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The impact of artificial sweeteners on the risk and course of large intestinal adenocarcinoma in the elderly

Martyna Goljat[1], Paweł Niewiadomski[1], Maciej Lazarek[1], Ewelina Flegiel[1], Karolina Graczykowska[1], Michał Denkiewicz[1], Ewa Rozmarynowicz[1], Magdalena Walczak[1], Marta Cybulska[1], Jakub Husejko[1], Kornelia Kędziora-Kornatowska[1]

1. Faculty of Health Sciences, Department and Clinic of Geriatrics, Nicolaus Copernicus University, Bydgoszcz

Abstract

Background: There are many confirmed risk factors for development of the colorectal cancer, which is one of the most common malignant tumor among both females and males. Moreover, it is a cause of significant percentage of all cancer-related deaths. Even with treatment, the 5-year survival rate is very low. We concentrate on impact of artificial sweeteners on risk and course of adenocarcinoma of colon.

Results: In recent years, consumption of low-calorie and calorie-free sweeteners (LCS) has increased. It may be caused by campaigns promoting obesity fighting, low calorie drinks, diets, as well as by increase of social awareness regarding negative health associations associated with high sugar consumption.

We can divide LCS into two main groups: semi-synthetic and synthetic sweeteners. Substances from the first group are homogeneous, however those from the second group have different physical and chemical properties, due to different structure.

LCS quickly gained a lot of interest and scientists are still questioning their safety, especially during prolonged use. Many studies have shown no link between LCS and carcinogenesis, however there are few studies concerning artificial sweeteners and colon cancer connection.

Discussion: It is important to remember that there are many dietary habits that are connected to development of colorectal adenocarcinoma. It is difficult to assess the effect of sweeteners separately.

Conclusions: The potential connection between LCS and development of colorectal cancer is not fully examined. Further studies of this correlation should be conducted.

Key words: cancer; adenocarcinoma; colon; rectum; colorectal cancer; sweeteners; diet

Introduction

The colorectal cancer is the most frequent malignancy of the gastrointestinal tract and is the most significant contributor to morbidity and mortality around the world. Every year in the USA there are more than 130,000 new cases and 55,000 deaths associated with colorectal adenocarcinoma. This constitutes about 15% of all cancer-related deaths, only lung cancer has greater mortality. Adenocarcinoma of colon incidence appears the most at 60 to 70 years of age, in comparison only approximately 20% of patients are 50 or less [1, 2].

In Europe it is considered to be the most common malignant tumor. Cancer of the large intestine (including rectum and anal canal) places second after lung carcinoma in Poland for both females and males. Moreover, discussed tumor causes about 10 000 deaths per year only in Poland [3]. The mortality rate in USA is estimated at 60%, however in Poland and Eastern Europe is significantly higher - about 80% [4].

Even with treatment, the 5-year survival rate is only 20%. Additionally, colorectal cancer screening remains underused which is significant factor multiplying mortality. Colonoscopy, which is the gold standard for screening of adenocarcinoma of colon should be done every 10 years for people aged 50 or more. Furthermore once a year they need to perform fecal occult blood test. However, some specialists suggest that even 40- year old men need this laboratory examination [3].

We can divide the risk factors of colorectal cancer into three groups: environmental, internal and genetical. The environmental factors are connected with low intake of vegetable fiber and high intake of refined sugars and animal fats. Smoking is a major contributor of many cancers and also plays a part in development of colorectal adenocarcinoma. Adenomas and Crohn’s diseases are examples of the internal ones. Group of genetic risk factors is related to familial colorectal neoplasia as Gardner syndrome or Classic FAP. Lynch Syndrome 1 and 2 are the other types of congenital factors. Probability of adenocarcinoma of colon in mentioned syndromes is about 100% (Lynch syndrome slightly less - 90%) [1, 3, 4].

In our work we concentrate on impact of artificial sweeteners on risk and course of adenocarcinoma of colon.

