REVIEW ARTICLE

Aspirin chemoprevention of gastrointestinal cancer in the next decade

A review of the evidence

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KEY WORDS

aspirin, Barrett's esophagus, chemoprevention, esophageal adenocarcinoma

ABSTRACT

Together, gastrointestinal (GI) cancers now account for 25% of neoplastic deaths in the West. In Poland, GI cancer rates are likely to increase further as westernization progresses. Given that conventional cancer therapies have made only modest reductions in cancer mortality, there is a great interest in chemoprevention to prevent or slow malignant transformation from premalignant lesions. The financial pressures in the immediate future require even more stringent criteria for chemopreventive agents – they must be cheap but also safe and efficacious. In this regard, several reviews have indicated that aspirin possesses many favorable qualities for chemoprevention. Furthermore, meta-analyses indicate that aspirin may decrease cancer by approximately 30%. Several large clinical trials are underway, including AspECT (Aspirin and Esomeprazole Chemoprevention Trial) that aims not only to prevent cancer but also decrease the gastric side effects by combining aspirin with potent acid-suppressing drugs. In conclusion, whether aspirin will be the world's first proven chemopreventive agent is currently unknown but the evidence looks hopeful.

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Received: August 23, 2010.
Accepted: August 23, 2010.
Conflict of interests:
J.A. Jankowski is a consultant to AstraZeneca.
Pol Arch Med Wewn. 2010; 120 (10): 407-412

The burden of gastrointestinal cancer in the West and the diagnosis of premalignant lesions Gastrointestinal (GI) cancer accounts for 25% of cancer mortality. Esophageal adenocarcinoma (EAC) has been increasing at 2% per year for the last 40 years, particularly in the West.[1] Despite improvements in multimodality therapy, the prognosis in EAC remains poor with an overall 5-year survival of less than 15%. Patients with Barrett's esophagus (BE) have a 30- to 125-fold increased risk of developing EAC compared with the general population, and progression from BE to EAC occurs at a rate of 0.5% to 1% per patient year of follow-up.[2,3] Incidence of EAC is highest in the United Kingdom (UK) (5.8–8.7/100,000), the Netherlands (4.4/100,000), United States (US) (3.7/100,000), and lowest in Poland 2.2/100,000.[4] In Poland, these low rates are likely to rise as Westernized lifestyles are locally adopted (meat diet instead of fish and vegetables, etc). The important issue is the recognition of the premalignant condition in BE at early stages, so that preventive cancer strategies can be applied to this "at risk" population. Unfortunately, it is estimated that for every case of diagnosed BE, 20 remain undiagnosed.[5] However, not all GI premalignant lesions remain undiagnosed. For example, colorectal adenomas are increasingly identified in the national bowel screening programs in the West. Up to 50% of patients attending the National Bowel Cancer Screening Programme in the UK who are fecal occult blood positive have adenomas identified on subsequent colonoscopy. These adenomas represent arguably an ideal pathological surrogate endpoints for colorectal cancer risk from which to stratify the application of cancer prevention strategies.[6] The conundrum is that current dogma indicates that these lesions should be meticulously

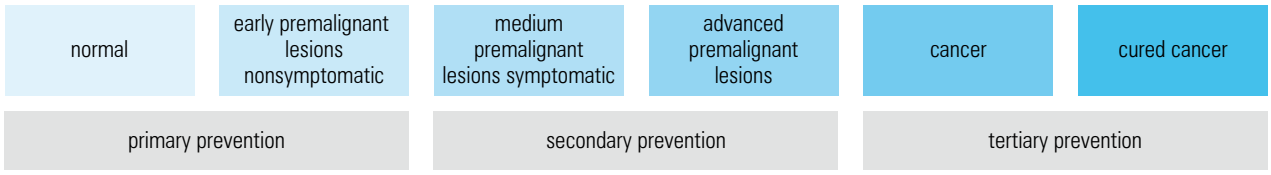

FIGURE The phases of chemoprevention

removed once diagnosed. As a consequence, colorectal cancer occurrence even in metachronous lesions is much less frequent, which makes adenomas less useful as surrogates of colorectal cancer risk in the majority of cases.[7]

