Aspirin 300 mg/day only (*n* = 236) Aspirin 300 mg/day + folic acid 0.5 mg/day (*n* = 236)	Folic acid 0.5 mg/day only (*n* = 234) Placebo only (*n* = 233)	3 years	3 years
Cole 2007/Baron 2003 (Aspirin/folate Polyp Prevention Study)[17]	History of adenomas Age 21–80 eligible (mean 57 or 58 in all groups, range not reported)	Aspirin 81 mg/day only (*n* = 169) Aspirin 325 mg/day only (*n* = 167) Aspirin 81 mg/day + folic acid 1 mg/day (*n* = 175) Aspirin 325 mg/day + folic acid 1 mg/day (*n* = 171)	Folic acid 1 mg/day only (*n* = 170) Placebo only (*n* = 169)	3 years (approximately)	3 years (approximately)
Benamouzig 2003 (APACC Study)[18]	History of adenomas Age 18–75 eligible (mean 58, range not reported)	Aspirin 160 mg/day (*n* = 73) or 300 mg/day (*n* = 67)	Placebo (*n* = 132)	1 year	1 year
Sandler 2003 study[19]	History of CRC Age 30–80 eligible (median age bracket 60–69, range not reported)	Aspirin 325 mg/day (*n* = 317)	Placebo (*n* = 318)	1 year	3 years (approximately)
Analysis of aspirin ± folic acid versus placebo ± folic acid includes an additional 100 patients randomized to aspirin, or placebo before folic acid component was added, giving the following numbers of patients per group: aspirin 81 mg/day (*n* = 377); aspirin 325 mg/day (*n* = 372); no aspirin (*n* = 372).					

Initial results showed that there was no statistically significant reduction in polyp size.[14] Nevertheless, there is evidence from the same study suggesting there might be a reduction in polyp size when analysing 133 patients at 1 year follow-up.[14] In the Burn 2011 study, 600 mg of aspirin was given daily to a group of HNPCC patients (*n* = 746), with a median follow up of 2.5 years; there was no statistically significant reduction in adenoma incidence.[11] The study reported a relative risk (RR) of 1.03 (95% confidence intervals (95% CI): 0.75–1.41), for adenoma incidence and RR 0.87 (95% CI: 0.39–1.96) for colorectal cancer incidence.[15] However, at a median follow-up of 4 years, there was a significant reduction in time to first HNPCC cancer (hazard ratio 0.62, 95% CI: 0.41–0.96).[14]

There were 4 RCTs (*n* = 2692) that assessed the effect of having 81–325 mg of aspirin daily in patients with intermediate risk (Table 2). One study consisted of individuals who had a history of CRC. Three of the studies were on patients who had a history of adenomas. Three of the studies had a 3-year follow-up. When the results from the 4 studies – aspirin versus no aspirin (non-treatment) – were analysed, there was a statistically significant 21% RR reduction in adenoma recurrence (RR 0.79, 95% CI: 0.68–0.92; *p* = 0.002).[16-19] A similar result was obtained when aspirin was compared with placebo. Aspirin compared with folic acid showed a significant 34% decrease in the incidence of advanced adenomas (RR 0.66, 95% CI: 0.51–0.84; *p* = 0.0008).[16-19] Yet the results were not significant for advanced adenomas when aspirin was compared with placebo. Folic acid, in association with aspirin, did not give a statistically significant reduction in adenoma and advanced adenomas. Of the 4 RCTs that used aspirin in the low-risk population, the 2 larger studies gave 100–325 mg of aspirin every other day to its participants.[20, 21] Results showed there was no effect on CRC over a follow-up period of 5–12 years. The other 2 studies,[22,23] which were smaller, administered a higher dose of aspirin (300–1200 mg/day) and showed there was no effect on CRC incidence at 10-year follow-up, but did reveal a 26% significant decrease in CRC incidence over a 23-year follow-up period (RR 0.74, 95% CI: 0.57–0.97). The greatest reduction in incidence was observed between 10–19 years. After 20 years of follow-up, deaths were reduced by 20% (HR 0.8, 95% CI: 0.72–0.88).[20-23] This information can be used to calculate the numbers needed to treat (NNT): the NNT is 29 at 20 years. This means for every 29 patients taking aspirin for 10 years, there is 1 less cancer related death at 20 years.

