CANCER, VASCULAR DISEASE and low-dose ASPIRIN

Fifty years of research

by

The Welsh Aspirin Group

1974 - 2024

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Commencing in 1956, 70 years ago, Aneurin Hughes, a physician in Neville Hall Hospital and Bob Tonks, a technician in Materia Medici in The Welsh National School of Medicine began to report a long series of animal and human studies of aspirin use in vascular disease.

Almost twenty years later, in 1974, Archie Cochrane, Peter Elwood et al. reported the first randomised trial of aspirin in the reduction of vascular disease mortality. The trial showed a reduction of about 24% in vascular disease deaths associated with low-dose aspirin (see Report 1 below). That report went viral, and it appears to have stimulated a global interest in the drug, and reports of research on aspirin, and the clinical use of aspirin in vascular disease and later in ischaemic stroke, became widely used across the world.

Twenty-five years later evidence favourable to the use of aspirin in the treatment of cancer began to accumulate, and a few of us set up 'The Welsh Aspirin Group' with the agreed aim to examine a wide range of issues of relevance to the possible benefits of aspirin as an additional treatment of cancer.

We have now put much of the published evidence on aspirin and the treatment of cancer into a website and this can be accessed with a google search using the title:

'The Welsh Aspirin Group.com'

We in the Group now feel an increasing responsibility to publicise the findings of our work. In what follows are brief summaries, and references to our publications on aspirin and cancer.

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On the safety of low dose aspirin: The most serious harmful effect of aspirin is its increase in the risk of bleeding. Vomiting blood, or blood in the faeces is a serious crisis, and especially for a patient already under treatment for a serious disease. However, within the community, and nothing to do with aspirin, oral or rectal bleeding occurs in around one or two people in every 1,000 each year, most often due to a stomach ulcer or an infection in the stomach. Such bleeds are serious and 5-10% lead to death.

Aspirin, even at a low dose, increases the risk of a bleed by about 50%. This means that the risk of a bleed in people taking aspirin, compared to the risk in people not taking aspirin, is 1.5, or a risk ratio (RR) of 1.5. This implies that within patients taking low-dose aspirin, only one in every three bleeds that occur in patients taking aspirin is likely to be truly due to aspirin, the other two bleeds being due to pathology in the stomach or intestine.

Probably the most widely influential warning about bleeding caused by aspirin was an item on the web issued by Reuters in June 2017, stating that: '*daily aspirin causes 3,000 deaths from bleeding in Britain every year'*. This claim which is still displayed on the web was uncontrolled. It is therefore totally invalid and very seriously misleading.

Reuters based their claim of 3,000 annual deaths upon a study of 3,166 older patients, all of whom were taking aspirin. There were no 'control' patients, not taking aspirin, and therefore no valid estimate of the independent contribution of aspirin to bleeding or to fatal bleeding can be made. Furthermore,65% of the patients had had a stroke and there have been reports of so-called 'neurogenic' bleeding from the stomach in patients with acute ischaemic strokes, with occurrence rates of 2-3% and a high risk of death.

We therefore conducted our own study of aspirin and the risk of bleeding and a computer-driven search of the published medical literature identified eleven suitable randomised trials. The table below summarises pooled results from all eleven trials.

Table 1. Stomach bleeding in a meta-analysis of data from 11 large randomised trials in which aspirin or placebo had been taken for an average of 2.8 years.

Occurrence of a stomach bleed - in 52,583 subjects randomised to placebo - in 54,,625 subjects randomised to aspirin	5 per1,000 8 per 1,000	**Risk ratio 1.55**
Proportion of bleeds that were fatal - in subjects on placebo - in subjects on aspirin	8% 4%	**Risk ratio 0.50**
Risk of a fatal bleed in trial participants - randomised to placebo - randomised to aspirin	4.7/10,000 3.7/10,000	**Risk ratio 0.77**

The table shows that five bleeds occurred in every 1,000 of the subjects not on aspirin, presumably from stomach ulcers or an infection of the stomach. As the allocation of aspirin or placebo to subjects had been random, it is reasonable to assume that the same frequency of non-aspirin related bleeds caused by an ulcer or an infection, will have occurred in the subjects randomised to aspirin. Thus, only three of the bleeds in every thousand (in 2.8 years) are likely to have been truly caused by aspirin.

