The role of aspirin in the prevention of ovarian, endometrial and cervical cancers

Nalinie Joharatnam-Hogan1, Fay H Cafferty1, Archie Macnair1, Alistair Ring2 and Ruth E Langley1

Abstract
Drug repurposing is the application of an existing licenced drug for a new indication and potentially provides a faster and cheaper approach to developing new anti-cancer agents. Gynaecological cancers contribute significantly to the global cancer burden, highlighting the need for low cost, widely accessible therapies. A large body of evidence supports the role of aspirin as an anti-cancer agent, and a number of randomized trials are currently underway aiming to assess the potential benefit of aspirin in the treatment of cancer. This review summarizes the evidence underpinning aspirin use for the prevention of the development and recurrence of gynaecological cancers (ovarian, endometrial and cervical) and potential mechanisms of action.

Keywords
aspirin, cervical cancer, endometrial cancer, ovarian cancer

Date received: 18 October 2019; revised: 30 July 2020; accepted: 7 September 2020

Introduction
Both the incidence and mortality from cancer continue to increase worldwide, despite advances in treatment.1 As cancer incidence in low- and middle-income countries increases and health costs rise across the economic settings, there is a need for low cost, widely accessible prevention and treatment strategies. Repurposing an established drug for a new therapeutic indication provides a significant advantage to the traditional drug development pathway, enabling faster and more cost-effective access to drugs for patients, with a well-known toxicity profile. Evidence supporting the chemopreventive effects of aspirin, in both the secondary prevention of malignancy (in the general population and in high risk individuals) and tertiary prevention of malignancy (in the adjuvant setting), has been accumulating over the last 40 years. The strongest evidence to date comes from the long-term follow-up of large randomized controlled trials (RCTs) primarily designed to evaluate the potential cardiovascular benefits of aspirin. Analysis of individual patient data from 51 trials including more than 77,000 participants demonstrated that individuals allocated to aspirin had a reduced risk of cancer incidence, particularly after more than 5 years of treatment (hazard ratio (HR): 0.81; 95% confidence interval (CI): 0.70–0.93).2 20-year risk of death from all solid cancers also remained lower in those allocated to receive aspirin (HR: 0.80, 95% CI: 0.72–0.88),3 with the benefit most apparent in gastrointestinal cancers, and more specifically adenocarcinomas. Further analysis of more than 17,000 participants from these randomized vascular trials demonstrated that allocation to aspirin was associated with a significantly reduced risk of developing cancer with metastases at presentation, possibly supporting the theory that circulating platelets facilitate tumour spread and metastases.4

1 MRC Clinical Trials Unit, University College London, Institute of Clinical Trials & Methodology, London, UK
2 Royal Marsden Hospital, NHS Foundation Trust, London, UK
Corresponding author:
Nalinie Joharatnam-Hogan, MRC Clinical Trials Unit, University College London, Institute of Clinical Trials & Methodology, 90 High Holborn, London WC1V 6JG, UK.
Email: n.joharatnam@ucl.ac.uk

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Evidence for the preventive effects of aspirin is strongest for colorectal cancer, such that the US Preventive Services Task Force (USPSTF) has recommended the initiation of low-dose aspirin for the prevention of colorectal cancer in adults aged 50–59 years, in individuals who have a greater than 10% 10-year risk of cardiovascular disease. Preclinical, epidemiological and randomized evidence have also provided the evidence synthesis to support the development of large randomized controlled trials assessing the adjuvant use of aspirin in several common solid tumours. However, the evidence supporting the role of aspirin in both reducing the incidence and recurrence of gynaecological cancers, namely, ovarian, endometrial and cervical cancers, has been less consistent and based mainly on epidemiological studies. This review presents the possible mechanism of action of aspirin in common gynaecological cancers and reviews the weight of the evidence for aspirin use in the prevention and adjuvant treatment of gynaecological malignancies, with the aim of determining if aspirin should be further investigated in a randomized clinical trial in these settings. We identified potential studies by searching the PubMed database, using the search terms ‘aspirin’, ‘cancer’, ‘ovarian’, ‘endometrial’ and ‘cervical’.