Frequency and causes of consumption of sweeteners

As an interesting alternative to sugars, low-calorie and calorie-free sweeteners (LCS) have appeared. Their consumption increases year by year among all age, weight, socioeconomic and racial-ethnic subgroups. The reasons for consumption of sweeteners are probably related to

recently carried out campaigns to prevent obesity and increase the popularity of diets aimed at weight reduction by reducing the content of carbohydrates in the diet. The increase in the popularity of LCS, especially in the elderly, may be the result of an increased incidence of type 2 diabetes in this age group, compared to the other age groups. Another reason for the growing trend in LCS consumption in recent years may be increase of social awareness regarding negative health associations associated with high sugar consumption. This could have led to promotion the transition to drinks and foods containing sweeteners. Studies show that LCS was more widely used by people with lower weight obesity and chronic illness associated with it, in people with higher education, higher income and among non-Spaniards [5, 6].

One can expect a further increase in LCS consumption due to campaigns and discussions concerning the ban on regular carbonated drinks in schools and the taxation of sugar-sweetened beverages, supported by price differentiation to promote healthier consumer choices. Also, the frequent incorporation of sweeteners into food and use in "diet" beverages in order to lower the calorific value of the products sold contributes to the increase in the unconscious consumption of large amounts of LCS [5].

LCS, despite not providing energy, can affect glucose metabolism, vascular function and satiety, as shown by recent studies in humans and animals. Recent studies suggest that the preference for sweets is related to the amount of refined sugar consumed and not to the total sugar intake of the individual. The development of preferences for highly sweet food and beverages can be caused by repetitive exposure to sweet substances (those who drink high-sweetened beverages prefer sweeter juice than people from a low-consumption group). In particular, young children are susceptible to developing nutritional patterns abounding in high-calorie foods due to early exposure to very sweet substances [5, 7].

The increase in consumption of LCS containing products was observed in all income groups, and according to the state of mass, there was a significant increase in LCS consumption in all groups (persons with normal weight, overweight persons and obese persons). In obese people, the increase in consumption of any products containing LCS was significantly higher than in people with overweight or normal weight. Similarly, in all age groups, a significant increase in the consumption of products containing LCS was observed [5].

A relationship has been noted between the consumption of LCS-containing products and lifestyle and a better diet than those who are not LCS consumers. People consuming LCS achieved higher results at the 2005 HEI (healthy eating index in 2005) compared to those who did not eat LCS. Consumers of LCS more often practiced recreational physical activity, had lower consumption of empty calories, including solid fats, and also less frequently smoked. It was also noticed that the consumption of fruit, vegetables, whole grains, meat and beans was higher in these people. The peak LCS consumption was for people in the 45-74 age group [8].

Consumption of LCS products is a helpful method supporting weight control and contributes to a lower intake of carbohydrates and sugars. Studies have shown that LCS drinkers have lower insulin levels, lower levels of HbA1c and lower HOMA-IR. It can be concluded that high intake of LCS reduces the risk of fulfilling pre-diabetic criteria and has no negative relationship with the glycemic response [9].

Chemical composition and structure of sweateners

Sweeteners is heterogeneous group of compounds used in the food industry instead sucrose, glucose and fructose. Its demonstrate different physical and chemical properties depending on the structure . First group of compounds is semi-synthetic fillers, this group includes: Sorbitol, Mannitol, Xylitol, Erythritol. In this group all substances is demonstrated similar properties, because all substances is homogeneous. Second group of compound is synthetic sweeteners, this group includes: Aspartame, Acesulfame potassium, Sodium cyclamate and many other substances less popular. In this group substances is demonstrated different physical and chemical properties, because all substances has different structure [10].

1. Sorbitol - (2R,3R,4R,5S)-hexane-1,2,3,4,5,6-hexol (Sorbitol)

Sorbitol is natural sugar alcohol (polyhydric alcohol, polyalcohols, alditols or glycticos). Typically it is odorless, noncariogenic, white, crystalline powder of a molecular mass 182,17 g/ mol. Sorbitol sweetness relative to sucrose is 60%. Its solubility in water is 2350 g/l, molecular formula is $C_6H_{14}O_6$ [11]. Sorbitol is highly hygroscopic, resistant to hydrolysis and high temperature [12, 13].