There is no simple way that a bleed caused by aspirin can be distinguished from a bleed from an ulcer or an infection, so although all the eight bleeds in every 1,000 may have been thought (and reported!) to be due to aspirin, in truth only three, or approximately one in every three bleeds are likely to have been caused by aspirin.

Of more importance, however, is the fact that the fatality rate of the bleeds in subjects taking aspirin (4%) was half that of the deaths cause by disease (8%), and this finding is consistent with conclusions drawn by a number of other authors, including meta-analyses of randomised trials.. **(see Report 3)** The overall severity of all bleeds due to aspirin is likely to be very much less that the severity of the bleeds caused by disease, and the overall conclusion is therefore indicated by the data in the bottom line of the table: that there is no evidence that aspirin was responsible for any additional deaths through bleeding.

The other bleeding risk attributable to aspirin – cerebral - is rare, but more serious. However, adequate treatment of blood pressure, if hypertension is present, has been shown in a randomised trial to remove any additional risk associated with taking aspirin. **(see Report 3)**

The overall conclusion on aspirin and bleeding is therefore simple: there is a low risk of a stomach bleed, but a fatal bleed from aspirin is most unlikely. Aspirin is therefore best avoided by subjects who have a history of a stomach ulcers or frequently experience indigestion, **(see Report 3 and 10)**

Aspirin and metastatic cancer spread: The very first paper on aspirin and cancer – over 50 years ago - appears to have been a report of studies which showed that aspirin delays the spread of cancer within the body. This was in animals, and it was followed by numerous reports confirming the effect in a wide range of cancers in human patients. Cancer cells can get into the blood stream and can seed a metastatic tumour in a distant organ. This is a very serious development, and the 'satellite' tumours can be a source of much of the pain and complications of cancer. Furthermore, many of the deaths are attributable to the metastases in distant organs, rather than to the primary tumour itself.

Very recently however, detailed research in Cambridge was reported which reveals the complex biological mechanisms which lead to the effect, thereby powerfully increasing confidence that it is a real effect of low-dose aspirin, and because of this. it is eminently reasonable to predict that the earlier the use of aspirin in subjects with cancer, including subjects suspected to possibly have cancer, the greater the likely benefit of subsequent treatment. **(see Reports 4 and 11)**

Aspirin and mortality: 1. Observational studies: A series of systematic searches of the medical literature identified 118 long-term cohort studies of patients with eighteen different cancers. A quarter of the patients in these cohorts - a total of 250,000 patients - reported taking daily aspirin. The following table shows a 20% reductions in deaths associated with the taking of aspirin.

Table 2: meta-analysis of 118 published observational reports.

GROUP	Cancer mortality		All-cause mortality	
	No. of studies	**HRs** (95% CIs) **ORs** (95% Cis)	**No. of studies**	**HRs** (95% CIs) **ORs** (95% Cis)
Colon cancer	24 One	HR 0,71 (0,62, 0.80) OR 0.78 (0.66, 0.93)	21 One	HR 0.81 (0.73, 0.91) OR 0.78 (0.65, 0.92)
Breast cancer	13 4	HR 0.84 (0.72, 0.98) OR 0.75 (0.36, 1.57)	9 None	HR 0.94 0.70, 1.25) -
Prostate cancer	15 One	HR 0.89 (0.78, 1.02) OR 1.02 (0.78, 1.34)	6 One	HR 1.00 (0.78, 1.27) OR 1.06 0.94, 1.19)
15 other cancers	18 5	HR 0.79 (0.70, 0.83) OR 0.49 (0.26, 0.95	21 5	HR 0.67 0.60, 0.75) OR 0.47 (0.26, 0.83)
All 118 cancers	70 11	**HR0.79** (0.73, 0.84) **OR 0.67** (0.45, 1.00)	56 7	**HR 0.79** (0.74, 0.86) **OR 0.57** (0.36, 0.89)

Note: a number of studies reported data on both Cancer and All-cause mortality

Overall, deaths from cancer were reduced by about 20%, (HR 0.79; 0.73, 0.84). An important bias in observational studies is selective publication of studies favourable to the intervention. A detailed examination of this in our data by a 'trim and fill' analysis indicated that publication bias was minor, and significant benefit from aspirin was maintained. **(see Report 6)**

