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Old and new face of aspirin

Stare i nowe oblicze aspiryny

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Abstract

Salicylic acid has been known as a therapeutic substance since antiquity. Since its inception, acetylsalicylic acid, i.e. its original acetylated derivative, has become one of the most popular analgesic substances. Over the years, it has gained the recognition of cardiologists, and its potential antineoplastic effects have been recently studied. By inhibiting cyclooxygenase 2 (COX-2), the drug reduces the formation of prostaglandins, which relieves inflammation, eases swelling and lowers fever. Moreover, aspirin has an anticoagulant effect owing to its inhibition of cyclooxygenase 1 (COX-1). The prophylactic outcome of acetylsalicylic acid in patients with cardiovascular diseases is undeniable, but its benefits in individuals without cardiac disease are controversial. However, research is ongoing to identify the group of beneficiaries of primary prevention precisely, and the results are expected in the near future. Another field of action of acetylsalicylic acid which is currently under investigation is related to the potential antineoplastic effect of the drug. Nowadays, most of the data indicate its positive effects in patients with a positive history of colorectal proliferative diseases. The antineoplastic activity of the drug is based on the inhibition of COX-2, an enzyme stimulating cell divisions. Therefore, the effect of the medicine may be visible in tumours characterised by an overexpression of this enzyme. A positive response to aspirin also depends on the human genome and specific mutations in cancer cells. By acting on platelet COX-1, aspirin reduces the metastatic potential of cancer, as platelet-derived substances promote the formation of metastases. To sum up, only a selected group of patients exhibit sensitivity to the anticancer effects of the drug. Nevertheless, the use of aspirin could turn out to be dangerous in people with a high risk of complications, so each patient should be treated individually.

Keywords: acetylsalicylic acid, colorectal cancer, cardiovascular disease, prevention

Streszczenie

Kwas salicylowy jako substancja lecznicza był znany już w starożytności. Odkąd powstał kwas acetylosalicylowy (potocznie zwany później aspiryną) – jego oryginalna acetylowana pochodna – lek ten stał się jedną z najpopularniejszych substancji przeciwbólowych. W miarę upływu lat zyskał on uznanie kardiologów, a ostatnio badane jest jego potencjalne działanie przeciwnowotworowe. Aspiryna poprzez inhibicję cyklooksygenazy 2 (COX-2) zmniejsza powstawanie prostaglandyn, co ogranicza stan zapalny, zmniejsza obrzęk oraz zwalcza gorączkę, a dzięki hamującemu wpływowi na cyklooksygenazę 1 (COX-1) działa antykoagulacyjnie. Profilaktyczne działanie kwasu acetylosalicylowego u osób obciążonych chorobami układu sercowo-naczyniowego jest niepodważalne, natomiast kontrowersyjne jest jego stosowanie u osób nieobciążonych kardiologicznie. Trwają jednak badania mające na celu definitywne określenie grupy beneficjentów profilaktyki pierwotnej. Wyniki będą znane w najbliższej przyszłości. Kolejnym obecnie badanym polem działania kwasu acetylosalicylowego jest jego potencjalne działanie przeciwnowotworowe. Obecnie najwięcej danych wskazuje na jego pozytywny wpływ u osób z dodatnim wywiadem w kierunku chorób rozrostowych jelita grubego oraz odbytnicy. Działanie antyproliferacyjne leku polega na hamowaniu COX-2, która pobudza podziały komórkowe. Dlatego też efekt jego działania może być widoczny w nowotworach cechujących się zwiększoną ekspresją tego enzymu. Pozytywna odpowiedź na aspirynę zależy od genomu danej osoby, jak również od określonych mutacji w komórkach nowotworowych. Lek ten, działając na płytkową COX-1, zmniejsza potencjał metastatyczny raka, gdyż substancje pochodzące z płytek krwi promują powstawanie przerzutów. Reasumując, można stwierdzić, że tylko wybrana grupa pacjentów jest wrażliwa na przeciwnowotworowe działanie kwasu acetylosalicylowego, a u osób z dużym ryzykiem powikłań jego stosowanie mogłoby się okazać niebezpieczne, dlatego do przypadku każdego chorego należy podchodzić indywidualnie.