Possible mechanism of action of aspirin as an anti-cancer agent

Aspirin is known to directly inhibit the enzyme cyclo-oxygenase (COX), of which there are two isoforms, COX-1 and COX-2. COX acts to catalyse the conversion of arachidonic acid to prostaglandins and other downstream inflammatory mediators including thromboxane, which play a role in immune modulation, cell proliferation, control of apoptosis and tumour growth. Although aspirin irreversibly inhibits COX 1 and 2, due to its short half-life nucleated cells regenerate COX isoenzymes within hours. Therefore, aspirin’s primary effect is considered to be on the anucleate platelet, via inhibition of COX-1 acetylation in platelets. Circulating platelets are thought to be involved in tumour cell spread and metastasis, via their facilitation of tumour cell interaction with the extracellular matrix and adhesion to circulating endothelial cells, enabling tumour cell immune evasion and formation of metastases. A recent study demonstrated that the in vitro exposure of colon carcinoma cells to platelets increased their metastatic potential, with an associated increase in thromboxane A2 and prostaglandin (PGE2). This was subsequently prevented by the in vivo administration of aspirin. Upregulated COX-2 and increased prostaglandin (PGE2) have been shown to occur in the vast majority of colorectal carcinomas, and the deletion of the COX-2 gene in mice models of familial adenomatous polyposis results in a reduction in the number and size of intestinal polyps. In vitro studies have shown similar overexpression of COX in ovarian tumours, and inhibition by aspirin leads to cell growth inhibition and induction of apoptosis. It has been demonstrated that COX-2 expression in extra-platelet nucleated cells is induced by adjacent activated platelets, suggesting that indirect inhibition of COX-2 may occur via inhibition of COX-1 in platelets by low-dose aspirin.

COX-independent pathways have also been proposed, based on the observation of the consistent potency of aspirin’s inhibition of cell proliferation in COX-2 negative cancer cells. Aspirin has been shown to inhibit the Wnt/β-catenin pathway, involved in cell signalling and tumorigenesis, and has also been demonstrated to inhibit NF-κB activation, resulting in enhanced apoptosis in neoplastic rather than normal epithelial cells. Other in vitro evidence has shown aspirin’s potential interaction with other pathways of tumorigenesis, including inhibition of cell signalling via mammalian target of rapamycin (mTOR) inhibition and adenosine monophosphate-activated protein kinase (AMPK) activation, key molecules implicated in carcinogenesis. Upstream metabolite phosphoinositide 3-kinase (PI3K) activates and phosphorylates AKT, which has downstream effects to activate mTOR, possibly explaining aspirin’s potential enhanced effects on PI3KCA mutated cancers (Figure 1). PIK3CA mutations and amplifications are common in endometrial, ovarian and cervical cancers, as well as colorectal cancers, and therefore these COX-independent pathways may be particularly relevant to these cancers.

As indicated in Figure 1, there are several theories about how aspirin may work as an anti-cancer agent and several pathways which may be affected by aspirin and...
lead to the inhibition of cancer growth. Further work is needed to understand platelet contribution to the progression and development of cancer.

Clinical evidence supporting the use of aspirin to prevent gynaecological malignancies

Aspirin use in the prevention of ovarian cancer

Ovarian cancer is the eighth most common cancer for both incidence and mortality worldwide, and 5-year survival remains in the region of 50%. This is largely driven by the frequently late presentation of the disease and advanced stage at diagnosis. There is an increasing drive towards using preventive approaches in the management of cancer and developing economical, effective chemopreventive agents, such as aspirin, to tackle the increasing burden of disease.

Epidemiological studies overall have largely supported a possible protective association of aspirin in ovarian cancer. The most recent meta-analysis of the effect of aspirin use on the risk of ovarian cancer analysed 22 studies including more than 15,000 ovarian cancer cases. Results showed a moderate inverse association of aspirin with ovarian cancer incidence, with an 11% (95% CI: 0.83–0.96) relative reduction in risk demonstrated, with a consistent result demonstrated in a similar study. However, when stratified by study design, this result was mostly driven by case-control studies, which is often subject to bias.

One of the largest meta-analysis evaluating aspirin’s effect on cancer risk reviewed more than 300 observational studies, including both cohort and case-control studies and a total of 737,409 cases. Overall, aspirin use was shown to reduce the relative risk (RR) of developing any cancer by 11% (95% CI: 0.87–0.91). Of the 21 separate cancer sites analysed, results were strongest for gastric cancer (RR=0.75, 95% CI: 0.65–0.86). Ten of the 21 tumour sites reviewed showed an improved cancer risk with aspirin use, including both ovarian (21 studies, 14,666 cases: RR = 0.89, 95% CI: 0.83–0.95) and endometrial cancers (14 studies, 11,537 cases: RR = 0.92, 95% CI: 0.85–0.99), with no significant association seen in cervical cancers (four studies, 1040 cases: RR = 0.89, 95% CI: 0.69–1.14). However, as with all observational epidemiological studies, these studies are vulnerable to various biases undermining causal inference, including measurement error for aspirin use, as analysis was based on baseline data rather than any change in aspirin exposure during follow-up. Pooled individual patient data from 12 population-based observational studies in the Ovarian Cancer Association Consortium, including almost 8000 cases, demonstrated an RR reduction of ovarian cancer by 20% (odd ratio (OR)=0.80, 95% CI: 0.67–0.96) in daily aspirin users, regardless of dose. An analysis stratified by dose showed that low-dose (<100 mg/day) users of aspirin was associated with a greater benefit in ovarian cancer risk reduction (OR=0.66, 95% CI: 0.53–0.83) versus no regular use, compared to high dose (OR=0.89, 95% CI: 0.73–1.08).