Of particular interest is the relatively small range in the estimates of the size of the reductions for aspirin within the eighteen different cancers, and a pooled reduction associated with aspirin in these is closely similar to the reduction in colon cancer deaths - suggesting that aspirin is probable benefit in a wide range – *if not all* - cancers. **(see Reports 6 and 10)**

Aspirin and mortality: 2. Evidence from randomised trials: The first randomised evidence on aspirin and cancer came from a series of inspired studies by Rothwell and colleagues. Beginning in 2007 they conducted retrospective long-term follow-up studies of patients who had already been randomised to aspirin in up to 51 earlier vascular disease trials. Consistently, in six studies based upon between five and fifty-one published aspirin trials, they reported reductions in the incidence of cancer and in cancer mortality associated with having been randomised to aspirin. **(see Report 13)**

Since then, a number of randomised trials have been reported and the results have been highly inconsistent, leading many of our clinical colleagues to argue that further evidence from randomised trials is required before aspirin is promoted as a treatment of cancer. On the other hand, we point out that inaction while waiting ignores the favourable evidence of aspirin upon both metastatic cancer spread and on vascular complications of cancer. We also wonder how much evidence, from how many randomised trials, adequately funded, of sufficient duration, with high levels of compliance with allotted treatments, and in how many different cancers will be required to resolve the uncertainties in the evidence already available? **(see Report 13)**

Using a quite different strategy, a group in Liverpool extracted extensive baseline data, including aspirin taking, from the records for 44,000 patients with colon cancer. Within a subset of these they constructed a formula giving predicted estimates of survival, which, if applied to the remainder of the patients gives increases in survival attributable to aspirin taking, of about four of five years.

Yet another approach to evaluate associations is Mendelian Randomisation. This is based on the fact that a mutation which mimics the effect(s) of a preventive measure or a drug such as aspirin, will have occurred at random within a population. Several studies using this strategy have yielded evidence favourable to aspirin in the treatment of cancer.

Aspirin and vascular complications of cancer: Aspirin has been repeatedly shown to reduce thromboembolism, including in patients with cancer, and the biological mechanisms involved have been well described. In the UK thrombotic complications of cancer were found to be elevated over three-fold in patient with cancer. and in the USA a study showed that amongst patients with twenty different cancers 11% of deaths had been certified as due to vascular disease (mostly MI). **(Reports 10 and 13)**

Aspirin and biological mechanisms in cancer: Aspirin has been shown to have effects consistent with benefit upon a wide range of cellular and biological mechanisms relevant to cancer initiation; cancer growth; metastatic spread and mortality. This again suggests that aspirin is likely to be beneficial in a wide range – *if not all* cancers. **(see Report 7)**

A mutation of particular interest is a defect in the DNA mismatch repair mechanism, a protective mechanism against cancer within all of us, the action of which is enhanced by aspirin. A defect in this, known as the Lynch Syndrome, carries a high risk of cancer of the colon and other organs. The prevalence of this defect has been estimated as one in 279, or 3.5 per thousand in the general population. Since 2019 NICE in the UK has recommended low-dose aspirin for patients found to have the syndrome. **(see Report 13)**

Evidence from low-income countries: One in every six deaths worldwide is due to cancer, giving an estimated 9.6 million deaths in 2018, with around 70% of the deaths occurring in low- and middle-income countries. WHO points out that most cancers in the poorer countries are diagnosed at a very late stage, when most treatments are no longer effective – even if treatments were available, which they are not in many countries. Against that background the promotion of aspirin could be of enormous benefit within developing countries, and, as one oncologist has predicted: 'a global impact [*upon cancer*] could be realised'. **(see Reports 10 and 13)**

In fact, a recent study of the use of aspirin in the treatment of patients with a history of cardiovascular disease in 51 countries has judged that there is an enormous under-use of aspirin in secondary prevention of vascular disease within low-income countries.

Cost and availability of low-dose aspirin: Low-dose aspirin is inexpensive, relatively safe in comparison with other cancer drugs, and readily available across the globe. A preliminary estimate is that its cost if used as a additional treatment of cancer is at most about £100 per **q**uality **a**djusted **l**ife **y**ear gained (QALY).