2. Mannitol - (2R,3R,4R,5R)-hexane-1,2,3,4,5,6-hexol (Mannitol)

Mannitol chemically is $C_6H_{14}O_6$. Its sweetness relative to sucrose is 50%. Mannitol is naturally occuring in sea algae, fresh mushrooms and exudates from trees (hence the name "brich sugar"). It is isomer of sorbitol [14]. Mannitol is white, odorless, crystalline powder of molecular weight 182,17 g/mol. Its is good soluble in water 216 g/l [15, 16].

3. Xylitol - (2S,4R)-pentane-1,2,3,4,5-pentol (Ksylitol)

A five-carbon sugar alcohol derived from xylose by reduction of the carbonyl group. It is as sweet as sucrose and used as a noncariogenic sweetener. Molecular Formula is $C_5H_{12}O_5$. Typically, xylitol is white, crystalline powder, practically odourless, xylitol has molecular weight 152.146 g/mol. Xylitol is very soluble in water 642 g/l [17].

4. Erythritol - (2S,3R)-butane-1,2,3,4-tetrol (Erytrytol)

Erythritol is a white, odorless, non-hygroscopic substance and is is soluble in water 610 g/l. Molecular weight of erythritol is 122.12 g/mol and it have sweetness of approximately 60-80% that of sucrose. Molecular Formula is $C_4H_{10}O_4$ [18].

5. Acesulfame potassium - potassium;6-methyl-2,2-dioxo-1-oxa-2λ^6-thia-3-azanidacyclohex-5-en-4-one (Acesulfam K)

Acesulfame potassium to belong to sweet sulfonamides, it is a potassium salt. The intensity of the sweet taste sensation is determined at the level of 150-200 in relation to sucrose, so it is more sweet than sucrose approximately 150-200 times sweeter. Acesulfame potassium is crystalline, odorless and very soluble in aqueous enviroment of 270 g/l [10]. Molecular formula is C4H4KNO4S. Molecular weight is 201.237 g/mol [19, 20].

6. Aspartame-(3S)-3-amino-4-[[(2S)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino]-4-oxobutanoic acid (Aspartam)

Aspartame is the most common sweetener, it is the dipeptid obtained by condensation of the alpha-carboxyl group of L-aspartic with the amino group of L-phenylalanine. Aspartame has approximately 200 times more intensity sweet taste than sucrose. Aspartame is characterized the cleanest tasty and it doesn't leave a bitter taste like the rest of sweeteners. It is not as water-soluble, thermally stable and chemically stable as other sweeteners. It is poorly soluble in water 13,5 g/l. Molecular weight is 294,307 g/mol. Molecular formula $C_{14}H_{18}N_2O_5$ [10, 21].

7. Sodium cyclamate - sodium;N-cyclohexylsulfamate

Sodum cyclamate is 30-50 times more intensity sweet taste than sucrose. It is characterized high termally stable and high solublility in water - above 1000 g/l. Odorless or almost odorless white crystals or crystalline powder. Molecular weight of sodium cyclamate is 201.216 g/mol. Molecular Formula C6H12NNaO3S. It is the sodium salt of cyclamic acid (cyclohexanesulfamic acid) [10, 22].

Pathophysiology of large intestinal adenocarcinoma

In western world, colorectal cancer is the most common cause of deaths due to cancers non-related with smoking and the most common cancer of digestive tract. Its most important cause might be diet, especially low-fiber, high-animal fat and poor in vegetables. One of the most important risk factors is also age- it is low at the age of 40 and starts to increase rapidly at the age of 50 and above [23]. Large intestinal adenocarcinoma may arise on the ground of adenoma as a result of mutation in gene of APC/beta-katenin tract or microsatellite instability (MSI) [24]. It tends to be a polypoid, ulcerating or infiltrative, and be annular or constrictive.

Adenocarcinoma locates almost evenly on the whole length of large intestine [23, 24].