Preventing gastrointestinal cancer; the paradigm of chemoprevention The aim of any cancer prevention program is simply to prevent or slow the progression of precancer to cancer to allow more effective treatment by earlier intervention. Even if earlier treatment is not possible, slowing the progression may lead to a patient's death from another unrelated disease at a later date. If we use EAC as our paradigm, the alternative strategies we need to test to see if we can prevent and reduce mortality from BE-associated EAC include: screening (detection of lesions in asymptomatic people without previous BE), surveillance to pick up EAC prior to symptomatic presentation of cancer, (e.g., dysphagia), lifestyle modification (e.g., cessation of smoking, weight reduction), treatment of dysplasia (by endoscopic or other minimally invasive methods), and identification of biomarkers (tissue or blood genetic factors) that predispose an individual to a higher risk of developing EAC. Unfortunately, screening is neither cost-effective nor effective in most GI cancers or their premalignant lesions. Surveillance may be cost-effective when the incidence of the respective cancer in the population to be surveyed is at least 0.5% to 1% per year. However, surveillance of BE even in high-incidence populations, such as the UK population, has major problems including low adherence to specified endoscopic guidelines by clinicians and considerable interobserver variations between pathologists on the degree of dysplasia present.[7,8] As a consequence, in most cases where cancer is detected, a longer lead time is achieved rather than true down-staging of EAC (incurable cancer diagnosed earlier rather than cancers that can be cured). Even this modest benefit has to be balanced against the morbidity and indeed mortality associated with surveillance (i.e., perforations, increased bleeding, etc). Cancer detection at earlier stages as a strategy has reaped quite impressive benefits even in early potentially curable lesions, which are harder to access by visual and biopsy methods, as in the case of breast lesions. Indeed, the recently described benefits of cancer reduction in breast cancer screening programs is a timely reminder that cancer prevention, if funded and organized properly, works effectively.[8]

The identification of those most at risk of developing cancer by the use of clinical and biological surrogates can optimize the risk-benefit ratio.[9] This has lead to the report of many biomarkers predicting malignant potential. But the National Institute of Health American criteria to validate biomarkers whether for cancer or benign disease are very strict needing 5 steps, namely biological hypothesis, development of reliable assays, linking biomarker with disease progression retrospectively, predicting outcome prospectively, and intervening solely on the basis of the biomarker, to see if there are true benefits. Unfortunately, none of the biomarkers currently being studied for GI cancer prognostication have been fully validated for clinical practice as of yet.[9]

In an effort to manage cancer prevention in the absence of other validated methods, chemoprevention has been developed. This can be subdivided into primary prevention of people with asymptomatic lesions, secondary prevention of people with premalignant lesions, and tertiary prevention of metachronous lesions in people who have already had cancer cured (FIGURE). This is the method whereby an agent, either dietary or drug based, is given to supplement the diet in an effort to decrease cancer. Chemopreventive agents need to fulfill several criteria in order to be effective in reducing cancer. First and most importantly, they need to have acceptable side effects because toxic effects, if serious, will affect mortality and, if minor, will also affect compliance. Second, they need to be cost-effective because healthcare providers, let alone patients, will not be able to undertake what will be many years of long-term expenditure for "invisible gains" (patients who might have cancers prevented in the future cannot be identified individually). Finally, the agent must be acceptable to patients taking it and its mechanism must be clear so they remain motivated; it would help if a measurable biomarkers of benefit or efficacy could be monitored annually. Chemoprevention is more cost-effective in high-risk groups such as those with changes of incipient cancer (e.g., dysplasia).[7,10] Chemoprevention strategies include targeting high-risk individuals or using safe medications with other recognized health benefits, especially over longer periods.[11] Compliance is a major issue with chemoprevention because patients generally feel well and therefore question the magnitude of any "hidden benefit" they receive. For example, the reported compliance of taking something as palatable as 100 mg aspirin on alternate days was 75% at 5 years and 67% at 10 years in the Women's Health Study. Interestingly, in this study of 39,876 women, no protective benefit of aspirin in preventing any cancers has been shown.[12] Could the 33% who stopped aspirin have been the very patients that would

TABLE Clinical trials investigating the effects of anti-inflammatory therapy on gastrointestinal cancers (courtesy of Anna Nicholson in Gastrointestinal Cancers and Inflammation, 2011)