Box 1. Amsterdam criteria II and revised Bethesda guidelines   for   diagnosing   HNPCC[12]

There should be at least 3 relatives with CRC or with a Lynch syndrome–associated cancer: cancer of the endometrium, small bowel, ureter, or renal pelvis.

- One relative should be a first-degree relative of the other 2

- At least 2 successive generations should be affected

- At least 1 tumour should be diagnosed before the age of 50 years

- FAP should be excluded in the CRC case if any

- Tumours should be verified by histopathological examination.

Revised Bethesda guidelines

1. CRC diagnosed in a patient aged < 50 years.

2. Presence of synchronous, metachronous colorectal or other Lynch syndrome–related tumours regardless of age.

3. CRC with MSI-H phenotype diagnosed in a patient aged < 60 years.

4. Patient with CRC and a first-degree relative with a Lynch syndrome–related tumour, with 1 of the cancers diagnosed at age < 50 years.

5. Patient with CRC with 2 or more first-degree or second-degree relatives with a Lynch syndrome–related tumour, regardless of age.

Table 3. Aspirin use in subsets of the general population (low risk)

Study	Population and age	Intervention (*n* randomized)	Control (*n* randomized)	Treatment duration	Follow-up duration
Cook 2005 (Women's Health Study)[20]	General population (women only) Age ≥ 45 eligible (mean 55, range not reported)	Aspirin 100 mg every other day, and/or vitamin E (600 IU every other day), and/or betacarotene (50 mg every other day for 2 years, stopped early due to lack of effectiveness) Study groups with respect to aspirin and vitamin E were: aspirin + vitamin E (*n* = 9966), aspirin only (*n* = 9968), vitamin E only (*n* = 9971); placebo only (*n* = 971)	Placebo (see groups on left)	10.1 years (aspirin and vitamin E) 2 years (betacarotene)	10.1 years
Gann 1993 (Physicians' Health Study, PHS)[21]	General population (male physicians) Age 40–84 eligible (mean 53, range not reported)	Aspirin 325 mg every other day (*n* = 11 037)(50% also received betacarotene 50 mg every other day)	Placebo(*n* = 11 034) (50%also received betacarotene 50 mg every other day)	5 years (for aspirin)	5 years (for aspirin)
Farrell 1991 (UK-TIA Aspirin Trial)[22]	General population regarding CRC; history of TIA or minor ischaemic stroke Age > 40 eligible (mean 60, range not reported)	Aspirin 300 or 1200 mg/day (not analysed separately) (*n* = 1632)	Placebo (*n* = 817)	1–7 years	23 years
Peto 1988 (British Doctors Aspirin Trial)[23]	General population (male physicians) Eligible age range not reported (mean age 62, range not reported)	Aspirin 300 or 500 mg/day (not analysed separately) (*n* = 3429)	Open control (*n* = 1710)	5–6 years	23 years

Discussion

Most evidence purporting aspirin's effectiveness in CRC has come from observational studies. Evidence from epidemiological studies demonstrate a significant risk reduction in tumour formation in the range of 20–50% in NSAID users.[24] Supporting this, a review also reported the benefits of using aspirin and its effect in reducing colonic polyp formation.[25] Furthermore, aspirin appears to reduce the incidence and recurrence of adenoma in those who have a high to moderate risk of developing CRC.[14-17] A recent molecular pathological epidemiological study demonstrated that regular aspirin use after diagnosis is associated with longer survival among patients with mutated-*PIK3CA* CRC, but not among patients with wild-type–*PIK3CA* CRC.[26] The findings from this study suggest that the *PIK3CA* mutation in colorectal cancer may serve as a predictive molecular biomarker for adjuvant aspirin therapy.[26] Until now, there have been no prospective studies investigating the benefit of using aspirin to reduce mortality in CRC. The ASCOLT trial is a double-blind prospective study that intends to investigate the long-term benefit of aspirin use in patients with Duke staging B or C CRC. The findings from this study can further add to the evidence base in

