® Postepy Hig Med Dosw (online), 2021; 75: 426–436
e-ISSN 1732-2693

www.phmd.pl
Review

Received: 04.05.2020
Accepted: 19.10.2020
Published: 16.06.2021

Selenium and cancer or adenoma related to the large bowel*

Selen a rak lub gruczolak jelita grubego

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*This work was supported by the grant titled „Behavioral and genetic determinants in colorectal cancer patients" number N41/DBS/000447, at Jagiellonian University Medical College, financed by the subsidy from Ministry of Science and Higher Education for the research in period 2020-2021, principal project investigator Aleksander Gałaś, MD, PhD.

Summary

The protective effect of selenium against colorectal cancer or adenoma is still a controversial issue. Although there are well-described (pato)physiological protective mechanisms of selenium against colorectal cancer, the results of the studies from 1998-2018 are inconclusive and need to be considered in the future. Neither observational nor experimental studies present consistent results. Although the Cochrane review showed that well-designed randomized clinical trials (RCTs) presented no beneficial effect of selenium supplementation on cancer incidence, well-designed RCTs confirming the protective effect of selenium supplementation against colorectal adenoma or colorectal polyp recurrence have been found in subject-related literature.

In the reviewed studies, selenium concentration was measured in the blood serum/toenail or in diet. It is of great importance to highlight that blood selenium concentration depends on the concentration of this micronutrient in food, which in turn depends on selenium content in soil, bioavailability of selenium, which is different in various geographical regions, and forms of selenium. Selenium circulating in blood as a component of selenoproteins participates in oxidoreduction, thus reducing the risk of developing colorectal cancer. Despite this well-known protective mechanism against colorectal cancer occurrence, half of the reviewed studies did not confirm the protective properties of selenium.

To sum up, the current state of knowledge on the association between selenium and colorectal cancer or adenoma has revealed not only inconclusive results of the studies, but has also shown that there is a need to conduct more prospective studies focused on selenium supplementation and colorectal cancer as this research is limited.

Keywords: **selenium, selenoproteins, colorectal cancer, adenoma, supplementation**

GICID 01.3001.0014.9364
DOI: 10.5604/01.3001.0014.9364
Word count: 6 045
Tables: 3
Figures: 4
References: 39

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Abbreviations: **CRC** – colorectal cancer, **DNA** – deoxyribonucleic acid, **NOS** – Newcastle Ottawa Scale, **NPCT** – Nutritional Prevention of Cancer Trial, **RCTs** – randomized clinical trials, **Se** – selenium, **SELECT** – the Selenium and Vitamin E Cancer Prevention Trial, **WHI** – Women's Health Initiative Observational Study.

INTRODUCTION

Selenium (Se) is a trace micronutrient essential for optimal body functioning and for proper growth and development of organisms [17, 29]. Selenium derived from food and dietary supplements occurs in the body in organic forms such as selenomethionine (Se-Met), selenocysteine (Se-Cys) and inorganic ones like selenites and selenates [17, 30]. All these forms are transformed to selenides (H_2Se), which are the main donor of selenium for the synthesis of selenoproteins [17]. Selenoproteins have enzymatic functions and play many other important roles in the human body. There are 25 selenoproteins in a humans including 12 enzymes [5 glutathione peroxidases (GPx), 3 thioredoxin reductases (TRx /TXNRD), 3 iodothyronine deiodinases (Dio), 1 selenophosphate synthetase 2] and 13 non-enzymes [15 kDa, H, I, K, M, N,O, P, R, S, T, V, W] [1, 29, 30]. Selenoproteins participate in a range of processes in cells: oxidoreduction, redox signalling, antioxidant defence, thyroid hormone metabolism and immune response [1, 29, 30]. Furthermore, selenoproteins are important from a genetic insight, as a concentration of selenium depends on different variants of polymorphisms observed in the genes of selenoproteins [15, 30]. Taking this into account, the deficiency of this micronutrient may cause a huge problem. For example, it may cause chromosome aberrations and mutations in DNA [24].

Long-term selenium deficiency may lead to the development of cancer, for example, colorectal adenocarcinoma [24, 29]. Colorectal cancer is one of the most common forms of cancer worldwide [11]. Colorectal cancer ranks as the third leading cause of cancer incidence in the world, being responsible for about 1.85 million cases annually [11]. There are many factors that influence the risk of colorectal cancer. One of them is the inadequately low selenium concentration in blood [8, 20]. It would be great to select those patients with a low selenium status who should undergo a colonoscopy - a method of screening study which is expensive and not accepted by the population, because of its specificity [22].

There are some studies conducted in different countries confirming that the higher the selenium concentration in the blood serum (with high folate intake in a study written by Connelly-Frost et al.), the lower the risk of the following outcomes: colorectal cancer incidence, colorectal cancer occurrence, colon cancer incidence, adenomatous polyps occurrence, all-cause mortality among CRC patients [6, 8, 20, 38, 39]. Furthermore, the higher the selenium concentration in toenails the lower the risk of colon cancer incidence [10].

The aim of this article is to summarize the current state of knowledge on the association between selenium and colorectal cancer or adenoma and to highlight problems for future studies.

METHODS

All of the studies used in the paper were found in PubMed Database by availing of the following key words: "selenium and colorectal cancer", "selenium supplementation and colon cancer risk", "selenium supplementation and rectal cancer risk", "selenium and serum and colon cancer risk", "selenium status and blood and cancer", "selenium and soil", "selenium and soil and Poland", "selenium*", "colorectal cancer*", "selenium or colorectal cancer". All of the selected articles (except for two papers) which were included in this review were published between 1998-2018. These two articles which have not been included, have been chosen from 1986-1987. A reason for that was a multicentre study, presenting the selenium level in serum from different regions in Europe, which has not been conducted in later papers. The second reason was a limited number of studies on the values of selenium concentration in blood compartments in Polish population.