Słowa kluczowe: kwas acetylosalicylowy, rak jelita grubego, choroba układu sercowo-naczyniowego, profilaktyka

HISTORY OF SALICYLIC ACID (ASPIRIN)

The first reports on the therapeutic properties of salicylic acid, a derivative of which is acetylsalicylic acid (ASA, colloquially referred to as aspirin), go back to ancient Egypt, but the substance is believed to have been used therapeutically for many years before the Egyptian civilisation. Salicylic acid was traditionally extracted from willow bark or leaves, and its therapeutic effects were already known to Hippocrates, Celsus or Pliny the Elder. The word "aspirin" comes from the German name for acetylsalicylic acid (*Acetylspirsäure*), while the German word for salicylic acid (*Spirsäure*) is derived from the name of an old plant species – *Spirea ulmaria* – from which a pain-relieving drug was originally obtained. The synthesis of acetylsalicylic acid was first described by Charles Gerhardt in 1853, however, the chemist failed to obtain the pure form of the substance or identify its structure. The commercial name Aspirin® for acetylsalicylic acid was coined by the German company Bayer which marketed the product. In 1897, Felix Hoffman, a chemist with Bayer, acetylated salicylic acid, thus creating the "iconic" pharmaceutical agent, the first drug obtained synthetically. The industrial production of aspirin started in 1899, ushering in a new era in the field of pharmacology. It was not until 1971 that John Vane discovered the mechanism of action of the drug, and demonstrated that acetylsalicylic acid, similarly to other nonsteroidal antiinflammatory drugs (NSAIDs), inhibits the activity of the enzyme cyclooxygenase (COX) which is responsible for the production of prostaglandins (PGs), i.e. substances involved in the pathogenesis of inflammation, swelling, pain and fever. Prostaglandins, however, are a highly heterogeneous group of compounds that also have a number of physiological functions. Based on its inhibitory effect on their production, ASA reduces the protective effect of prostaglandins on the gastric mucosa which is exposed to hydrochloric acid, and disrupts renal function and platelet aggregation[1]. Initially, aspirin was widely used as an analgesic, anti-inflammatory and antipyretic agent, gaining considerable popularity. However, the inhibition of platelet aggregation due to the effects of acetylsalicylic acid was not observed and used therapeutically until the second half of the 20th century. Studies conducted by John Vane and his associates helped to elucidate both the beneficial and adverse effects of ASA. In addition to blocking COX activity, the drug also decreases the synthesis of thromboxane, producing an anticoagulant response. By reducing the production of PGs in the central nervous system, ASA induces an antipyretic effect. Analgesic properties are achieved through the inhibition of the synthesis of PGs both in the central and peripheral nervous systems. The drug also produces anti-inflammatory action in blood vessel walls, without affecting COX. In 1982, Vane was awarded the Nobel Prize in Medicine for his work on the properties of acetylsalicylic acid.

Currently, the compound has a wide range of therapeutic applications, and it is an ingredient of a number of drugs, with Acard, Aspirin, Polocard and Polopiryna being the most popular in Poland. Small doses of ASA (75–150 mg) sufficient to inhibit platelet COX-1 activity and, as a consequence, the synthesis of thromboxane, are used for their protective effect on the cardiovascular system. The anti-inflammatory and analgesic effect inhibitory towards the inflammation-inducing COX-2 requires the use of higher doses (usually 2–6 g/day) and brings benefits in rheumatology, among other medical areas.