Trial	Effects if any	Gastrointestinal disease	Years of follow-up	Patients recruited	Drugs studied
AspECT	ongoing	Barrett's esophagus	10	2513	aspirin and proton-pump inhibitors
CALGB 9270	ongoing	previous colorectal cancer	7	1100	aspirin and placebo
CAPP 1	no effect	familial adenomatous polyposis	8	411	aspirin and corn-starch
CAPP 2	no effect no effect	hereditary nonpolyposis colorectal cancer	4	1012	aspirin and corn-starch
UKCAP	6% polyp reduction	colorectal adenomas	4	939	aspirin, folic acid, and placebo
AFPPS	decreased adenomas	colorectal adenomas	4	1121	aspirin, folic acid, and placebo
APACC	decreased adenomas	colorectal adenocarcinomas	4	272	aspirin or placebo
Victor	decreased adenomas decreased cancer	colorectal cancer	7	2210	rofecoxib and placebo
APPROVe	decreased adenomas	colorectal adenomas	4	2587	rofecoxib and placebo
CBET	no effect	Barrett's esophagus and dysplasia	2	222	celecoxib or placebo

have benefited from taking it? Regardless if suboptimal compliance occurs in a "monitored population" in a research study, what would happen in a less motivated population in a routine primary care setting? The likelihood is that compliance with the continued ingestion of any chemopreventive agent could be an issue.

Possible chemopreventive agents This review will not cover dietary agents and the long list of drugs that are currently being studied because this is comprehensively discussed elsewhere.[7,13] A list of larger trials will be discussed instead (TABLE). Furthermore, despite the huge list of potential chemopreventive agents, there are no agents licensed currently for chemoprevention in adults. The drug-based medications gaining the most recent interest have been nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin and cyclooxygenase-2 (COX-2) agents for all GI cancers and proton-pump inhibitors (PPI) for EAC.

In certain diseases, different agents seem appropriate. For example, since ⅔ of patients with BE have symptomatic reflux disease, acid-suppressing agents would seem most logical for chemoprevention of EAC.[14] In this regard, PPI therapy has been shown to decrease the number of Australian patients developing dysplasia with BE and increase the time for dysplasia to develop in the others.[15] A report in the United States was more dramatic indicating a reduction in the risk of esophageal cancer or dysplasia in BE patients by 60%.[16]

COX-2 plays a pivotal role in the development of many cancers. Furthermore, a prospective study on BE showed substantially lower incidence of EAC in those patients who are currently taking NSAIDs with those who have never taken them, a reduction by 58%.[17] However, the only randomized trial evaluating selective COX-2 inhibitors, CBET (Chemoprevention for Barrett's Esophagus Trial), found no statistically significant difference in change in dysplasia from baseline with treatment with celecoxib.[18] Several chemopreventive trials have shown the efficacy of selective COX-2 agents of about 25%. However, there was an associated 2.5-fold increase in ischemic cardiac events after only just 6 months of therapy.[19]

Aspirin: the oldest and the best agent One of the oldest agents that has recently been found to have cancer chemopreventive effects is aspirin, which has been used in clinical practice since the 19th century.[7] Aspirin is a synthetic analog of naturally occurring salicylates, found in fruits and vegetables (particularly in the organic ones because pesticide use decreases fruit salicylate by secondary mechanisms). A systematic review demonstrated a protective role for aspirin and NSAIDs in reducing EAC by medication type: aspirin was protective: odds ratio (OR) 0.5; while NSAIDs were less effective: OR 0.75.[20] Increased frequency of use was associated with greater protection.[20] This was supported by a meta-analysis of 34 case-control and 13 cohort studies, which found a relative risk (RR) of developing EAC to be 0.51 (reduction by 49%) when taking aspirin and 0.65 (reduction by 35%) when taking NSAIDs.[21] In a US case-control study, patients who had used aspirin at least once a week for at least 6 months had a decreased risk of EAC (OR 0.37) as well as other upper GI cancers.[21] An Irish case-control study, FINBAR, also found that patients who used aspirin had a reduced RR of both BE (OR 0.53) and EAC (OR 0.57).[22] Meta-analysis data from 2 case-control and 4 cohort studies indicated that the RR of developing EAC was only 0.41 in the case-control studies and 0.83 in the cohort studies[10] of patients using aspirin with a pooled RR of 0.72.[23]