In PubMed Database, a total of 408 records on the relationship between colorectal cancer or adenoma risk and selenium in humans were found. After applying 2-stage screening 35 publications left, as presented in Figure 1. Next, they were verified for odds ratio or hazard ratio reporting and study design supporting possible causality (cross-sectional studies have not been included). Additionally, reviews and metaanalyses were excluded. This resulted with the inclusion of 17 studies (5 case-control studies, 5 nested case-control studies, 2 cohort studies, 5 trials) for analysis. Fully adjusted models for the whole study groups for colorectal cancer and adenoma were used to present the results.

Additionally, a New Castle Ottawa Scale and a Jadad Scale were applied for assessing the quality of studies.

ADVERSE EFFECTS OF DEFICIENCY AND EXCESS OF SELENIUM

The typical causes of selenium deficiency in an organism are as follows: a diet that is poor in selenium (in poor

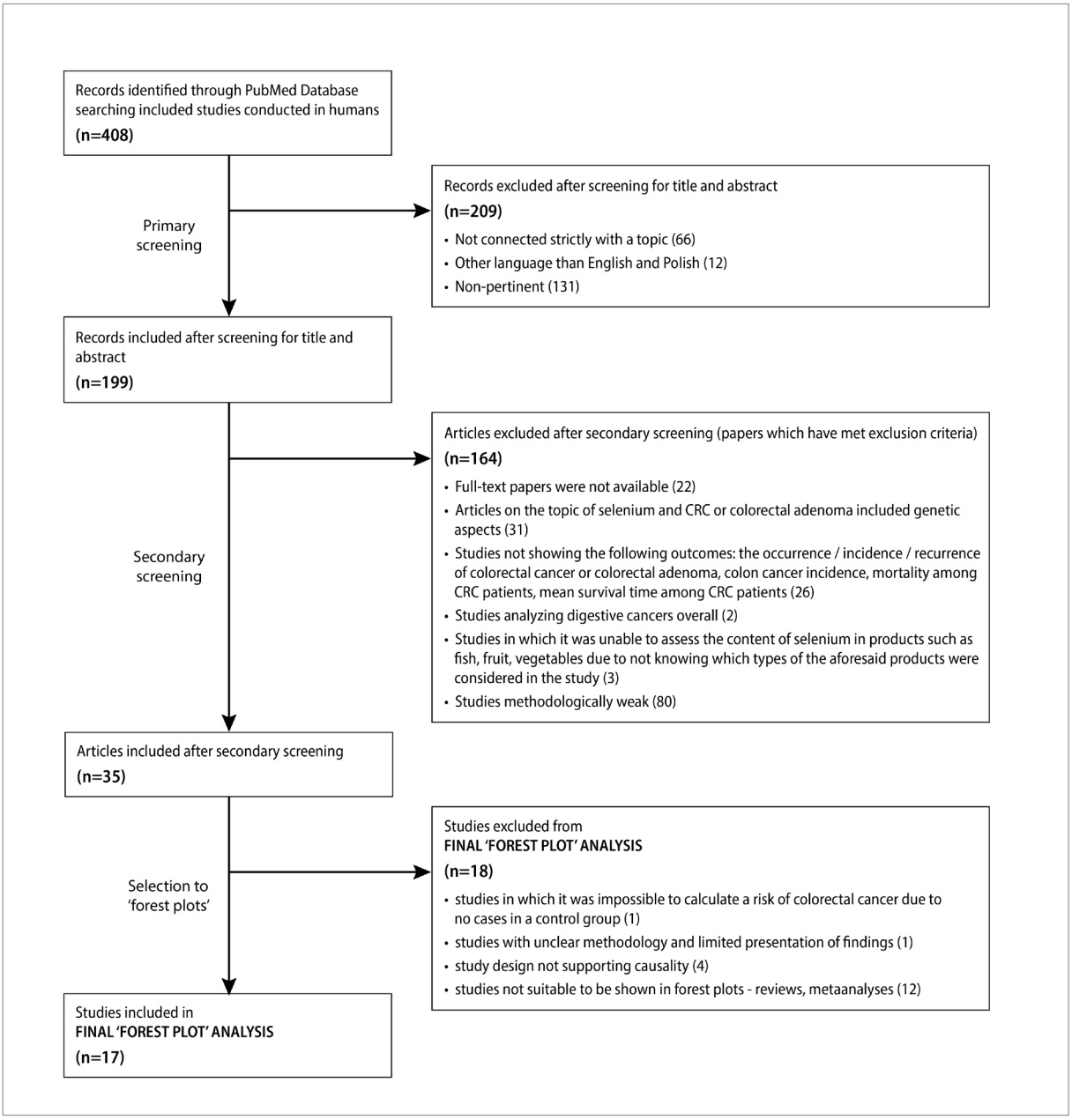

Fig. 1. Search strategy

selenium areas or in the case of eating fast food or food that is poor in selenium), environmental factors (soil that is poor in selenium, leaching bedrocks with selenium, pollution), gastrointestinal tract disorders (i.e. inflammatory bowel disease), abnormal selenoprotein synthesis, alterations of protein function and abnormal selenium transport in an organism [24]. These often lead to the negative effects of selenium deficiency such as: a progression of several inflammatories (rheumatoid arthritis, Keshan disease, Kashin-Beck disease), an exacerbation of inflammation, an intensification of degenerative changes of the central nervous system (among others, Parkinson's disease), muscle weakness, infertility, a progression of cancers, especially colorectal, liver, thyroid and breast cancer [1, 24, 29].