ADVERSE REACTIONS

Despite its indisputable therapeutic benefits acetylsalicylic acid can also cause adverse reactions. It is contraindicated in children and adolescents for the treatment of viral infections, as it can cause Reye syndrome. The most common adverse reactions caused by acetylsalicylic acid include dyspepsia, diarrhoea and nausea, which should not be overlooked. Also, treatment with ASA can result in gastrointestinal erosions and ulcers. The most dangerous complication associated with high mortality is bleeding from the upper gastrointestinal tract. The risk of this complication is particularly high in patients over 65 years of age, with a history of peptic ulcer disease or an episode of gastrointestinal bleeding. The risk of complications in the upper gastrointestinal tract may increase even in patients taking low doses of ASA[2]. One method to reduce the level of risk in particularly susceptible patients involves proton pump inhibitors (PPIs). It needs to be stressed, though, that PPIs, like all medicines, carry a risk of causing adverse reactions, the most common of which are headaches, diarrhoea, constipation, flatulence and abdominal pain. Long-term treatment with PPIs may be associated with altered gut bacterial composition, which in turn may contribute to the development of diseases including irritable bowel syndrome, bacterial overgrowth syndrome or some of the infectious bowel diseases. Acetylsalicylic acid has numerous interactions with concurrently taken drugs and foods. In combination with alcohol, it can result in gastric mucosal bleeding. Concurrent use with ibuprofen reduces the antiplatelet and cardioprotective effects of ASA. It should also be stressed that combining several NSAIDs increases toxic effects on the gastrointestinal tract. Even at low doses, aspirin increases the likelihood of bleeding in patients taking oral anticoagulants by inhibiting platelet aggregation and prolonging the bleeding time[3]. In addition to pharmacodynamic interactions, concern should also be given to pharmacokinetic interactions between ASA or other NSAIDs with other drugs. For example, the concomitant use of ASA during lung cancer treatment with methotrexate counteracts the anticancer effect of the drug[4]. Both methotrexate and ASA are excreted into urine using the transporter OAT3[5], so inhibiting its clearance increases the blood concentration of the antifolate, often to a toxic level.

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Acetylsalicylic is a category C drug, which means it should not be taken by women during pregnancy, especially in the third trimester, as it can cause premature closure of the foetal ductus arteriosus.

At present, almost two centuries after the first synthesis of acetylsalicylic acid, this drug remains one of the most popular and widely used pharmaceuticals, and a number of studies are under way to investigate its novel therapeutic applications.

CARDIOVASCULAR EFFECTS

Despite a downward trend in the cardiovascular mortality rate, diseases of the cardiovascular system remain the most common cause of death in Europe. Based on the 2014 statistics, the highest standardised mortality rates for ischaemic heart disease in the European Union countries were recorded in Lithuania, Latvia, Hungary and Slovakia, where they exceeded 350 deaths per 100,000 population. In contrast, France, the Netherlands, Spain, Portugal, Belgium, Luxembourg, Denmark and Italy had the most favourable mortality rate from cardiovascular diseases, with fewer than 100 deaths per 100,000 population. A very important aspect of contemporary medicine is the prevention of diseases, particularly disorders of the cardiovascular system. Preventive measures include an appropriate diet, physical activity, reduction of stimulant use, regular examinations and avoidance of stress. The prophylactic use of ASA at low doses is common among patients in whom there is evidence of cardiovascular diseases, and among individuals who are at an increased risk of such conditions. However, the prophylactic use of ASA by healthy individuals is a controversial issue. The number of preventable vascular events in this group may be similar to the number of bleeding episodes induced by the drug. The World Health Organization does not recommend low-dose ASA in patients whose 10-year risk of myocardial infarction is lower than 30%[6], whereas the Polish Cardiac Society[7] advises against the use of low-dose ASA for primary prevention in all individuals without cardiovascular diseases on account of an increased risk of severe bleeding. Population-wide recommendations are based on statistical analysis of a large group of people and fail to reflect individual preferences, which may lead to excessive or insufficient treatment. An alternative may involve therapeutic recommendations developed on the basis of individually assessed risk and including patient preferences. Acetylsalicylic acid causes irreversible inhibition of COX-1 in blood platelets, and hence also blocks the formation of thromboxanes responsible for vasoconstriction and irreversible platelet aggregation. For this reason, its activity is used in the prevention and therapy of cardiovascular diseases. Treatment with ASA is also associated with the risk of complications involving mainly the gastrointestinal tract. Patients at high cardiovascular risk due to occlusive vascular disease may benefit from long-term antiplatelet therapy (e.g. ASA), which reduces one-year risk of major vascular events (i.e. non-fatal myocardial infarction or stroke, cardiovascular death). Acetylsalicylic acid is the best-studied drug in the context of long-term preventive therapy in patients after myocardial infarction or stroke. A meta-analysis of 16 studies involving a total of 17,000 people[8] showed that ASA reduced overall mortality by 10% in individuals with cardiovascular or cerebrovascular disease. The treatment was associated with a significant rate of bleeding, but the benefits outweighed the risk of major haemorrhagic events.