Long-term follow-up of the Women’s Health Study has not supported the use of aspirin in ovarian cancer. This was a large randomized trial of 100 mg alternate-day aspirin versus placebo in almost 40,000 healthy female health professionals. Although long-term follow-up over 18 years showed a reduced incidence in colorectal cancer, neither significant benefit was demonstrated in the incidence of invasive ovarian cancer (HR: 0.85, 95% CI: 0.65–1.12) and endometrial cancer (HR: 1.00, 95% CI: 0.83–1.20) nor a difference when grouped as reproductive cancers (breast, endometrium, ovary, cervix and vagina; HR: 0.94, 95% CI: 0.83–1.06). However, the association between use of aspirin and risk of cancer development has been shown to have a duration and dose-response relationship, possibly explaining the lack of effect seen in this alternate-day dosing study. In a large Danish population–based study of more than 60,000 individuals, no association was seen between epithelial ovarian cancer risk and ‘ever use’ of aspirin (OR=0.94, 95% CI: 0.85–1.05), defined as ≥2 prescriptions on separate dates. However, a statistically significant benefit was demonstrated only after continuous long-term use of aspirin (OR=0.56, 95% CI: 0.32–0.97), which was defined as one continuous treatment period, from the start of treatment until 1 year before the index date.

Aspirin use in the prevention of endometrial cancer

As with ovarian cancer, studies evaluating the effect of aspirin on the risk of endometrial cancer are far less prevalent than for gastrointestinal cancers. Results from a meta-analysis of 13 observational studies and 11,323 cases showed that regular aspirin use is associated with a possible decreased risk of endometrial cancer, although not to a statistically significant degree (OR = 0.89, 95% CI: 0.79–1.01). A substantially stronger inverse association was shown on comparison of highest frequency of use with non-use, with a risk reduction of 37% (OR = 0.63, 95% CI: 0.45–0.88). Further analysis by body mass index (BMI) revealed a greater association in women with a BMI over 30 (OR = 0.56, 95% CI: 0.33–0.95), although based on only two case-control studies (n = 869 cases). Obesity is a well described risk factor for endometrial cancer. It is hypothesized that as the effect of obesity-driven unopposed oestrogen, obesity-driven chronic inflammation may play a supplementary mechanism in oncogenesis of endometrial cancer, possibly explaining aspirin’s enhanced effect in this cohort of patients.

Other meta-analyses have demonstrated similar inverse associations of aspirin use and endometrial cancer, predominantly in the setting of obesity. A meta-analysis
using data from a pooled population–based case-control study, the Australian National Endometrial Cancer Study, of 1398 cases, showed an almost 50% relative reduction in risk (OR = 0.54, 95% CI: 0.38–0.78) in women reporting a frequency of ≥2 tablets of aspirin used per week, although doses were not specified.41 The pooled risk estimate for obese women, with a BMI over 30 kg/m² was 0.72 (95% CI: 0.58–0.90), with no association seen for non-obese women. Most recently, the Epidemiology of Endometrial Cancer Consortium performed a pooled individual-level analysis of more than 7000 women with endometrial cancer from seven cohort and five case-control studies. An almost 20% reduction in risk was observed in obese and overweight women using aspirin 2–6 times per week (OR = 0.81, 95% CI: 0.68–0.96), but again the effect was lost in normal weight women.43 This large study included previously unpublished data. These findings are in contrast to pharmacodynamic studies of serum thromboxane inhibition by aspirin, as a marker of platelet inhibition, whereby lower thromboxane inhibition has been shown in obese, diabetic subjects, implying poor aspirin responsiveness,44 suggesting that either a non-platelet-driven mechanism of action for cancer chemoprevention is occurring in this cohort or possibly the excess cancer seen in obese individuals may be platelet-driven mechanism.

**Aspirin use in the prevention of cervical cancer**

There is little data surrounding aspirin use and the prevention of cervical cancer despite it being a huge burden of disease as the fourth most commonly occurring cancer in women worldwide.45 The main oncogenic driver of cervical cancer, human papillomavirus (HPV) infection, is relatively well understood and is the main focus of prevention strategies. A recent meta-analysis of the risk of cancer with aspirin use, surmised no association with cervical cancer, although included only one case-control study and three cohort studies.52 The largest of these, including 724 cases, was a UK population–based cohort study, finding no association between low-dose aspirin and the risk of cervical cancer (OR = 1.07, 95% CI: 0.80–1.44).46 Similarly, the standardized incidence ratio (SIR) for cervical cancer was not significantly reduced following 9-year follow-up in a Danish population–based study of more than 29,000 individuals prescribed low-dose aspirin; however, only 15 cases of cervical cancer were presented during follow-up (SIR = 0.9, 95% CI: 0.5–1.6).47 perhaps accounted for by the older age of entry in this study (mean age at entry – 70 years). Only one case-control study has suggested a possible association, in which frequent, long-term aspirin use (seven tablets per week for 5 years) decreased the relative odds of cervical cancer by 54% (OR = 0.46, 95% CI: 0.22–0.95), although as previously the large CI reflects the relatively small sample size of the study.48 Most evidence supporting the use of aspirin to prevent cervical cancer appears to be in the preclinical setting,49,50 where it has been demonstrated that aspirin exposure increases apoptosis and angiogenesis. Overexpression of COX-2 and prostaglandins has been seen in invasive cervical cancer tissue, and COX-2 transcription has been shown to be regulated by HPV 16 oncoproteins.51 and further large observational studies are required to better understand this association.