In contrast, selenium excess (selenosis) also causes some health damage, such as nail deformation or hair loss. Other symptoms of selenosis, such as depression, emotional problems, nervousness, nervous system disorders, vomiting, garlic breath, poor skin and dental health, while paralysis may also occur [30].

SELENIUM LEVEL IN BLOOD AND BLOOD COMPARTMENTS

The selenium level in the blood depends on the country – the bioavailability of this micronutrient and concentration in soils in that country. In Poland, the average concentration of selenium in blood serum is ~80µg/l [20]. A concentration of approximately 100µg/l of Se in blood serum

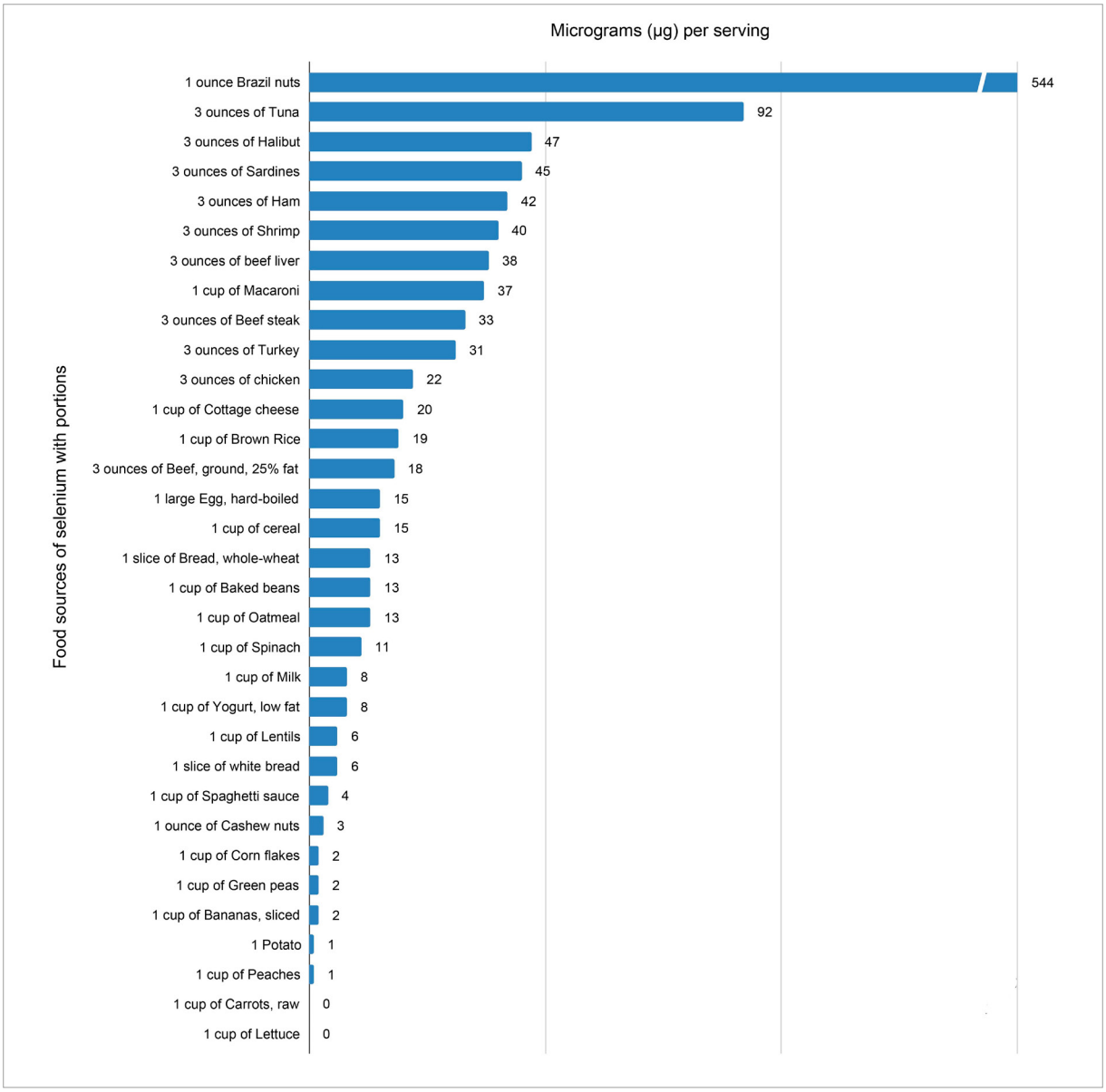

Fig. 2. Food sources of selenium in diet and content of selenium in different products. 1 ounce = 28.35 g; 1 cup = 150 g

is considered to be preventive [20]. The concentration of selenium in blood and blood compartments was also studied by Wąsowicz and Zachara in Poland [37]. In their study, the mean concentration of selenium measured in a healthy Polish sub-population was 78 µg/l in plasma, 101.1 µg/l in whole blood and 133.1 µg/l in red blood cells [37]. In comparison to Poland, the National Health and Nutrition Examination Survey 2003-2004 showed that in the American population, the average concentration of selenium in serum was equal to 140µg/l [19]. A multicentre study evaluated in Denmark measured the selenium level in serum in 502 samples from different regions in Europe [33].

The results showed that the highest concentrations of selenium in serum were observed, among others, in the United Kingdom (Ipswich 107 +/- 13 µg/l, London 109 +/- 14 µg/l) and the lowest was noted in Germany (Bavaria 70 +/- 10 µg/l; Giessen 68 +/- 10µg/l, Heidelberg 76 +/- 9µg/l) and Greece (63±14µg/l).