PERSONALISED PRIMARY PREVENTION

The advantages of ASA in secondary prevention are indisputable, but the benefit-to-risk ratio in primary prevention is less clear. Recommendations included in guidelines apply to large populations. An attempt to individualise recommendations for the use of ASA in primary prevention of cardiovascular diseases and cancer was a study by Milo A. Puhan of Johns Hopkins University[9]. The Benefit-Harm Charts show that the benefit-to-risk balance varies greatly depending on the population receiving primary prevention. Low-dose treatment with ASA can bring more benefits than risks in men, elderly patients and individuals at a low risk of severe gastrointestinal bleeding. An important role is also attributed to patient preferences. The tool described in the study offers a possibility to select priority targets. For example, if stroke prevention is a priority and the risk of major bleeding is deemed less important, the majority of patients will benefit from low-dose ASA use. Conversely, if the risk of gastrointestinal bleeding is recognised as equally important, the balance of benefits relative to harms associated with low-dose ASA treatment will probably be unfavourable. Based on the studies, a platform was established to help with the assessment of benefits of the prophylactic use of ASA depending on the selected age category, sex, health goals of the evaluated patient and 10-year risks of severe bleeds/myocardial infarction. The study highlights the limitations of current guidelines with respect to the personalisation of therapeutic recommendations. In addition, recommendations issued by scientific societies focus on the evaluation of potential benefits in relation to diseases of one system (e.g. cardiovascular). The risk of bleeding associated with aspirin should be considered in the context of the antineoplastic and cardioprotective properties of the drug. The tool discussed in the study still has a number of weak points that need to be addressed before it can be used on a large scale.

PROPHYLACTIC USE OF ACETYLSALICYLIC ACID

In 2009, an independent team of experts evaluating the efficacy of preventive medicine – USPSTF (U.S. Preventive Services Task Force) – compiled a list of recommendations for using ASA in the prevention of cardiovascular diseases on the basis of six large randomised clinical trials.

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In 2016, the recommendations were updated to incorporate the findings of five additional trials[10]. The USPSTF recommends the initiation of prophylactic treatment with low-dose aspirin in adults aged 50–59 years old with a 10-year cardiovascular disease (CVD) risk of 10% or greater who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. In patients aged 60–69 years who have a 10% or greater 10-year CVD risk, the decision of whether to use aspirin as a preventative measure should be based on the individual. Persons who are not at increased risk for bleeding, and have a life expectancy of at least 10 years may benefit from the described prophylactic effects. According to the USPSTF, the current clinical evidence is insufficient to determine the balance of benefits and harms of initiating prophylactic ASA treatment in adults younger than 50 years, and aged 70 years and older.