Although aspirin also reduces adenoma recurrence (and possibly also downstream the incidence and mortality in colorectal cancer [CRC]), the exact type, dose, frequency, and duration of

use needed to produce these effects is not entirely clear.[23-27] The evidence indicates that aspirin can decrease recurrence of colorectal adenomas in patients with previously treated CRC (RR = 0.65 at 325 mg per day) or with a recent history of colorectal adenomas (RR = 0.81 at 81 mg per day).[26,27] However, there was contradictory data because 325 mg aspirin per day in this latter study did not significantly decrease colorectal adenoma recurrence in participants with a recent history of colorectal adenomas.[27] Furthermore, CRC incidence was similarly ineffective in the Physicians Health Study.[23] What is more, a recent large randomized trial of Lynch syndrome patients showed no cancer prevention effect with low-dose aspirin after 4-year therapy.[28] Moreover, aspirin's chemopreventive actions do not act on everyone.[7] The main reasons for this may be increased aspirin-metabolizing enzymes, which decrease aspirin's chemopreventive effectiveness.[7] In addition, some people have higher levels of mucosal inflammation and this again decreases aspirin's chemopreventive efficacy by 50%.

Aspirin, however, decreases fatal myocardial infarction (MI) vascular events in people with known vascular disease by one sixth and all other vascular death by ¼ (Antithrombotic Trialist's Collaboration, 2002). In people without known vascular disease, aspirin decreases risk of MI vascular events by ⅓, but there is no evidence of an effect on cerebrovascular accidents and death.[7] The risk of MI in the general population is 2/1000 between 20 and 59 years of age and increases to 5/1000 above 60 years. Therefore, aspirin has considerable cardiac protective roles as well as chemopreventive roles in patients above 60 years of age. However, in those with no risk factors for ischemic heart disease, primary prevention by aspirin is currently unproven and has little objectivity to recommend it.[29]

Aspirin as chemoprevention against EAC is also cost-effective, assuming a risk reduction of 50% and a 0.5% per year progression rate from BE to cancer.[30] Aspirin remains cost-effective even when a risk reduction of only 10% is calculated. However, a validated model has predicted that if all white men aged 40 years had commenced aspirin chemoprevention in 1965, just over 7,000 cases of EAC could have been prevented.[31]

Aspirin is acceptable to BE patients with 76% willing to take it as chemoprevention.[32] The remainder were concerned about the side effects, especially the risk of GI bleeding. Given that recent evidence has shown that at least 21% of BE patients died of cardiac disease, the majority of BE patients indicated unwillingness to take celecoxib due to its reported 2-fold higher risk of cardiac events.[33]

Aspirin has a number of potentially negative points. First and most importantly, the only randomized controlled trials have been disappointing as regards CRC prevention.[23] In addition, large case-control studies have shown little benefit of aspirin in reducing CRC risk. There are several issues with regard to side effects of aspirin, especially GI bleeding, hemorrhagic stroke, and, rarely, allergic reactions.[33,34] This is one important reason why aspirin cannot be given to everyone, as it increases the GI bleed rate 2- to 4-fold, especially in patients over 70 years of age.[19]

However, when aspirin is given with a PPI, especially after *Helicobacter pylori* eradication, the risk of bleeding complications after aspirin or NSAID use is dramatically decreased (by 50%–90%).[19] In this regard, AspECT (Aspirin and Esomeprazole Chemoprevention Trial) is assessing the role of a PPI with or without aspirin in decreasing the risk of EAC and cardiac disease in patients with BE. The incidence of adenomas and CRC will be secondary endpoints.[29] This trial assesses potentially synergistic agents to deal with both potential anticancer effects as well as cardiac protective effects and represents an important type of trial design. Furthermore, the combination of aspirin and acid-suppressing agents may also decrease the GI side effects of aspirin. To date, 85% of patients remain on their randomized study medications and few serious GI side effects have been reported.[29] The idea that all people will be taking aspirin seems ill-founded, as even in populations at a high risk for IHD only 50% are taking aspirin.