FOOD SOURCES OF SE AND FORMS OF SELENIUM IN FOOD

A diet that is rich in selenium is essential for the optimal body functioning. In a human organism, selenium derived from the diet is incorporated directly into selenoproteins. Selenium consumed in foods and supplements exists in a number of organic and inorganic forms such as selenomethionine (plant and animal sources and supplements), selenocysteine (animal sources), selenate and selenite (supplements) [30]. Bioavailability and metabolic processes depend on the form in which selenium

Table 1. Daily seleniuim intake through different geographic regions

Geographic differences in a daily selenium intakes (µg/day)	
Region	**Selenium intake (Mean ± standard error or range)**
China, disease-free area	13.3± 3.1
China, Keshan disease area	3–11
China, seleniferous area	1338
South Sweden, conventional diets	40± 4
Finland, before selenium fertilization	26
Finland, after selenium in fertilization	56
Slovakia	27± 8
Poland	**30–40**
United Kingdom, 1974	60
United Kingdom, 1995	33
Italy	41
Germany	38–48
France	47
India, conventional diet	48
Canada	98–224
United States, all	80± 37
United States, seleniferous area	216
Venezuela	80–500

is transported into the organism. For example, selenomethionine is more effective in increasing the apparent selenium status because it is non-specifically incorporated into proteins in place of methionine. Before entering the available selenium pool, it must be catabolised to an inorganic precursor. Selenomethionine is a less-available metabolic source of selenium than selenite or selenate. They need only to be reduced to selenide to provide selenophosphate – the precursor of selenocysteine - the active form of selenium in selenoproteins [17]. There are multiple types of food containing selenium [34]. Most of them are presented.

Figure 2 shows that brazil nuts, fish, ham, meat, and pasta are the richest sources of selenium (>20 µg per serving), while cottage cheese, brown rice, beef, eggs, wheat cereals, whole-wheat bread, baked beans, oatmeal, and frozen spinach have an average content of selenium (11-20 µg per serving). The slightly lower content of selenium is observed in milk, yogurt, lentils, white bread, spaghetti sauce, cashew nuts (3-8 µg per serving), while the lowest selenium content is observed in cornflakes, green peas, bananas, potatoes and peaches (1-2 µg per serving). Carrots and lettuce are selenium-less sources (0 µg). Depending on the region, the dietary intake of selenium may differ even between people with the same or similar diet [4, 9; Table 1].

It is of great importance to remember that the selenium content in food depends on the Se level in the soil. In many countries, including Poland, the content of selenium in the soil has not been widely investigated. In the majority of soils in Poland, the concentration of selenium varies from 0.06 (sandy soils) to 2.3-4.2 ppm (tertiary clays) [25]. The average selenium concentration in soils in Poland on a global scale is equal to 0.33 ppm, which is a low concentration comparing to other countries in the world, i.e. the U.S., where the concentration of Se is toxic for plants because it reaches 1250 ppm [25].

THE IMPACT OF DIFFERENT FOOD SOURCES ON SELENIUM LEVEL IN THE BLOOD

Borawska et al. [4] in 2004 in her studies showed the differences in the impact of food sources on serum selenium concentration in three groups: all participants, selenium-inadequate individuals (<70 µg/l) and selenium-adequate individuals (>70 µg/l). In the first group, the consumption of tea, processed vegetables and fish were positively correlated with selenium concentration in serum, while a negative correlation was found in case of alcohol consumption. In the second group, the frequent consumption of ham, honey and tea were positively correlated with selenium concentration in serum, whereas the consumption of alcohol and cottage cheese was inversely correlated with serum selenium concentration. In the third group of individuals, the consumption of wholegrain bread and jam, marmalade or jelly positively affected the selenium concentration in serum and were important contributors to variability in an individual's sera, while the frequent eating of fresh vegetables and white bread or rolls led to a significant decrease of selenium concentration in serum [4]. Eating fresh vegetables reduces the level of selenium in the blood because of containing fibre (pectins) and phytate. However, processed vegetables and fruit are rich in selenium because of the process which modifies the fibre structure by destroying pectins [4].

DIET AND MORBIDITY/MORTALITY RATES

In subject-related literature, there are multiple examples of studies showing the association between diet and morbidity/mortality rates associated with colorectal cancer. For example, in a cohort study conducted by Yang B et al. [39] in 2014, 28% lower all-cause mortality among colorectal cancer patients was observed in participants who ate ≥4.2 µg Se/day vs <0.6 µg Se/day. However, in another cohort study investigated by Hanse et al. [12] in 2013, selenium in a diet increased colorectal cancer risk by 20%. In a further study - case-control study conducted by Kune and Watson [18] in 2006, different values of colorectal cancer risk reduction were observed depending on the value interval (for those >81-99 µg/day Se vs ≤80 µg/day Se – 28% reduction in risk was observed; for those >100-118 µg/day Se vs ≤80 µg/day Se – 36% reduction in risk was observed; for those >119-145 µg/day Se vs ≤80 µg/day Se – 47% reduction in risk was obtained; for those >145 µg/day Se vs ≤80 µg/day Se –there was no reduction). In the last analyzed study, connected with selenium measured in a diet – a nested case control study written by William et al. [38]