**Impact of aspirin on individuals at high risk of malignancy**

The impact of aspirin on hereditary cancer risk has been evaluated in the Colorectal Adenoma/Carcinoma Prevention Programme (CAPP). The CAPP2 trial recruited almost 1000 people with Lynch syndrome (hereditary non-polyposis colon cancer or HNPCC), caused by a germline mutation in DNA mismatch repair (MMR) genes.52 Lynch syndrome carriers are known to have a lifetime incidence of colorectal cancer and endometrial cancer of approximately 75% and 50%, respectively,53 as well as increased risks of other solid tumours. Random allocation to 600 mg of aspirin for 2 years or more significantly reduced the development of colorectal cancer (HR: 0.41, 95% CI: 0.19–0.86) compared with placebo.52 Intention to treat secondary outcome analysis demonstrated a 37% reduction in the incidence of all non-colorectal Lynch syndrome associated cancers (of which there were a total of 38), including endometrial cancer, with aspirin use (HR: 0.63, 95% CI: 0.34–1.19). The number of participants developing endometrial cancer in the trial was small (18) and, of these, five had been randomized to aspirin and 13 to placebo. Further analysis of this cohort showed an increased risk of all Lynch syndrome related cancers in obese individuals by 1.77× (95% CI: 1.06–2.96), and this increased risk was suppressed in those receiving aspirin.54

Other high risk hereditary populations include individuals with a BRCA1 or BRCA2 mutation, who have an associated lifetime risk of developing ovarian cancer of almost 40%.55 However, currently, there is no evidence to date of any specific activity of aspirin in cancers associated with germline BRCA mutations, although a clinical trial is currently underway (NCT03480776).

**Aspirin use in the adjuvant setting of gynaecological cancers**

Pooled individual data from large randomized vascular studies have demonstrated an improvement in cancer mortality and reduction in the risk of developing cancers presenting with metastases, suggesting a possible role for aspirin in the treatment of established cancer.54 Epidemiological data from the Nurses’ Health Study have been analysed to assess aspirin use in the adjuvant setting, post-diagnosis of epithelial ovarian cancer. From more than 238,000 participants, 1143 cases of ovarian cancer
developed and were deemed eligible for analysis. Participants reporting post-diagnosis use of aspirin were shown to have an improved ovarian cancer-specific survival (HR: 0.68, 95% CI: 0.52–0.89; Table 1), however, interestingly no association was observed for pre-diagnosis aspirin use.56 These results were compatible with a similar study showing a significant reduction in recurrence-free survival and overall mortality in patients with surgically treated ovarian cancer with post-diagnosis aspirin use.57 Conversely, a Danish population–based cohort study of 4117 patients examining the association between post-diagnosis use of low-dose aspirin and epithelial ovarian cancer mortality found no reduction in cancer-specific mortality (HR: 1.02, 95% CI: 0.87–1.20), with similarly neutral hazard ratios demonstrated with pre-diagnosis use.58 However, results from this study are limited by the assumption that post-diagnosis use of low-dose aspirin was defined as ≥1 prescription filled after the diagnosis of ovarian cancer. Table 1 summarizes studies of aspirin in the post-diagnostic setting of gynaecological cancers.

In a retrospective review of patients with a rarer form of ovarian cancer, clear cell carcinoma, who had undergone primary cytoreductive surgery followed by platinum-based chemotherapy, aspirin use correlated with a significantly longer overall survival (HR: 0.13, 95% CI: 0.13–0.81, p = 0.015) and also disease-free survival.59 It has been suggested in some studies that patients with PIK3CA-mutated colorectal cancer may have a superior cancer-specific survival and overall survival if they take aspirin after diagnosis, compared to patients with wild-type PIK3CA colorectal cancer.62 PIK3CA mutations occur at a frequency of 30% in clear cell ovarian carcinomas and are much less common in other histological subtypes of ovarian cancer, possibly explaining the strength of association seen with aspirin in this study.63 However, this was a small retrospective study, including only 77 patients, and further work is warranted to better understand aspirin’s possible therapeutic role in the less common subtype clear cell ovarian cancer.