PREVENTION IN THE ELDERLY

ASPREE (ASPirin in Reducing Events in the Elderly) is an international, randomised, double-blind clinical trial enrolling a total of 19,000 patients aged 70 and older in the USA and Australia[11]. The purpose of the trial is to determine whether aspirin at a dose of 100 mg/day is effective at preventing cardiovascular disorders, dementia diseases, depression and some types of cancer in comparison to the control group. The results of the trial will be weighed against the risk of adverse reactions associated with the use of this drug by patients in this age range. The first findings of the 5-year study are scheduled to be announced in 2018. If the use of ASA is shown to be generally beneficial in the assessed age group, millions of healthy elderly people around the world might take the medicine on a preventative basis. However, if it is demonstrated that ASA fail to yield any benefits, many elderly people will probably discontinue the drug.

DIABETIC PATIENTS

Another large trial is ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes), designed to assess the benefits of prophylactic treatment with aspirin in combination with a statin compared to a statin alone in patients with type 1 or 2 diabetes mellitus over the age of 50 years[12]. The aim of ACCEPT-D is to assess whether 100 mg/day of aspirin prevents cardiovascular events in patients without clinically manifest vascular disease and treated with simvastatin. Despite high cardiovascular risk in diabetic patients, there is no evidence for the effectiveness of prophylactic strategies in this group of patients, which further increases the value of the trial. The findings of the study may become the basis for new guidelines for the prevention of cardiovascular events.

EFFECT ON CANCER

Recent reports have drawn attention to the role of aspirin in oncology. The drug is claimed to prevent proliferative processes, and even to support conventional therapeutic modalities.

A number of studies show a beneficial effect of regular ASA use on reducing the risk of colorectal adenoma or carcinoma. A positive effect of the substance (and other NSAIDs, including coxibs) in people with a positive history of proliferative changes in the colon is associated with the inhibition of COX-2 activity in cancer cells[13]. The enzyme induces inflammatory responses and the process of cell proliferation, which is why its inhibition is likely to play a role in reducing the proliferation of tumour cells.

INCREASED EXPRESSION OF COX-ENCODING GENE

The majority of colorectal cancers overexpress the gene encoding cyclooxygenase[14]. In order to evaluate the importance of increased expression of COX-2 in cancer tissues, Chan et al. conducted a study enrolling patients diagnosed with stage I, II, or III colorectal cancer. Histopathological specimens were obtained from neoplastic lesions and, following special treatment, incubated with anti-COX-2 antibodies[15]. In this way, it was possible to divide the study group into subgroups of patients with cancer types characterised by the absence or presence of increased expression of the enzyme, compared to the healthy colonic epithelium and inflammatory cells. The study's participants were also stratified according to their use of acetylsalicylic acid drugs: a group of patients taking ASA both before and after cancer diagnosis, a group taking the drug regularly only before or after their diagnosis, and a group of patients not using ASA at all. Based on the cancer-specific and overall mortality among the patients in the trial, it was concluded that both indicators were significantly lower only in patients who started taking ASA after the diagnosis of cancer, while those who had used the drug prior to their diagnosis failed to benefit significantly from its further use. Furthermore, the benefit was observed solely in patients whose cancer cells were characterised by overexpression of the COX-2 gene, which shows that ASA treatment is beneficial only in some patients with colorectal cancer. In similar studies, Bastiaannet et al. found that the effect of the correlation increases with more regular use of the substance, with increased prescription rates translating more significantly into decreased mortality rates[16]. In addition, the authors identified elderly patients not treated by chemotherapy as the group achieving the greatest benefits in terms of survival among the entire group of study patients. The study also compared acetylsalicylic acid with other NSAIDs which do not seem to have a positive effect on the life expectancy of patients with colorectal cancer, and possibly may even shorten survival. The effect of other NSAIDs is not fully

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elucidated, as studies continue to yield different – and often contradictory – results. Also, Coghill et al. demonstrated the benefits of other anti-inflammatory drugs, but also highlighted that the benefits were restricted to patients taking NSAIDs before the diagnosis of colorectal cancer. The improvement in survival was positively correlated with long-term NSAID use and proximal disease[17].