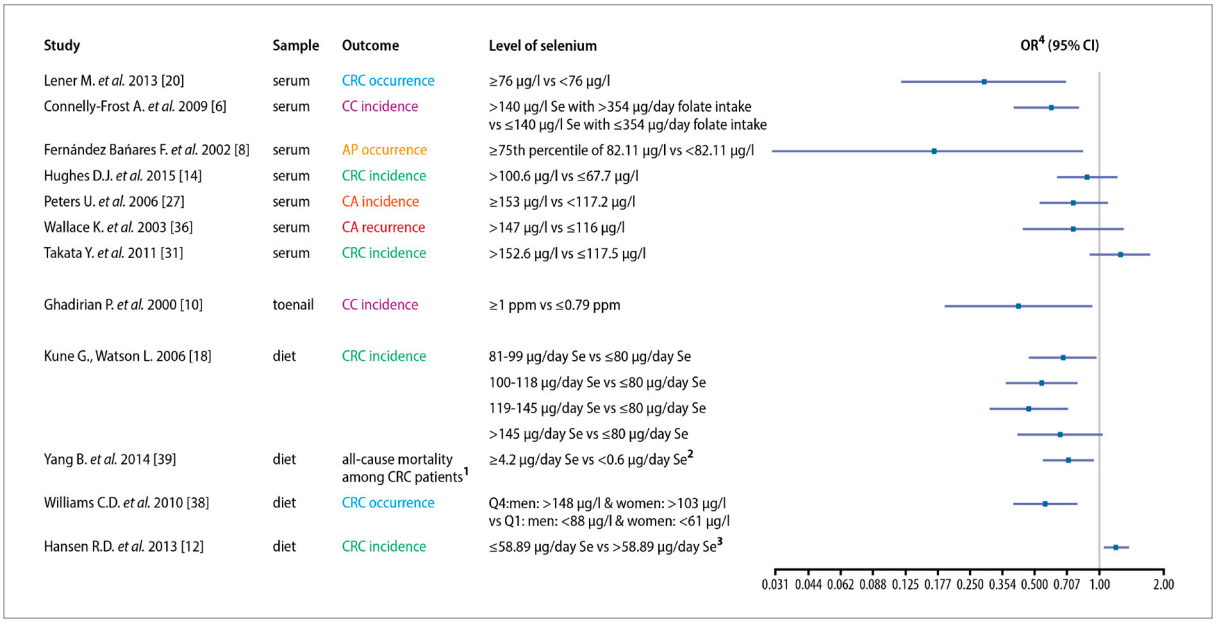

Fig. 3. Observational studies on CRC and selenium – an overview.
[1]all-cause mortality among patients with nonmetastatic colorectal cancer
[2]calculated from original paper: ≥7 servings of milk/week vs <1 serving of milk/week (1 serving of milk=1 cup of milk=200 g of milk; 100 g of milk = 2 µg Se
[3]58.89 µg/day – a cut off point of total selenium
[4]OR (95% CI) – odds ratio and 95% confidence interval
CC – colon cancer; AP – adenomatous polyps; CA – colorectal adenoma.
CC – colon cancer; AP – adenomatous polyps; CA – colorectal adenoma

in 2010, the reduction in colorectal cancer risk by 44% was found. In general, different results were obtained in the studies described above. The results of the studies were inconsistent as shown in Fig. 3.

SELENIUM LEVEL IN BLOOD OR TOENAIL AND MORBIDITY

To study the relationship between the selenium level in blood and colorectal cancer or adenoma risk 3 case-control studies, 4 nested case-control studies and one cohort study were considered. For example, in a case-control study established by Lener et al. [20] in 2013, the level of selenium measured in the blood ≥76 µg/l vs <76 µg/l lowered the risk of colorectal cancer occurrence by 79% (OR = 0.29; 95%CI = 0.12-0.70). Further case-control studies conducted by Connelly-Frost et al. [6] in 2009 and by Fernández-Bañares et al. [8] in 2002, confirmed the reduction in the risk of colon cancer incidence [6] and adenomatous polyps occurrence [8]. In the first study written by Connelly-Frost et al. [6] the level of selenium measured in the blood >140 µg/l Se with >354 µg/day folate intake vs ≤140 µg/l Se with ≤354 µg/day folate intake reduced the risk of colon cancer by 40% (OR = 0.60; 95% CI = 0.40-0.80), whereas in the second study evaluated by Fernández-Bañares et al. [8] the level of selenium measured in serum ≥75th percentile of 82,11µg/l vs <82.11µg/l reduced the risk of colorectal adenomatous polyps occurrence by 83% (OR=0.17, 95%CI=0.03-0.84). Further observational studies - nested case-control studies [14, 27, 31, 36] - did not present a reduction in the risk of colorectal cancer incidence [14, 31], colorectal adenoma incidence [27] and colorectal adenoma recurrence [36].

The final one - a cohort study evaluated by Psathakis et al. [28] in 1998 showed that colorectal cancer patients with a selenium level <70 µg/l had a significantly lower mean survival time and a lower cumulative cancer-related survival rate than patients with a selenium level >70 µg/l (p=0.0009), i.e. a higher cancer-related mean survival time (92 months) and higher five-year (72%) and ten-year (48%) survival rates were observed in patients (with T3/T4 tumor stage) with a serum selenium level >70 µg/l compared to the subjects with a serum selenium level <70 µg/l (mean survival time: 35 months; five and ten-year survival rates: 0) [28].

In addition, in the period of time: 1998-2018 only one study was found to present the relationship between selenium level in toenail and colon cancer incidence – a case control study conducted by Ghadirian et al. [10] in 2000. In this study the level of selenium ≥1.0 ppm vs ≤0.79 ppm measured in toenail was associated with a reduction in the risk of colon cancer by 58% (OR = 0.42; 95% CI = 0.19-0.93).

The dependencies described in this section have been illustrated in Figure 3.