Most common location of primary tumor of large intestinal cancer is rectum (61,3%), other locations are- sigmoid colon (20,9%), transverse colon (5,7%), ascending colon (4,9%), caecum (4,1%) and descending colon (3,2%) [25].

In initial stages the colorectal cancer is clinically silent or gives non-specific symptoms, like pain in the abdomen, flatulence, red or occur blood which may appear in stool (typical for right side cancers) and changes in peristalsis. However these symptoms are frequently belittled by patients. In more advanced stages of caecal cancers and cancers of the right side of colon patients may suffer from weakness and fatigue as chronic bleeding causes the iron deficiency anemia. The ill also complain about weight loss. The cancer of left side of colon manifests by alternate constipations and diarrhoea, shrinks, discomfort, nausea, gaseousness, occlusions and abdominal pain. Rectal cancer is signalled by straining at stool, smaller stools, bleeding and sudden pressure at stool.In the final stages colorectal cancer gives metastasis to the abdominal wall, causes bladder symptoms, sciatic nerve pain, small intestinal obstruction and ascites [23, 24, 26].

The colorectal cancer tends to invade locally wing to circular growth, but also spreading by lymphatic tract, blood vessels, to peritoneum and around nerves. Its main metastasis are to regional lymph nodes, liver and lung, but also to bones, kidneys, suprarenal glands and brain [26, 27].

Reports on the effect of sweetener intake on colorectal cancer

Colorectal cancer is not only among the most commonly diagnosed cancers in the world, but also a major cause of cancer-related deaths. For decades extensive research has been conducted in order to determine colorectal cancer risk factors and help to prevent it.

As a result it has been proven to have strong associations with many lifestyle and dietary factors, such as high consumption of sugar, processed meat or saturated fats [28-30].

Furthermore its incidence is significantly higher in economically developed countries [30].

Artificial sweeteners appeared in last few decades and started to gain lots of interest. Their consumption significantly increased and is still increasing, as they are advertised as healthier alternative, that can help to lose weight and are also cheaper to manufacture [31]. Since

artificial sweeteners conquered the market scientists have been questioning their safety and its possible link to carcinogenesis.

The debate about potential cancer risk in artificial sweeteners began with 1970s saccharin study which found increased occurrence of bladder cancer in laboratory rats and early case-control human research confirmed it [32, 33]. Although larger epidemiological studies

failed to prove such a link in humans, the possible risk of carcinogenic effect of artificial sweeteners is still widely debated [34].

Reports about the influence of artificial sweeteners on colon cancer risk are conflicting and inconclusive. Plenty of studies have shown lack of association between artificial sweeteners and carcinogenic risk although none of them specifically regarded colon cancer risk.

However there are three studies concerning artificial sweeteners and colon cancer connection.

In one case control study in 2014 artificial sweeteners were observed to have direct link with colon cancer risk. The study compared 150 patients with colorectal cancer and 300 control subjects. It was found that the odds of consuming artificial sweeteners are significantly higher among patients than control group, and it has been established as a third risk factor of colorectal cancer after consuming red meat and preserved food [35].

Another study was conducted on Caco-2 and HT-29 cells - colon cell lines. The research proved that high concentration of artificial sweeteners can cause hyperplasia of the colon cells and fragmentation of their DNA [36]. Although the authors of the study have raised a question if it is not due to the pH changes. Moreover the concentration used on the cell lines is not achievable after oral administration. The study also mentions the association of cyclamate with metastatic adenocarcinoma of the colon in non-human primates that was initially found in 2000 research regarding carcinogenicity of cyclamate and reviewed in 2004. However the authors of both studies concluded that there is no proof for carcinogenicity of cyclamate, as the tumors appeared at a rate often observed in monkeys [37, 38].

The most recent study shows positive correlation between consumption of artificial sweeteners and increased recurrence-free survival and overall survival in patients with III stage colon cancer [39]. The authors hypothesized that the correlation can be caused by reducing the consumption of sugar sweetened beverages which are directly linked to cancer risk by substituting them with artificially sweetened ones.