FORMATION OF METASTASES

Another study on the role of acetylsalicylic acid in colorectal cancer was conducted in mice, and focused on the effect of platelets and substances released by platelets on the migration of cancer cells into the circulation and, consequently, on the formation of distant metastases[18]. It was observed that in order to metastasise colorectal cancer cells needed to assume a mesenchymal phenotype, which gave them an ability to migrate into the vascular lumen[19]. The transformation signals include auto- and paracrine processes involving substances produced by thrombocytes[20]. This was confirmed by the incubation of platelets with tumour cells stimulating their activation and, as a result, the production of thromboxane (TXA) and prostaglandin E_2 (PGE_2). Consequently, an increased expression of Twist1 – a factor repressing the transcription of E-cadherin – leads to a reduced expression of E-cadherin in the epithelium[21]. A reduced amount of adhesion protein increases the mobility of cancer cells, which facilitates their dissemination. To verify these conclusions, different samples were injected into murine blood vessels. After the injection of HT29 tumour cells alone, an increase in thromboxane metabolites in urine was observed. However, the increase was considerably higher when the tumour cells were previously incubated with human platelets, which points to the activating effect of cancer. On the other hand, a study of the expression of E-cadherin and Twist1 depending on sample type showed the expression of adhesion protein to be decreased in samples of tumour cells mixed with platelets, whereas no such phenomenon was observed after the addition of acetylsalicylic acid, i.e. a platelet COX-1 inhibitor (or other platelet-inhibiting substances such as P2Y12 inhibitors or PGE_2 receptor antagonists) to the study sample. The inhibitory effect of ASA can, however, be abolished through the addition of exogenous prostaglandin (PGE_2). In addition to exploring aspects at the molecular level, the researchers have also evaluated the metastatic potential of cancer cells. Autopsy examinations of rodent lung tissues showed that pulmonary metastases developed in the animals which were injected with tumour cells incubated with thrombocytes, but in those which additionally received ASA prior to injection, no dissemination occurred[18]. Considering the results of the experiment, and the fact that platelets aggregate around tumour cells and form a coating protecting the tumour against the defence mechanisms of the immune system, and facilitate migration from vascular lumen by enhancing adhesion to the endothelium[22], it can be assumed that the inhibition of the activity of these morphotic blood elements may be able to restrict the growth and dissemination of cancer.

PROPHYLACTIC ANTICANCER APPLICATION OF ACETYLSALICYLIC ACID

All the effects of ASA described above apply to patients diagnosed with neoplastic disease, but another aspect worth consideration is whether the drug can also provide benefits to individuals who have not developed colorectal cancer. The research effort focused on the genetic susceptibility to the anticancer effects of aspirin which is determined by single nucleotide polymorphisms (SNPs). The SNPs affecting the quality of response to the drug include rs2965667 on chromosome 12p12.3, located near the region encoding microsomal glutathione S-transferase I (MGST-1), and rs16973225 on chromosome 15q25.2, adjacent to the region encoding interleukin 16 (IL-16)[23]. Individuals with rs2965667-TT genotype (the most common type) taking acetylsalicylic acid or another NSAID on a regular basis had a significantly lower risk of colorectal cancer compared to ASA non-users. Importantly, the effect was not observed in the population with rare TA and AA genotypes, and the risk of neoplastic transformation during ASA treatment in these individuals had even increased. With respect to the SNPs located on chromosome 15, a positive response to the drug was noted exclusively in individuals with the most popular genotype rs16973225-AA; the substance had no impact on the development of the disease in people with AC or CC genotypes. An analysis of the role of these chromosomal *loci* may explain why their changes can be associated with varying susceptibility to medication. MGST-1 belongs to the family of membrane-associated proteins which are involved in eicosanoid and glutathione metabolism (MAPEG), similarly to prostaglandin E_2 synthase (MGST1L1). The two proteins show considerable homology in their sequential structure[24]. Both MGST1 and MGST1L1 demonstrate increased activity in some neoplastic diseases including colorectal cancer[25]. MGST1L1 in conjunction with COX-2 are involved in the synthesis of PGE_2, and hence promote carcinogenesis by stimulating the Wnt signalling pathway which plays a key role in the development of colorectal cancer[26]. The inhibition of both enzyme proteins belonging to the MAPEG family through the regular intake of NSAIDs (including ASA) can prevent neoplastic transformation. Another membrane protein encoded on chromosome 12 is phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 gamma (PIK3C2G). The protein also induces COX-2 and, consequently, increases the concentration of PGE_2, which affects the apoptosis of cancer cells. In addition to COX-2 inhibition, acetylsalicylic acid and other NSAIDs can also block the entire signalling pathway through their