determining aspirin's place in CRC treatment. Identifying particular molecular markers and other biomarkers in CRC might aid in predicting individual prognosis and recurrence rates.[27] Furthermore, the development of clinical, genetic, and molecular predictors can produce more tailored screening or chemopreventative methods which stands to reduce or prevent CRC incidence and mortality.[27]

In colorectal cells, protein phosphatase A (PPA) plays an important part in regulating the oncogenic Wnt/β-catenin (CTNNB1) pathway. Aspirin seems to have an effect on the Wnt/CTNNB1 pathway by increasing phosphorylation of PPA, in essence, inhibiting it.[28] The lack of PPA causes a decrease in the activity of the Wnt/CTNNB1 pathway.[28] Furthermore, *BRAF* is a member of the Raf kinase family, and an important regulator of the mitogen-activated protein kinase (MAPK) pathway.[29-31] Activating mutations in the *BRAF* oncogene are observed in approximately 10–15% of colorectal cancers.[29,30] Experimental evidence suggests that Raf–MAPK signalling plays an important role in upregulation of prostaglandin endoperoxidase synthase 2 (*PTGS2* or cyclooxygenase-2 (COX-2) enzymes) and prostaglandin E2 synthesis.[32,33] This acts as a molecular explanation for

aspirin's efficacy in CRC prevention. Aspirin reduces cancerous cell growth by inhibiting COX-2, which is found in abundance in colorectal neoplastic cells.[34] Therefore, aspirin can be used to reduce COX-2 production by colorectal cells. It appears that higher doses of aspirin are needed to inhibit the action of COX-2.[28] Aspirin seems to prevent more proximal colonic cancers than distal colonic cancers.[30] This effect of aspirin could possibly be because proximal colon cancers secrete less COX-2 than distal colon cancers. In terms of non-aspirin NSAIDs, celecoxib is the only drug that is currently licensed for cancer chemoprevention by the European Medicines Agency.[31] The effectiveness of celecoxib over aspirin in chemoprevention is somewhat unclear.

It is important to identify the specific CRC subtypes that are prevented by aspirin. A recent study found that regular aspirin use was associated with a significantly lower risk of *BRAF*–wild-type cancer (multivariable hazard ratio (HR) = 0.73, 95% CI: 0.64–0.83; age-adjusted incidence rate difference (IRD) = −9.7, 95% CI: −12.6 to −6.7 per 100 000 person-years).[32] While regular aspirin use was not associated with a lower risk of *BRAF*-mutated cancer (multivariable HR = 1.03, 95% CI: 0.76–1.38; age-adjusted IRD = 0.7, 95% CI: −0.3 to 1.7 per 100 000 person-

years).[32] The association of aspirin use with colorectal cancer risk differed significantly according to *BRAF* mutation status.[32]

Low-risk groups

The Women's Health Study found that aspirin use had no effect in the incidence of any particular cancer.[16] Furthermore, the Physicians' Health Study also reported that aspirin had no effect in reducing the incidence of colorectal cancer after 5 years of treatment.[17] However, these findings are rather inconsistent. Observational studies have shown the effect of delayed cancer chemoprevention to take approximately 10 years to be effective in regular aspirin users.[24] A review that analysed cancer-related deaths in 8 trials discovered that participants who were given aspirin for 4 years and when followed-up for 5 years had considerable protection against cancer.[21]

High-risk groups

The effect of cancer chemoprevention can be attributed to continued exposure to aspirin. Results from the Burn 2011 study also supports these findings.[15] Taking regular aspirin reduces the incidence of CRC, but the effect only becomes noticeable after 3–4 years. It is clear that taking aspirin for several years offers considerable protection against cancer. It is unclear whether aspirin use needs to be continuous. Furthermore, it is unclear whether withholding aspirin treatment after 10 years has any long-term extra protective effect.