U-SHAPED CURVE AND THRESHOLD POINTS

A "U" shaped curve was described to present the relationship between the selenium level and health effects suggesting health pathologies associated with selenium deficiency and excess. This has been described in publications written by Jabłońska et al. [15] and Cai et al. [5].

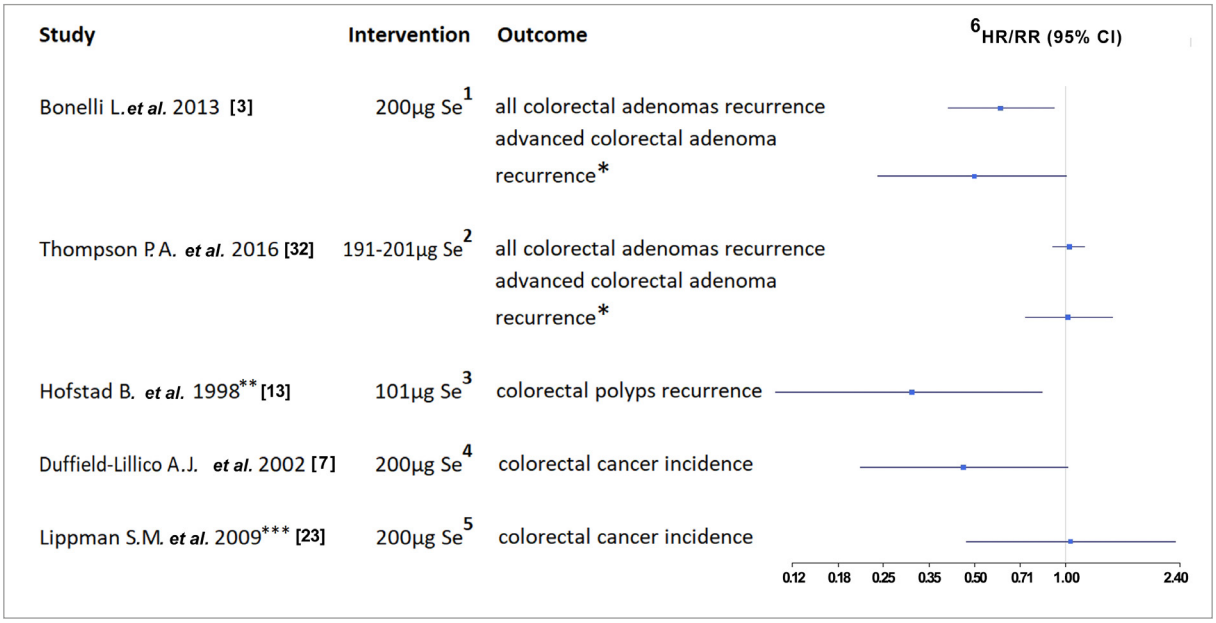

Fig. 4. Experimental studies on CRC and selenium – an overview.
*advanced colorectal adenoma characteristics: size ≥10 mm, villous component, high-grade dysplasia
**odds ratio as in original paper
***HR with 95% CI was calculated from the original HR 1.05 99% CI (0.66–1.67)
[1]tablets: 200 µg Se with 30 mg zinc, 2 mg vitamin A, 180 mg vitamin C, 30 mg vitamin E
[2]200 µg yeast tablets (191-201 µg selenium content)
[3]coctail: 4 g calcium carbonate, 101 µg selenium (from 170 µg sodium selenite), 15 mg β-carotene, 75 mg α-tocopherol, 150 mg ascorbic acid
[4]200 µg of Se supplied in a 0.5-g high selenium baker's yeast tablet
[5]200 µg Se/day from L-selenomethionine
[6]hazard ratio/risk ratio and 95% confidence interval

In the Pomeranian University educational materials [21], it was presented that the threshold concentration of selenium for a great increase in cancer risk for Polish population was 60 µg/l in serum, whereas approximately 65 µg/l in serum for a great increase in colorectal cancer risk.

Interestingly, in studies written by Lener et al. [20] in 2013, the threshold point for selenium level in serum for an increase in colorectal cancer risk was 55 µg/l for Polish and 65 µg/l for Estonian populations.

THE EFFECT OF SELENIUM SUPPLEMENTATION ON MORTALITY AND MORBIDITY RATES

The results of studies are inconsistent, albeit well-described (pato) physiological protective mechanisms against colorectal cancer or adenoma. Some intervention studies confirmed the protective role of selenium against colorectal adenoma [3] and baseline adenomas associated with polyps recurrence [13], however, there are also a lot of studies that did not confirm an inverse association between selenium and colorectal cancer or adenoma and amongst them: intervention studies [7, 23, 32] and meta-analyses [2, 5, 26, 31]. Beginning from meta-analyses - a meta-analysis written by Pais et al. [26] in 2013, did not show a reduction in colorectal cancer incidence (RR = 0.88; 95%CI = 0.55-1.40; p = 0.59), colorectal adenoma recurrence (RR = 0.70; 95% CI = 0.43-1.14; p = 0.16) and overall mortality (RR = 0.91; 95% CI = 0.82-1.02; p = 0.09) among intervention vs placebo groups for different doses of selenium supplementation. Further results of meta-analysis conducted by Takata et al. [31] in 2011 did not notice a reduction in colorectal cancer risk either (OR = 1.26; 95% CI = 0.91-1.73). A further two meta-analyses did not confirm an inverse association between selenium and colorectal cancer risk either: (OR = 0.90; 95% CI=0.77-1.05) [2], (pooled OR = 0.89;95% CI = 0.67-1.17) [5]. However, the last analyzed meta-analysis conducted by Jacobs et al. [16] in 2004, showed a significant 34% reduction in the risk of colorectal cancer with selenium (OR=0.66; 95%CI = 0.50-0.87). Different, yet also inconclusive results were obtained in experimental studies (Fig.4). In a trial conducted by Bonelli et al. [3] in 2013 the risk of all colorectal adenomas recurrence was decreased by 39% (HR=0.61; 95% CI=0.41-0.92) after supplementation with 200 µg Se with 30 mg zinc, 2 mg vitamin A, 180 mg vitamin C, 30 mg vitamin E. However, in the same study, a reduction in risk of advanced colorectal adenoma recurrence was not observed (HR=0.50; 95%CI=0.24-1.01). In the next intervention study written by Thompson et al. [32] in 2016, in which the same study outcomes as had been analyzed in a study evaluated by Bonelli et al., were considered, no reduction in the risk of all colorectal adenomas recurrence (RR=1.03; 95% CI=0.91-1.16) and advanced colorectal adenoma recurrence (RR = 1.02; 95% CI = 0.74-1.43) was observed with selenium (200 µg yeast tablets containing from 191 to 201 µg