Evaluation of survival outcomes in a multicentre retrospective study of 1687 patients with stage I–IV endometrial cancer, post-hysterectomy, reported improved 5-year disease-free survival by 10% with low-dose aspirin use (90.6% versus 80.9%, adjusted HR: 0.46, 95% CI: 0.25–0.86), particularly in those aged younger than 60 years and with a BMI over 30 kg/m.60 However, aspirin use was only assessed at diagnosis rather than over a prolonged follow-up period. Conversely, a large prospective UK-based cohort study of 3058 newly diagnosed endometrial cancer patients showed no association of low-dose aspirin on endometrial cancer survival with initiation post-diagnosis (adjusted HR: 0.85, 95% CI: 0.58–1.26) despite a longer mean 6.1-year follow-up,61 again indicating that further studies in this setting are warranted.64

### Aspirin toxicity

Aspirin has been used for many decades, and therefore the toxicity profile is well understood. Despite the breadth of evidence of the benefits of aspirin in certain gastrointestinal tumours, its use in cancer chemoprevention is often hindered by concerns about toxicity, particularly bleeding. Data from six cardiovascular primary prevention RCTs, analysed by the Antithrombotic Trialists’ Collaboration, of 95,000 individuals in randomized trials of aspirin versus control demonstrated only a modest increase in the risk of major gastrointestinal and extra-cranial bleeds from 0.07% per year to 0.1% per year on aspirin (HR: 1.54; 95% CI: 1.30–1.82, p = 0.0001), with a similar difference shown in the risk of intracranial bleeds.65 A series of recent primary prevention trials, the ASPREE, ARRIVE and ASCEND trials, have confirmed this increased risk of major bleeding.66–68 However, an analysis of the benefits and harms of prophylactic use of aspirin in the general population has estimated that the cumulative effects of long-term aspirin on 20-year risk of death has a net relative benefit in relation to both cancer and vascular mortality.

| Tumour type, study design | Study and sample size | HR (95% CI) |
|---------------------------|-----------------------|-------------|
| Ovarian cancer (OC)       | Nurses’ Health Merit et al.56 n = 1143 | OC-survival HR 0.68 (0.52–0.89) |
|                           | Bar et al.57 n = 143  | Overall survival 0.50 (0.29–0.84) |
|                           | Verdoodt et al.58 n = 4117 | OC-mortality HR 1.02 (0.87–1.20) |
|                           | Wield et al.59 (clear cell) n = 77 | Disease-free survival HR 0.13 (0.13–0.83) |
|                           | Wield et al.59 (clear cell) n = 77 | Overall survival HR 0.13 (0.13–0.81) |
| Endometrial cancer (EC)   | Matsuo et al.60 n = 1687 | Five-year disease-free survival HR 0.46 (0.25–0.86) |
|                           | Sanni et al.61 n = 3058 | EC-specific survival HR 0.23 (0.08–0.64) |
|                           |                       | EC-specific survival HR 0.91 (0.69–1.20) |

HR: hazard ratio; CI: confidence interval; OC: ovarian cancer; EC: endometrial cancer.
outweighing the risks of serious bleeding.\textsuperscript{69} Age has been shown to be a significant risk factor for harm, with serious long-term sequelae shown to be minimal in individuals under the age of 70 years.\textsuperscript{70,71} The ASPREE trial randomized 19,000 older healthy participants, predominantly over 70 years, to 100mg of aspirin or placebo and found no difference in the primary outcome (a composite of permanent physical disability, dementia and death).\textsuperscript{66} Although subgroup analysis initially demonstrated an increase in cancer mortality, subsequent analysis showed an increase in metastatic cancer only, not incident cancer, which may be explained by an increase in bleeding from undiagnosed metastatic disease in these older participants. Any assessment of aspirin use for the prevention and management of gynaecological cancers should primarily determine the risk/benefit profile to the individual, giving particular consideration to age.

**Conclusion**

Although the evidence is less extensive than for gastrointestinal cancers, there is an increasing suggestion of benefit from aspirin in ovarian malignancies. Data suggest a possible inhibitory effect of aspirin on the development of endometrial cancer, particularly in obese individuals; however, there is little evidence of an association of aspirin use and cervical cancer incidence. Currently, there is insufficient data to support the use of aspirin in the adjuvant setting for gynaecological cancers outside of a clinical trial. A more targeted approach may be required, utilizing biomarkers, either MMR deficient mutations or potentially PIK3CA mutated cancers or based on specific baseline characteristics, such as individuals with endometrial cancer and a high BMI, which may prove more effective targets for treatment, although these all require further exploration.