A 'jury' evaluated the evidence. In a 'Citizen's Jury' sixteen members of the public in Cardiff were invited to represent the general public, and among a number of issues presented for discussion was aspirin and the treatment of cancer. The 'Jurors' expressed a desire that patients and the public be more closely and more openly involved in decision-taking in all matters relevant to health and argued that patients should be presented with evidence on medicines with possible health benefits - *'even before there is unanimity within doctors'.* **(see Report 8)**

Prevention of cancer by aspirin: This present document focuses upon the potential role of low-dose aspirin in the ***treatment***, and not the prevention of cancer. Concern has however arisen because a major randomised trial of aspirin and cancer prevention (ASPREE) has reported in an average 4.7 year follow-up, a significant increase in new cancer cases in subjects aged over 70 years who had been randomised to take aspirin. On the other hand, a large series of published studies with randomisation of aspirin and placebo has shown a reduction in new incident cases of cancer… *but the reduction appeared only after aspirin had been taken for at least 5 years*. Further work on aspirin and the prevention of cancer is clearly needed before these conflicting studies can be interpreted and their relevance - if any - to cancer treatment judged with confidence.

Finally, a warning: If aspirin has been taken for a while it should never be stopped suddenly. Sudden withdrawal can increase the risk of thrombosis.

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After twenty-years of work and numerous discussions with clinical and other colleagues, we in the Welsh Aspirin Group, feel a very considerable and increasing responsibility to report these and other findings of our research as widely as possible - to medical and other colleagues, to bodies concerned with the identification and treatment of cancer, to the cancer charities, and ultimately, to patients with cancer and their caregivers, encouraging them to raise the topic of aspirin with their own doctors.

Reports on low-dose aspirin, vascular disease and cancer treatment

published by The Welsh Aspirin Group 1974 – 2024

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Chair and secretary of the Welsh Aspirin Group.
Prof Richard Adams, Christine Delon, Prof Marcus Longley, Prof Simon Nobel, Janet Pickering, Majd Protty, Prof John Watkins, Anna Yeatman.

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4. **Aspirin in the treatment of cancer: reductions in metastatic spread and in mortality: a systematic review and meta-analysis of published studies**. Public Library of Science 2016. http://dx.doi.org/10.1371/journal.pone.0152402.
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6. **Aspirin and cancer survival: a systematic review and meta-analyses of 118 observational studies of aspirin and 18 cancers.** eCancer 2021;15:1258 http://dx.doi.org/10.3332/ecancer 2021,1258.
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11. **Preserving the benefits of an 'early' diagnosis with low-dose aspirin**. IN Chatting with the King about Cancer. https://doi.org/10.1136/bmj.q342 all rapid-responses
12. **Ethical principles relevant to the use of aspirin as a treatment of cancer**. Journal of Cancer Research 2024;2:1-5

AN OVERALL SUMMARY

The Aspirin Paradox: Unlocking the global potential of aspirin for vascular disease and cancer management.

a complete copy of this summary is available on our web-page, accessed by a Google search using the link:

The Welsh Aspirin Group.com

CODICIL

A recent independent study published in Public Health

Review Article Effect of aspirin use on cancer incidence and mortality: an updated systematic review and meta-analysis.

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"…262 studies were included in the current systematic review, involving a total of 78,021,375 patients (including 16,883,321 aspirin users)…"

"…Overall, 113 studies were included for cancer mortality (Suppl.Fig. 1). All studies showed a 19 % reduction in cancer mortality (HR = 0.81, 95 % CI 0.78–0.85; P < .01). Similarly, the risk of cancer was reduced in aspirin users (n = 157 studies; HR = 0.81, 95 % CI 0.78–0.84; P < .01; Suppl.Fig. 2). In both analyses, heterogeneity was high (I2 = 88 % and 92 %, respectively)."

"…A recent umbrella meta-analysis by Elwood et al.[15] found almost identical risk reductions across 18 cancers, corroborating our findings…"

Reference 15 in Petrelli et al.

.Elwood PC, Morgan G, Delon C, et al. Aspirin and cancer survival: a systematic review and meta-analyses of 118 observational studies of aspirin and 18 cancers. ecancermedicalscience. 2021;15:1258

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