Table 2. Quality of intervention studies measured with a use of a Jadad Scale

Intervention studies	Number of points in a Jadad Scale
Bonelli L. et al. 2013 [3]	3
Thompson P.A. et al. 2016 [32]	2
Hofstad B. et al. 1998 [13]	3
Duffield-Lillico A.J. et al. 2002 [7]	5
Lippman S.M. et al. 2009 [23]	4

selenium). That difference in results between a study written by Bonelli et al. [3] and Thompson et al. [32] may be associated with a sample size (411 participants vs 1374 participants). A study conducted by Thompson et al. [32] in 2016, with more than two times larger sample size, presented more reliable results. Further intervention study conducted by Hofstad et al. [13] in 1998 showed that only medication (OR = 0.31; 95% CI = 0.11-0.84) and the baselinenumber of adenomas (OR = 0.15; 95% CI = 0.06-0.41) were significantly associated with polyp recurrence. That may be a consequence of a small sample size (n=58). Further intervention studies: written by Duffield-Lillico et al. [7] in 2002 (NPCT study) and by Lippman et al. [23] in 2009 (SELECT study) did not show a reduction in the risk of colorectal cancer incidence (for NPCT HR=0.46; 95% CI=0.21-1.02); (for SELECT study HR=1.04; 95% CI=0.47-2.32) after supplementation with 200 μg of selenium. Those described results of intervention studies have been presented in Figure 4.

DISCUSSION

Although there are well-described protective physiological mechanisms of selenium against colorectal cancer or adenoma, the results of studies are inconclusive. When analyzing the results from experimental studies in this paper, it was concluded that two intervention studies out of five analyzed confirmed the protective role of selenium against colorectal cancer. These findings were not confirmed in the latest systematic review (2018) [35]. This review presented the fact that well-designed and well-conducted randomized clinical trials (RCTs) showed no beneficial effect of selenium supplementation on cancer incidence. However, those results from a Cochrane review have some weaknesses due to the study design, not to mention the failure to take consideration of sex in the analysis in the NPCT study, while also the unclear risk of bias due to blinding in NPCT 2002 study.

The findings of this review showed that the statistically significant intervention studies had been of moderately good quality (two of them scored 3 points on the Jadad Scale) (Table 2), what gave the opportunity to deny the results of a systematic review. Considering studies with non-significant results, with 2, 4 or 5 points on the Jadad Scale (Table 2), it was observed that two of them [7, 23], although their non-significance, were well-designed, had been of good quality (4 or 5 points), had a large sample size and were of high internal validity. However, they were not entirely bias free (not to mention the failure to take consideration of sex in the analysis in the NPCT study and the unclear risk of bias due to blinding in NPCT study; different formulations and doses of selenium, except 1-selenomethionine, have not been tested in the SELECT study; intervention effects in the selenium-deficient population and in current smokers have not been evaluated).

In addition, when analyzing the results of observational studies in this review, 6 out of 12 analyzed confirmed the protective role of selenium against colorectal cancer or adenoma. Studies with significant results earned 4, 5 or 6 stars in a Newcastle Ottawa Scale, whereas studies with non-significant results earned 5-7 stars (Table 3). Amongst the studies with significant results and high quality (5-6 stars) were: one cohort study [39] and three case-control studies: Lener et al. [20], Connelly-Frost et al. [6], Fernández-Bańares et al. [8]. A cohort study had a high internal validity due to taking into consideration many variables such as age, sex, education, demographics, medical history, physical activity, body size, cancer screening and early detection, diet, and other factors. Therefore, if the results of this cohort study show the cause-and-effect relationship which is not only associated with an effect of acting between the independent variable (selenium intake) and the dependent variable (colorectal cancer or adenoma occurrence), but also other confounders, it is classified as a study of high internal validity. However, when assessing an external validity of this cohort study, it was quite good, because of randomization which has ensured a possibility of generalization the results into a target population. Amongst the case-control studies only one [6] out of three had a relatively large sample size (643 cases vs 1048 controls), giving the opportunity to: study interactions between nutrients, estimate the risk by stage and evaluate several potential biases (high internal validity). Other case-control studies, i.e. a study written by Lener et al. [20] in 2013, had a low sample size (169 cases vs 169 controls) and data on the recruitment of the cases in this study were not available, thus providing difficulty of assessing the representativeness of a sample (low internal validity). The lowest sample size was observed in a case-control study written by Fernández-Bańares et al. [8] in 2002 (52 cases vs 35 controls), in which only two groups were analyzed: subjects <60 years old and >60 years of age. This division of age could limit the results of this study. It is suggested that younger people should be included in this study as well, to increase a sample size (low internal validity). However, amongst the non-significant studies with a high NOS Scale score (5-7 stars) well-designed nested case-control studies were found [14, 27, 31, 36]. Two of them [27, 31], had a better study design than the others due to well-conducted recruitment of a study group. Considering a small number of significant, well-designed studies, there may be a need to investigate more systematic reviews to broaden the scope of the topic. Finding more studies with statistically significant results, large sample size, good quality and validity will help to achieve a better view on the association between selenium and cancer or adenoma of the large bowel. All the observational studies divided by study type, study population and sample size, have been illustrated in table 3.