Most data supporting the possible role for aspirin in the prevention of cancer exist in the observational setting for gynaecological cancers, and several clinical trials are underway. The STICs and STONEs trial (NCT03480776), a randomized phase II, double-blind, placebo-controlled trial of aspirin in the prevention of ovarian cancer in women with BRCA1 and BRCA2 mutations, is currently recruiting in Canada. This well-defined subpopulation with a high lifetime risk of developing ovarian cancer could represent a population more likely to benefit from chemoprevention.\textsuperscript{55} However, more evidence is required to justify a clinical trial in endometrial or cervical cancers. In other tumour types, large adjuvant trials, including the Add-Aspirin Trial (NCT02804815) evaluating the role of aspirin on disease recurrence and survival following primary radical treatment for breast, colorectal, gastro-oesophageal and prostate cancer, are still recruiting participants.\textsuperscript{72} These trials, among others, could better answer the hypothesis of aspirin as a potential chemopreventive agent and increase understanding of its possible mechanism of action.

**Declaration of conflicting interests**

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: R.E.L. and the MRC Clinical Trials Unit at UCL report non-financial support from Bayer Pharma AG (supply of trial drugs) during the conduct of the study. R.E.L. reports grants from CRUK and NIHR and honorarium from the Aspirin Foundation during the conduct of the study. N.J.-H. reports a clinical trial fellowship grant from CRUK. All other authors declare no competing interests.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: R.E.L. is the Chief Investigator of the Add-Aspirin Trial, an academic study which is jointly funded by Cancer Research UK (Grant No. C471/A15015), the National Institute for Health Research Health Technology Assessment Programme (Project No. 12/01/38) and the MRC Clinical Trials Unit at UCL (MC_UU_12023/28). In India, the trial receives support from the Sir Dorabji Tata Trust and in the Republic of Ireland, Cancer Trials Ireland provide additional support. The authors received no financial support for publication of this article.

**Disclaimer**

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

**ORCID iD**

Nalinie Joharatnam-Hogan \textsuperscript{13} https://orcid.org/0000-0001-8406-2732

**References**

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394–424.

2. Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 2012; 379: 1602–1612.

3. Rothwell PM, Fowkes FG, Belch JF, 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.

4. Rothwell PM, Wilson M, Price JF, et al. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet 2012; 379: 1591–1601.

5. Coyle C, Cafferty FH and Langley RE. Aspirin and colorectal cancer prevention and treatment: is it for everyone. Curr Colorectal Cancer Rep 2016; 12: 27–34.

6. Bibbins-Domingo K and U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive
Services Task Force recommendation statement. *Ann Intern Med* 2016; 164: 836–845.

7. Langley RE, Burdett S, Tierney JF, et al. Aspirin and cancer: has aspirin been overlooked as an adjuvant therapy? *Br J Cancer* 2011; 105: 1107–1113.

8. Plescia OJ, Smith AH and Grinwich K. Subversion of immune system by tumor cells and role of prostaglandins. *Proc Natl Acad Sci USA* 1975; 72(5): 1848–1851.

9. Schrör K. Pharmacology and cellular/molecular mechanisms of action of aspirin and non-aspirin NSAIDs in colorectal cancer. *Best Pract Res Clin Gastroenterol* 2011; 25(4-5): 473–484.

10. Thun MJ, Jacobs EJ and Patrono C. The role of aspirin in cancer prevention. *Nat Rev Clin Oncol* 2012; 9: 259–267.

11. Gasic GJ, Gasic TB and Murphy S. Anti-metastatic effect of aspirin. *Lancer* 1972; 2: 932–933.

12. Honn KV, Tang DG and Crissman JD. Platelets and cancer metastasis: a causal relationship. *Cancer Metastasis Rev* 1992; 11(3-4): 325–351.

13. Guillem-Llobat P, Dovizio M, Bruno A, et al. Aspirin prevents colorectal cancer metastasis in mice by splitting the crosstalk between platelets and tumor cells. *Oncotarget* 2016; 7: 32462–32477.

14. Eberhart CE, Coffey RJ, Radhika A, et al. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. *Gastroenterology* 1994; 107(4): 1183–1188.

15. Oshima M, Dinchuk JE, Kargman SL, et al. Suppression of intestinal polyp size in ApcΔ716 knockout mice by inhibition of cyclooxygenase 2 (COX-2). *Cell* 1996; 87: 803–809.

16. Uddin S, Ahmed M, Hussain A, et al. Cyclooxygenase-2 inhibition inhibits PI3K/AKT kinase activity in epithelial ovarian cancer. *Int J Cancer* 2010; 126: 382–394.

17. Dixon DA, Tolley ND, Bemis-Standoli K, et al. Expression of COX-2 in platelet-monocyte interactions occurs via combinatorial regulation involving adhesion and cytokine signaling. *J Clin Invest* 2006; 116(10): 2727–2738.

18. Yu HG, Huang JA, Yang YN, et al. The effects of acetylsalicylic acid on proliferation, apoptosis, and invasion of cyclooxygenase-2 negative colon cancer cells. *Eur J Clin Invest* 2002; 32(11): 838–846.