If it is taken for the sake of an argument that aspirin chemoprevention works, the optimal dose of aspirin for cancer prevention is still unknown. Large, population-based studies suggest that a larger dose may be needed for chemoprevention compared with cardioprotection.[35,36] These larger doses would cause an increased risk of GI bleeding; however, combining profound acid-suppressing drugs with aspirin would be expected to address these concerns.[37]

Targeting chemoprevention The question arises who do we think will get aspirin? Everyone or only those with certain prespecified demographic, biomarker, or clinical parameters? Currently, since the identification of the former is still poorly characterized in gastroenterology, it might be that anyone who has a proven adenoma or chronic reflux gets aspirin as long as they had no GI bleeding before. Patients with a high cardiovascular risk profile would also benefit from aspirin. Studies have suggested that risk reduction starts at 10 years and increases with duration of chemoprevention. The most advantageous time to start chemoprevention is proposed to be 10 years prior to the peak onset of the cancer, the sixth decade for colonic cancer, and the seventh decade for BE.

More randomized trial data needed Aspirin and other NSAIDs, along with PPIs, are promising chemopreventive agents. To date, attempts to stratify patients for selection by use of molecular biomarkers have proved disappointing.[38] The largest randomized control trial in the subject, AspECT, is currently taking place and the results

will help guide future practice. It is possible that genetic biomarkers by modern genome-wide technology will provide the information of who is likely to benefit most.[4] We need even larger-scale studies based in primary care where patients with heartburn are randomized to aspirin whether they have known premalignant lesions or not. In this regard, we are planning the ACE trial (Aspirin Chemoprevention for Everyone) in a 60,000 patient pilot in primary care.

Acknowledgements We would like to thank Anna Nicholson for helping prepare the table of trials assessing aspirin and other NSAIDs as chemopreventive agents.

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ARTYKUŁ POGLĄDOWY

Chemioprofilaktyka raka przewodu pokarmowego z użyciem kwasu acetylosalicylowego w następnym dziesięcioleciu

Przegląd danych naukowych

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STRESZCZENIE

Nowotwory złośliwe przewodu pokarmowego są przyczyną 25% zgonów wywołanych przez nowotwory w krajach zachodnich. Prawdopodobnie w Polsce nastąpi dalsze zwiększenie zapadalności i chorobowości na nowotwory złośliwe przewodu pokarmowego w miarę zbliżania się do krajów Europy Zachodniej. Tradycyjne metody terapii spowodowały jedynie umiarkowane zmniejszenie umieralności na nowotwory złośliwe i dlatego istnieje duże zainteresowanie chemioprofilaktyką, stosowaną w celu zapobiegania albo spowolnienia przekształcenia zmian przedrakowych do nowotworów złośliwych. Ograniczenia finansowe wymagają zastosowania w najbliższej przyszłości jeszcze surowszych kryteriów oceny środków chemioprofilaktycznych. Muszą one być niedrogie, ale również bezpieczne w stosowaniu i skuteczne. Liczne prace przeglądowe wskazywały, że kwas acetylosalicylowy ma wiele korzystnych właściwości w chemioprofilaktyce. Ponadto metaanalizy wskazują, że kwas acetylosalicylowy może zmniejszyć liczbę zachorowań na nowotwory złośliwe o około 30%. W toku jest wiele szeroko zakrojonych badań klinicznych, w tym badanie AspECT (Aspirin and Esomeprazole Chemoprevention Trial), którego celem jest nie tylko zapobieganie nowotworom złośliwym, ale też zmniejszenie częstości występowania działań niepożądanych ze strony żołądka dzięki połączeniu kwasu acetylosalicylowego z silnie działającym lekiem hamującym wydzielanie kwasu w żołądku. Podsumowując: obecnie nie wiadomo, czy kwas acetylosalicylowy będzie pierwszym środkiem w chemioprofilaktyce zaakceptowanym w skali światowej, ale dostępne dane naukowe są obiecujące.

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Praca wpłynęła: 23.08.2010.
Przyjęta do druku: 23.08.2010.
Zgłoszono sprzeczność interesów: Prof. Janusz Jankowski jest konsultantem firmy AstraZeneca.
Pol Arch Med Wewn. 2010; 120 (10): 407-412
Tłumaczył lek. Michał Tomaszewski