There are other studies that assess general relationship between artificial sweeteners consumption and cancer occurrence. For instance long-term studies in animal models found sucralose to be noncarcinogenic and have no genotoxic activity even in significantly higher exposure levels and therefore safe to use as a non-caloric sugar alternative [40, 41]. Another case-control study indicated that there is no association between artificial sweeteners and the risk of several types of cancer [42]. Other systematic review that analyzed 599,741 participants has concluded that collected data is inconclusive to attest any relationship between artificial sweeteners and cancer [34].

There is still concern about long-term effects of artificial sweeteners and further studies should be conducted in order to determine safety of their consumption and possibility of promoting colorectal carcinogenesis.

Discussion

In the development of colorectal adenocarcinoma, abnormal eating habits are of great importance. The influence of artificial sweeteners on the aforementioned cancer was described in the article, however, one should remember about the occurrence of many products that increase the risk of getting sick. Saturated fats are often mentioned. As shown in animal models, a diet high in fat leads to neoplasia in the large intestine to a greater degree than obesity or metabolic syndrome. Attention was drawn to the fact that people who consume large amounts of fat do not have to be obese, so there may be cases where a person who is not obese but has poor eating habits may be more likely to develop cancer of the large intestine than a person suffering from

for obesity [43]. For the sake of promising results, attempts to do the same project should be considered, but with replacing fat intake with artificial sweeteners to see if those who are consuming sweeteners who are not obese are more at risk than those who are obese.

Research conducted by Niku et al. emphasized that Western-type diet (WD), which is characterized by high consumption of products rich in saturated fats, sugar and its artificial substitutes, and low in calcium, vitamin D and fiber, increases the risk of adenocarcinoma in large intestine. In these studies, WD has been shown to interact with the heterozygous mutation in the Apc gene, which has led to metabolic and immunological changes in the colon mucosa [44]. This allowed for a better understanding of the mechanisms leading to the development of colorectal cancer, which is affected by incorrect dietary habits and confirmed previous assumptions about the importance of diet in the etiology of the cancer in question.

The importance of abnormal eating habits, including the use of artificial sweeteners, in the development of colorectal adenocarcinoma is demonstrated by the results of research by Liu et al., where the presence of correlation between microbiome, inflammation and Wnt-signalising was described. The mentioned factors jointly contribute for cancer within the large intestine [45]. The described correlation should be studied still, but taking into account strictly defined eating habits, which would allow to examine whether the use of artificial sweeteners leads to the development of colorectal cancer through the said mechanism.

Due to the fact that cancer in the large intestine is becoming more common in the world, intensive measures should be taken to stop growth trends. It may be helpful to observe that there are geographical differences in the incidence of colorectal adenocarcinoma, which may be associated with differences in dietary habits in different areas. These conclusions suggest the possibility of finding a diet or individual products that reduce the risk of developing the cancer in question. A lot of research has already been carried out to find these types of products, which has resulted in the isolation of substances known as nutraceuticals that are used in chemoprevention of cancer in the large intestine. These include stilbenes (from grapes and red wine), isoflavones (from soy), carotenoids (from tomatoes), curcuminoids (from spice turmeric) and catechins

(from green tea) [46]. The intake of these compounds can be considered with regular use of artificial sweeteners to reduce the risk of developing colorectal adenocarcinoma.

Conclusions

Colorectal cancer is a common type of cancers especially in developed countries [47]. On global scale more than 1 million persons will get colorectal cancer every year. In spite of the use of new generations medicines for treatment this type of cancer in the last years cure rates persist low [48].

In recent years, sweeteners have become increasingly popular in the diet in developed countries [36]. They are used as replacements for sweet taste without increasing calorie intake [49]. Although they are considered safe, there are data that sweeteners can affect the development of colon cancer [36].

However, we would like to emphasize that scientific data are ambiguous and contradictory and require further verification because the potential mechanisms affecting artificial sweeteners on the development of colorectal cancer have not been fully explained. Therefore further studies should be conducted.

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