19. Drew DA, Cao Y and Chan AT. Aspirin and colorectal cancer: the promise of precision chemoprevention. *Nat Rev Cancer* 2016; 16(3): 173–186.

20. Stark LA, Din FV, Zwacka RM, et al. Aspirin-induced activation of the NF-kappaB signaling pathway: a novel mechanism for aspirin-mediated apoptosis in colon cancer cells. *FASEB J* 2001; 15(7): 1273–1275.

21. Din FVN, Valanciute A, Houde VP, et al. Aspirin inhibits miTOR signaling, activates AMP-activated protein kinase, and induces autophagy in colorectal cancer cells. *Gastroenterology* 2012; 142(7): 1504–1515.

22. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PI3KCA mutation, and colorectal-cancer survival. *N Engl J Med* 2012; 367: 1596–1606.

23. Salvesen HB, Werner HM and Krakstad C. PI3K pathway in gynecologic malignancies. *Am Soc Clin Oncol Educ Book*. Epub ahead of print 30 May 2013. DOI: 10.1200/EdBook_AM.2013.33.e218.

24. Jacobs UJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancer* 2016; 387: 945–956.

25. Akhmedkhanov A, Toniole P, Zeleniuch-Jacquotte A, et al. Aspirin and epithelial ovarian cancer. *Prev Med* 2001; 33: 682–687.

26. Nagle CM, Ibiebele TI, DeFazio A, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, acetaminophen and ovarian cancer survival. *Cancer Epidemiol* 2015; 39(2): 196–199.

27. Ammundsen HB, Faber MT, Jensen A, et al. Use of analgesic drugs and risk of ovarian cancer: results from a Danish case–control study. *Acta Obstet Gynecol Scand* 2012; 91(9): 1094–1102.

28. Bonovas S, Filioussi K and Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *Br J Clin Pharmacol* 2005; 60(2): 194–203.

29. Murphy MA, Trabert B, Yang HP, et al. Non-steroidal anti-inflammatory drug use and ovarian cancer risk: findings from the NIH-AARP diet and health study and systematic review. *Cancer Causes Control* 2012; 23(11): 1839–1852.

30. Zhang D, Bai B, Xi Y, et al. Is aspirin use associated with a decreased risk of ovarian cancer? A systematic review and meta-analysis of observational studies with dose-response analysis. *Gynecol Oncol* 2016; 142(2): 368–377.

31. Baandrup L, Faber MT, Christensen J, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. *Acta Obstet Gynecol Scand* 2013; 92(3): 245–255.

32. Qiao Y, Yang T, Gan Y, et al. Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. *BMC Cancer* 2018; 18: 288.

33. Trabert B, Ness RB, Lo-Ciganic WH, et al. Aspirin, non-aspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the ovarian cancer association consortium. *J Natl Cancer Inst* 2014; 106(2): djt431.

34. Cook NR, Lee I, Zhang SM, et al. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. *Ann Intern Med* 2013; 159: 77–85.

35. Chan AT, Giovannucci EL, Meyerhardt JA, et al. Aspirin dose and duration of use and risk of colorectal cancer in men. *Gastroenterology* 2008; 134(1): 21–28.

36. Dehendorff C, Olsen JH, Baandrup L, et al. Low-dose aspirin use and the risk of ovarian cancer in Denmark. *Ann Oncol* 2014; 26: 787–792.

37. Verdoordt F, Friis S, Dehendorff C, et al. Non-steroidal anti-inflammatory drug use and risk of endometrial cancer: a systematic review and meta-analysis of observational studies. *Gynecol Oncol* 2016; 140(2): 352–358.

38. Takuchi T, Blake EA, Matsuo K, et al. Aspirin use and endometrial cancer risk and survival. *Gynecol Oncol* 2018; 148(1): 222–232.

39. Friedenreich CM, Langley AR, Speidel TP, et al. Case-control study of inflammatory markers and the risk of endometrial cancer. *Eur J Cancer Prev* 2013; 22: 374–379.

40. Modugno F, Ness RB, Chen C, et al. Inflammation and endometrial cancer: a hypothesis. *Cancer Epidemiol Biomarkers Prev* 2005; 14(12): 2840–2847.

41. Neill AS, Nagle CM, Protani MM, et al. Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of...
endometrial cancer: a case-control study, systematic review and meta-analysis. *Int J Cancer* 2013; 132: 1146–1155.

42. Zhang D, Bai B, Xi Y, et al. Can aspirin reduce the risk of endometrial cancer?: a systematic review and meta-analysis of observational studies. *Int J Gynecol Cancer* 2016; 26(6): 1111–1120.