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direct activity on PIK3, which is another benefit associated with their use[27].

An analysis of the pathophysiology of colorectal cancer and the genetic background of the disease reveals a significant rate of mutations within the *BRAF* and *KRAS* genes in colorectal cancer cells[28]. They are oncogenes belonging to the family of mitogen-activated protein kinases (MAPK) which may contribute to an increase in COX-2 expression[29]. In view of the links between signalling pathways associated both with MAPK and PIK3, it can be assumed that an evaluation of the mutation status within the listed genes in cancer cells may be important for estimating the biological effect of ASA in colorectal cancer[30]. Patients with Lynch syndrome (with *BRAF* mutation as a biomarker of the condition) may be good candidates for benefiting from daily low-dose aspirin[31]. Important insights were also gained from a study conducted by Frouws et al. comparing patients diagnosed with colorectal cancer having wild and mutant forms of the *BRAF* and *KRAS* genes. The group was additionally divided into subgroups of participants taking small doses of ASA and not taking the drug[32]. A comparison of mortality rates in the study's participants demonstrated that low-dose ASA use was associated with benefits – manifested as improved survival – only in *BRAF* wild-type tumours. In contrast, no such effect was found in the group of patients with *BRAF*-mutated tumours. No correlation was found between the genetic status of *KRAS* and the response to acetylsalicylic acid therapy. Based on research efforts, in the future the *BRAF* gene may become a marker useful in the assessment of cancer patient eligibility for incorporating acetylsalicylic acid into therapy.

Since excessive proliferation can be viewed as a common feature of neoplastic lesions, the presumption arises that more solid tumour types may overexpress COX-2 or have similar genomic mutations as colorectal cancer, which might in turn point to the benefit of aspirin in the treatment of other oncological diseases. The effect of acetylsalicylic acid on a number of cancer types such as breast, prostate, oesophageal and colon cancer is currently being investigated[33]. The findings may prove to be crucial for the final determination of the value of ASA in the therapy of neoplastic diseases, which has not as yet been fully elucidated.

CONCLUSIONS

Taking into account the considerable number of people who might be eligible for primary cardiac prevention, the potential benefits to public health could be high. The near future will probably bring the announcement of results of the large studies evaluating the advantages of using acetylsalicylic acid for primary prevention of cardiovascular diseases across various age groups. It is possible that the findings will resolve at least partially the disputable issue of acetylsalicylic acid use. The use of ASA for cancer prevention is not a standard approach, and there is no sufficient evidence to support its use in this indication. It may be assumed that a part of the population will benefit from this strategy in the future. Nevertheless, if a drug is used for prophylactic purposes only, it is important to take note of potential adverse reactions including gastrointestinal bleeding or ulcers, and assess realistically whether the risk of their occurrence is not too high in relation to a reduction in cancer incidence.

Conflict of interest

The authors do not declare any financial or personal links with other persons or organisations that might adversely affect the content of the publication or claim any right to the publication.

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