Higher doses of aspirin appear to reduce the incidence of CRC. Another study gave HNPCC carriers a daily dose of 600 mg of aspirin for a mean period of 25 months and reported a substantial reduction in cancer incidence after 55.7 months.[15] This is consistent with evidence from observational data that showed that the risk of CRC is halved in those who regularly use aspirin.[34] Furthermore, the data suggest that doses of 325 mg or more might be necessary for maximum chemoprevention.[35] In addition, follow-up of recent trials that focused on aspirin use in cardiovascular disease showed taking a dose of 75 mg or more for several years reduced death from proximal colon cancers.[34] Nevertheless, another trial reports 81 mg of aspirin to be more effective than 325 mg at reducing CRC incidence.[17] This displays the uncertainty regarding the lowest effective aspirin dose for chemoprevention.

Higher doses of aspirin are implicated in peptic ulcers, and genitourinary and gastrointestinal (GI) bleeds in patients.[36] It has also been suggested that the GI bleeding rate with 300 mg of aspirin is 60% higher than with placebo, and represents an attributable

rate of 2.5 events per 1000 patient-years.[17] In rare cases, intracranial haemorrhage has also been reported. The risk of bleeding rises from 1% in untreated to 2–3% in regular aspirin users over a 10 year period.[34] This is further compounded by dose and age.[37] Aspirin precipitates bleeding by inhibiting cyclooxygenase-1 enzymes that are responsible for activation and aggregation of platelets.

Currently, aspirin is used as prophylaxis in high-risk individuals with cardiovascular disease. Interestingly, this is not the case for individuals with a low risk as the possibility of bleeding outweighs the cardiovascular benefits of aspirin use. The risk of bleeding and GI ulceration increases, especially after the age of 60.[39] Due to uncertain benefits, the risks to the GI system, and uncertainty surrounding the dose and duration of aspirin usage in reducing CRC incidence, more trials are needed to assess this effect in older patients.

There is sufficient evidence showing that aspirin has a chemopreventative effect on groups with a high to moderate risk of developing CRC.[14-17] However, the best age to commence aspirin use is still unclear. The peak incidence of cancers tend to occur in the seventh decade of life in low risk groups.[10] Usually, individuals develop premalignant lesions in their 50s or 60s before CRC

becomes apparent.[4] Considering the 10–20 year delay in aspirin's effectiveness as a chemopreventative agent, the best time for CRC prevention will be between 40–50 years.[33] It is possible that the side effects of aspirin increase after the age of 60. Therefore, any long-term treatment needs to take place before this age. Even though this seems an attractive proposition, treating entire populations with aspirin to avert CRC in a small minority is difficult. Rarer side effects are more apparent when whole populations are treated, which ultimately can skew the benefit–risk profile of aspirin. An individual's risk for developing CRC can be reviewed by assessing their genetics, age, family history, lifestyle, and environmental factors. By evaluating the risk of who may develop CRC, aspirin can be offered to individuals of greater propensity. This stands to improve the benefit–risk ratio of aspirin as a chemoprevention intervention.

Conclusion

Individuals with a high to moderate risk are more likely to develop CRC, and aspirin reduces the incidence and recurrence of advanced adenoma formation in these sets of patients.[14-17] There is evidence to suggest that aspirin has an effect on reducing CRC in the general population.[18,19] It is notable that there is no evidence of long-term follow up for low-

dose aspirin use. There are side effects associated with aspirin such as peptic ulcer formation and GI bleeds. Therefore, the benefit–risk ratio of aspirin needs to be carefully considered for each risk group (i.e. high, intermediate or low risk of having CRC) before recommending aspirin as a form of chemoprevention.

Learning Points

What is already known

- Most CRC cases are sporadic. Only 5% of CRCs are genetically inherited.