43. Webb PM, Na R, Weiderpass E, et al. Use of aspirin, other nonsteroidal anti-inflammatory drugs and acetaminophen and risk of endometrial cancer: the epidemiology of endometrial cancer consortium. *Ann Oncol* 2018; 31: 310–316.

44. Patrono C and Rocca B. Type 2 diabetes, obesity, and aspirin responsiveness. *J Am Coll Cardiol* 2017; 69: 613–615.

45. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin* 2016; 66(4): 271–289.

46. Wilson JC, O’Rorke MA, Cooper JA, et al. Non-steroidal anti-inflammatory drug use and cervical cancer risk: a case-control study using the clinical practice research datalink. *Cancer Epidemiol* 2013; 37(6): 897–904.

47. Friis S, Sørensen HJ, McLaughlin JK, et al. A population-based cohort study of the risk of colorectal and other cancers among users of low-dose aspirin. *Br J Cancer* 2003; 88: 684.

48. Friel G, Liu CS, Kolomeyevskaya NV, et al. Aspirin and acetaminophen use and the risk of cervical cancer. *J Low Genit Tract Dis* 2015; 19(3): 189–193.

49. Yueling W, Hongmin Z, Lin L, et al. Effect of aspirin alone or combined with cisplatin on human cervical carcinoma HeLa cells. *J Med Colleges of PLA* 2010; 25: 11–18.

50. Xiang S, Sun Z, He Q, et al. Aspirin inhibits ErbB2 to induce apoptosis in cervical cancer cells. *Med Oncol* 2010; 27(2): 379–387.

51. Young JL, Jazaeri AA, Darus CJ, et al. Cyclooxygenase-2 in cervical neoplasia: A review. *Gynecol Oncol* 2008; 109(1): 140–145.

52. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAP2 randomised controlled trial. *Lancet* 2012; 378: 2081–2087.

53. Kastrinos F and Stoffel EM. History, genetics, and strategies for cancer prevention in Lynch syndrome. *Clin Gastroenterol Hepatol* 2014; 12(5): 715–727; quiz e41–3.

54. Movahedi M, Bishop DT, Macrae F, et al. Obesity, aspirin, and risk of colorectal cancer in carriers of hereditary colorectal cancer: a prospective investigation in the CAP2 study. *J Clin Oncol* 2015; 33: 3591–3597.

55. Tsorek D, Panzarella T and Oza A. Aspirin in prevention of ovarian cancer: are we at the tipping point. *J Natl Cancer Inst* 2014; 106(2): djt453.

56. Merritt MA, Rice MS, Barnard ME, et al. Pre-diagnosis and post-diagnosis use of common analgesics and ovarian cancer prognosis (NHS/NHSII): a cohort study. *Lancet Oncol* 2018; 19(8): 1107–1116.

57. Bar D, Lavie O, Stein N, et al. The effect of metabolic comorbidities and commonly used drugs on the prognosis of patients with ovarian cancer. *Eur J Obstet Gynecol Reprod Biol* 2016; 207: 227–231.

58. Verduoti F, Kjaer SK, Dehlerhoff C, et al. Aspirin use and ovarian cancer mortality in a Danish nationwide cohort study. *Br J Cancer* 2018; 118: 611–615.

59. Wield AM, Walsh CS, Rimel BJ, et al. Aspirin use correlates with survival in women with clear cell ovarian cancer. *Gynecol Oncol Rep* 2018; 25: 78–81.

60. Matsuo K, Cahoon SS, Yoshihara K, et al. Association of low-dose aspirin and survival of women with endometrial cancer. *Obstet Gynecol* 2016; 128(1): 127–137.

61. Sanni OB, Mc Menamin UC, Cardwell CR, et al. Commonly used medications and endometrial cancer survival: a population-based cohort study. *Br J Cancer* 2017; 117: 432–438.

62. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. *N Engl J Med* 2012; 367: 1596–1606.

63. Kuo KT, Mao TL, Jones S, et al. Frequent activating mutations of PIK3CA in ovarian clear cell carcinoma. *Am J Pathol* 2009; 174(5): 1597–1601.

64. Pierce SR, Doll KM, Davidson B, et al. Endometrial cancer outcomes in diabetic women treated with metformin, statins, and aspirin. *Gynecol Oncol* 2014; 133: 43.

65. Antithrombotic Trials’ (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; 373: 1849–1860.

66. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 2018; 379: 1509–1518.

67. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2018; 392: 1036–1046.

68. Group ASC. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 2018; 379: 1529–1539.

69. Cuzick J, Thorat MA, Bosetti C, et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. *Ann Oncol* 2014; 26: 47–57.

70. Thorat MA and Cuzick J. Role of aspirin in cancer prevention. *Curr Oncol Rep* 2013; 15: 533–540.

71. Li L, Geraghty OC, Mehta Z, et al. Frequent activating mutations of PIK3CA in ovarian clear cell carcinoma. *Am J Pathol* 2018; 117: 432–438.