Table 3. Quality of observational studies measured with a use of a Newcastle Ottawa Scale (NOS)

Observational studies	Name of study	Population	Sample size	Number of earned stars in a Newcastle Ottawa Scale (NOS)
Lener M. et al. 2013 [20]	case-control	no data available on cases recruitment; controls were selected from Polish and Estonian registers	338 (169 colorectal cancer patients; 169 controls)	6
Connelly-Frost A. et al. 2009 [6]	case-control	cases from North Carolina cancer registry; population-based control (selected from 33-county area in central North Carolina)	1691 (643 cases; 1048 controls)	5
Fernández-Bañares F. et al. 2002 [8]	case-control	hospital-based cases; controls belonging to a big survey performed in Spain were included in the study	87 (52 cases; 35 controls)	6
Hughes D.J. et al. 2015 [14]	nested case-control	cases were identified during EPIC follow-up with a use of population cancer registries (Denmark, Italy, Netherlands, Spain, United Kingdom) and other methods: health insurance records, pathology registries, active contact of study subjects; controls were matched 1:1 by a study center, but no other data were available on the control's recruitment	1932 (966 cases; 966 controls)	7
Peters U. et al. 2006 [27]	nested case-control	cases and controls were randomly selected from 42 037 participants in the screening group of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	1525 (772 cases; 777 controls)	6
Wallace K. et al. 2003 [36]	nested case-control	cases and controls were recruited (including special criteria) from participants of the placebo-controlled trial (those have been chosen at six clinical centers in the U.S.)	552 (276 cases; 276 controls)	5
Takata Y. et al. 2011 [31]	nested case-control	cases were recruited mostly with a use of mass mailing which were age-targeted and media announcements in areas surrounding the 40 WHI clinical centers across the U.S.; controls were selected from all eligible women in the WHI study who were alive and had not been diagnosed with CRC at the time of the case's diagnosis;	1609 (804 cases; 805 controls)	5
Ghadirian P. et al. 2000 [10]	case-control	mainly hospital-based cases, identified through the admission offices of 5 major teaching hospitals; population-based controls (modified random-digit dialing method)	1736 (1048 cases, 688 controls)	4
Kune G., Watson L. 2006 [18]	case-control	cases from the etiological arm of population-based investigation; controls were randomly chosen from community, Melbourne, Australia	1442 (715 cases; 727 controls)	5
Yang B. et al. 2014 [39]	cohort	participants from Cancer Prevention Study II Nutrition Cohort. II Nutrition Cohort was selected as a subgroup of larger CPS cohort in which approximately 1.2 million of people were enrolled by volunteers in all 50 states, the District of Columbia and Puerto Rico	2284	6
Williams C.D. et al. 2010 [38]	nested case-control	cases were chosen from the North Carolina Central Cancer Registry; controls <65 years were selected by using lists provided by the North Carolina Division of Motor Vehicles and the Center for Medicaid and Medicare Services for those 65 and older; controls were selected from subjects (African American or White) resided in one of 33 counties in central and eastern North Carolina. A randomized recruitment procedure was used for identifying cases and controls	2076 (1057 cases; 1019 controls)	4
Hansen R.D. et al. 2013 [12]	cohort	population-based cohort, which based on 54 208 members of the Diet, Cancer and Health Cohort Study	54 208	5

Furthermore, it is of great importance to adequately interpret the results of the studies. In the Selenium and Vitamin E Cancer Trial (SELECT) conducted by Lippman et al. [23] in 2009, the reason for negative results was high serum selenium concentration at the baseline (137 μg/l/serum) within a selected group of American men. In this trial, in the participants with high serum selenium concentration at the baseline (>122 μg/l), the preventive effect was not observed because of the fact that the positive effect of selenium supplementation is possible only in individuals with low baseline serum selenium concentration (≤105,2 μg/l/serum/plasma) [23]. This is consistent with NPCT trial results obtained by Duffield-Lillico et al. in 2002 [7].

In summary, although half of the studies confirmed the protective effect of selenium against CRC or adenoma, the relation between selenium and CRC or adenoma risk is still a controversial issue and requires further investigation.

There are some limitations to the present study. Firstly, the presented review is not a systematic review; secondly, the analyzed studies did not include the genetic factors that might modify a relation between selenium and colorectal cancer or adenoma risk; thirdly, one of the reviewed studies did not include a division of sex [7]. The strength of this article is the thoroughly verified literary data. The reviewed literature shows how broad the topic is and the exclusion criteria have been clearly shown. To get clarity in forest plot overviews - similar outcomes, as well as the same types of studies were grouped together, thus providing a better view of the study results.

CONCLUSIONS

- The review shows that the protective effect of selenium against colorectal cancer or adenoma has not been confirmed in half of the reviewed studies. The inconclusive results need to be considered in the future.
- Considering a small number of significant, well-designed studies, there may be a need to investigate more systematic reviews in order to present a better view on the association between selenium and cancer or adenoma of the large bowel.

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The author has no potential conflicts of interest to declare.