Review

WOMEN'S HEALTH

Women's Health
Volume 16: 1–8
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DOI: 10.1177/1745506520961710
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The role of aspirin in the prevention of ovarian, endometrial and cervical cancers

Nalinie Joharatnam-Hogan[1], Fay H Cafferty[1], Archie Macnair[1], Alistair Ring[2] and Ruth E Langley[1]

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 6LJ, UK.
Email: n.joharatnam@ucl.ac.uk

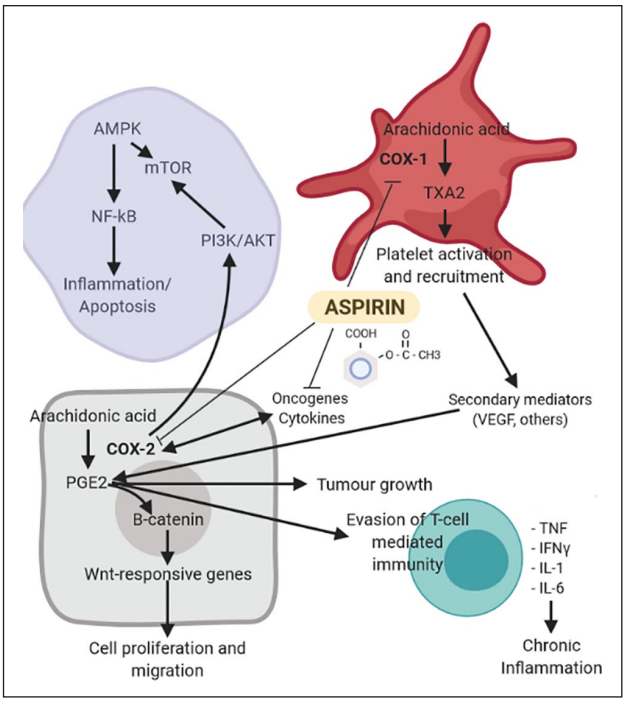

Figure 1. Potential anti-oncogenic mechanisms of action of aspirin.

Evidence for the preventive effects of aspirin is strongest for colorectal cancer,[5] 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.[6] 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.[7] 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.[8,9] 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.[10] Circulating platelets are thought to be involved in tumour cell spread and metastasis,[11] 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.[12] 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).[13] 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,[14] 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.[15] 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.[16] It has been demonstrated that COX-2 expression in extra-platelet nucleated cells is induced by adjacent activated platelets,[17] 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.[18] Aspirin has been shown to inhibit the Wnt/β-catenin pathway, involved in cell signalling and tumorigenesis,[19] and has also been demonstrated to inhibit NF-κB activation, resulting in enhanced apoptosis in neoplastic rather than normal epithelial cells.[20] 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,[21] 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[22] (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.[23]

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%.[1] 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[24] 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.[25–29] 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,[30] with a consistent result demonstrated in a similar study.[31] 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.[32] 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).[32] 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.[32] 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.[33] 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).[34] However, the association between use of aspirin and risk of cancer development has been shown to have a duration and dose-response relationship,[35] 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.[36] 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).[37] 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),[38] and a lower estimate seen in cohort studies (RR = 0.80, 95% CI: 0.56–1.14; n = 1629 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,[38–40] 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.[41,42] 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/m^2 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.[32] 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.[3,4] 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

Table 1. Aspirin use in the adjuvant setting of gynaecological cancers.

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) 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) EC-specific survival HR 0.23 (0.08–0.64)
	Sanni et al.[61] n = 3058	EC-specific survival HR 0.91 (0.69–1.20)

HR: hazard ratio; CI: confidence interval; OC: ovarian cancer; EC: endometrial 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 cancer.

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,

outweighing the risks of serious bleeding.[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.[70,71] The ASPREE trial randomized 19,000 older healthy participants, predominantly over 70 years, to 100 mg of aspirin or placebo and found no difference in the primary outcome (a composite of permanent physical disability, dementia and death).[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.[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.[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 https://orcid.org/0000-0001-8406-2732

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