- FAP and HNPCC form the majority of genetically inherited CRCs.

- Patients with FAP or HNPCC develop CRC much earlier than the general population.

What this study adds

- There is evidence supporting the use of aspirin in reducing the risk of colorectal cancer in genetically predisposed patients and moderate-risk groups.

- It is unclear what is the optimum dose to start, and the duration of administration that will provide effective chemoprevention. More research is needed to address these questions.

- Aspirin usage is associated with side effects and, therefore, careful consideration needs to be given to the risk benefit ratio of chemoprophylaxis.

References

1. Weitz J, Koch M, Debus J, Hohler T, Galle PR and Buchler MW. Colorectal cancer. *Lancet*. 2005;365:153-65. DOI: 10.1016/S0140-6736(05)17706-X.

2. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol*. 2006;24:2137-50. DOI: 10.1200/JCO.2005.05.2308.

3. Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1688-94. DOI: 10.1158/1055-9965.EPI-09-0090

4. Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. *CA Cancer J Clin*. 2009;59:366-78. DOI: 10.3322/caac.20038.

5. Bishehsari F, Mahdavinia M, Vacca M, Malekzedeh R, Mariani-Cinstantini R. Epidemiological transition of colorectal cancer in developing countries: environmental factors, molecular pathways, and opportunities for prevention. *World J Gastroenterol*. 2014;20(20):6055-72. DOI: 10.3748/wjg.v20.i20.6055.

6. Colussi D, Brandi G, Bazzoli F, Ricciardiello L. Molecular pathways involved in colorectal cancer: implications for disease behavior and prevention. *Int J Mol Sci*. 2013;14(8):16365-85. DOI: 10.3390/ijms140816365.

7. Bardhan K, Liu K. Epigenetics and colorectal cancer pathogenesis. *Cancers (Basel)*. Jun 2013;5(2):676-713. DOI: 10.3390/cancers5020676.

8. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell*. 1990;61:759-67. DOI: 10.1016/0092-8674(90)90186-I.

9. Ogino S, Chan A, Fuchs C, Giovannucci E. Molecular pathologic epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. *Gut*. 2011;60(3):397-411. DOI: 10.1136/gut.2010.217182.

10. Atkin WS, Saunders BP. Surveillance guidelines after removal of colorectal adenomatous polyps. *Gut*. 2002;51(Suppl. 5):V6-9. DOI: 10.1136/gut.51.suppl_5.v6.

11. Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. *Gastroenterology*. 1987;93:1009-13.

12. Vansen H, Moslen G, Alonso A, Bernstein I, Bertario L, Blanco I, *et al*. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). *J Med Genet*. 2007;(6):353-62. DOI: 10.1136/jmg.2007.048991.

13. Mishra N, Hall J. Identification of patients at risk for hereditary colorectal cancer. *Clin Colon Rectal Surg*. 2012 June;25(2):67-82. DOI: 10.1055/s-0032-1313777.

14. Burn J, Chapman PD, Bishop DT, Dixon R, Turner F, Coaker J, *et al*. Results of the CAPP1 Study: aspirin and resistant starch are beneficial in familial adenomatous polyposis. *Am J Hum Genet*. 2003;73:abstract-202.

15. Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S *et al*. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet*. 2011;378(9809):2081-7. DOI: 10.1016/S0140-6736(11)61049-0.

16. Logan RF, Grainge MJ, Shepherd VC, Armitage NC, Muir KR, ukCAP Trial Group. Aspirin and folic acid for the prevention of recurrent colorectal adenomas. *Gastroenterology*. 2008;134:29-38. DOI: 10.1053/j.gastro.2007.10.014.

17. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, *et al*. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med*. 2003;348:891-9. DOI: 10.1056/NEJMoa021735.

18. Benamouzig R, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, *et al*. Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. *Gastroenterology*. 2003;125:328-36. DOI: 10.1016/S0016-5085(03)00887-4.

19. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, *et al*. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med*. 2003;348:883-90 (erratum appears in *N Engl J Med*. 2003;348:1939). DOI: 10.1056/NEJMoa021633.

20. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, *et al*. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005;352:1293-304. DOI: 10.1056/NEJMoa050613.

21. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. *J Natl Cancer Inst.* 1993;85:1220-4.

22. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UKTIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry.* 1991;54:1044-54.

23. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, *et al.* Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed).* 1988;296: 313-16.

24. Grau MV, Sandler RS, McKeown-Eyssen G, Bresalier RS, Haile RW, Barry EL, *et al.* Nonsteroidal anti-inflammatory drug use after 3 years of aspirin use and colorectal adenoma risk: observational follow-up of a randomized study. *J Natl Cancer Inst.* 2009;101:267-76. DOI: 10.1093/jnci/djn484.

25. Martínez ME, Marshall JR, Giovannucci E. Diet and cancer prevention: the roles of observation and experimentation. *Nat Rev Cancer.* 2008;8:694-703. DOI: 10.1038/nrc2441.

26. Domingo E, Church D, Sieber O, Ramanoorthy R, Yanagisawa Y, Johnstone E, *et al.* Evaluation of *PIK3CA* mutation as a predictor of benefit from nonsteroidal anti-inflammatory drug therapy in colorectal cancer. *J Clin Oncol.* 2013;31(34):4297-306. DOI: 10.1200/JCO.2013.50.0322.

27. Reimers MS, Zeestraten E, Kuppen P, Liefers GJ, van de Velde CJ. Biomarkers in precision therapy in colorectal cancer. *Gastroenterol Rep (Oxf).* 2013 Nov;1(3):166-83. DOI: 10.1093/gastro/got022

28. Bos CL, Kodach LL, van den Brink GR, Diks SH, van Santen MM, Richel DJ, *et al.* Effect of aspirin on the Wnt/beta-catenin pathway is mediated via protein phosphatase 2A. *Oncogene.* 2006;25:6447-56. DOI: 10.1038/sj.onc.1209658.

29. Ogino S, Chan AT, Fuchs CS, Giovannucci E. Molecular pathological epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. *Gut.* 2011;60(3):397-411. DOI: 10.1136/gut.2010.217182.

30. Lao VV, Grady WM. Epigenetics and colorectal cancer. *Nat Rev Gastroenterol Hepatol.* 2011;8(12):686-700. DOI: 10.1038/nrgastro.2011.173.

31. European Medicines Agency. *Onsenal: EPAR – Summary for the Public.* European Medicines Agency website. 9 November 2009 (updated 6 April 2011). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000466/WC500044631.pdf (accessed 20 August 2014).

32. Nishihara R, Lochhead P and Kuchiba A. Aspirin use and risk of colorectal cancer according to *BRAF* mutation status. *JAMA.* 2013;309(24):2563-71. DOI: 10.1001/jama.2013.6599.

33. Phipps AI, Buchanan DD, Makar KW, Burnett-Hartman AN, Coghill AE, Passarelli MN, *et al. BRAF* mutation status and survival after colorectal cancer diagnosis according to patient and tumor characteristics. *Cancer Epidemiol Biomarkers Prev.* 2012;21(10):1792-8. DOI: 10.1158/1055-9965.EPI-12-0674.

34. Rothwell PM, Fowkes FGR, Belch JFF, Ogawa H, Warlow CP, Meade TW, *et al.* Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet.* 2011;377:31-41. DOI: 10.1016/S0140-6736(10)62110-1.

35. Cuzick J, Otto F, Baron JA, Brown PH, Burn J, Greenwald P, *et al.* Aspirin and non- steroidal anti-inflammatory drug for cancer prevention: an international consensus statement. *Lancet Oncol.* 2009;10:501-7. DOI: 10.1016/S1470-2045(09)70035-X.

36. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS, *et al.* Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA.* 2005;294:914-23. DOI: 10.1001/jama.294.8.914.

37. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ.* 2000;321:1183-7. DOI: 10.1136/bmj.321.7270.1183.