Original Communication

Selenium dietary intake and survival among CRC patients

The prospective Cracow cohort study

Malgorzata Augustyniak and Aleksander Galas

Department of Epidemiology, Chair of Epidemiology and Preventive Medicine, Jagiellonian University Medical College, Krakow, Poland

Abstract: *Background:* Despite advances in prevention and treatment, colorectal cancer remains the second most common cause of cancer death. To date, little is known about the role of prediagnostic selenium intake in colorectal cancer survival. *Objective:* The purpose of the study was to verify whether selenium intake in habitual diet before diagnosis is associated with survival in colorectal cancer patients. *Study design:* This was a prospective observation of patients primarily recruited for a case-control study between 2000 and 2012 in Cracow, Poland. A group of 671 incident cases of colorectal cancer was included. Habitual diet was assessed using a validated 148-item food questionnaire. 338 deaths were identified throughout 2017 by the Polish National Vital Registry. To evaluate the impact of dietary selenium on survival, the multivariable Cox regression model was used. *Results:* After standardization for several potential confounders (including key determinants, such as radical surgery, chemotherapy, tumor stage, and dietary factors), a decrease in the risk of death from colorectal cancer was observed in the group with higher dietary selenium intake (≥48.8 μg/day, group mean: 63.9 μg/day) compared to the group with lower dietary selenium intake (<48.8 μg/day, mean: 38.5 μg/day) (HR=0.73; 95% CI: 0.54–0.98) (the median was used for categorization). *Conclusion*: Our study suggests selenium as an additional dietary factor which may be associated with survival among colorectal cancer patients referred to surgery. Due to the observational nature of the study, the results should be taken with caution. These preliminary findings, however, provide the basis for well-structured clinical trials.

Keywords: Selenium intake, colorectal cancer, survival

Abbreviations

CRC: colorectal cancer; Se: selenium; GII: glucose intolerance issues; BMI: body mass index; SFFQ: semi-quantitative food frequency questionnaire; HR: hazard ratio; CI: confidence interval; SD: standard deviation; Q1–Q3: quartile 1 to quartile 3; chi^2: Chi-square test; MW: the U-Mann-Whitney test; KS: the Kolmogorov-Smirnov test; df: degrees of freedom; μg/day: micrograms per day; μg/L: micrograms per liter; g/day: grams per day; mg/day: milligrams per day; g/week: grams per week; kcal/day: kilocalories per day; kg/m^2: kilograms per square meter; TNM: TNM system for staging cancer (T-refers to the size and extent of the primary tumor, N-refers to the number of nearby lymph nodes that have cancer, M-refers to whether the cancer has metastasized); Dukes' staging: is a pathological staging based on resection of the tumor and measures the depth of invasion through the mucosa and bowel wall; A (T1, N0, M0): cancer limited to the mucosa and submucosa; B1 (T2, N0, M0): cancer extending to the muscularis; B2 (T3, N0, M0): cancer extending to serosa and beyond serosa; C (Tx, N1, M0): cancer affects to regional lymph nodes; D (Tx, Nx, M1): distant metastases (i.e. liver, lungs).

Introduction

Despite advances in prevention, screening, and treatment, colorectal cancer (CRC) is one of the three most frequent cancer sites representing mortality and morbidity in high-income countries [1]. CRC is responsible for approximately 1 million deaths worldwide on an annual basis [2]. The available data show that 5-year net survival rates for colon and rectal cancer patients (C18–C20) aged 15–99 and being diagnosed in the period 2010–2014 in Europe, range from 56.1% (the Czech Republic) to 64.8% (Germany) and from 52.3% to 64.2% (the Czech Republic vs. Austria), respectively [3]. In Poland, the 5-year net survival rates are 52.9% for colon cancer and 48.4% for rectal cancer, which are low when compared to the survival rates in other European countries, such as the Czech Republic, Lithuania, Latvia, Estonia, Slovenia, Spain, Germany, UK, Austria, Finland [3], Australia, New Zealand, Norway, Denmark, United Kingdom, and Canada [4].

To date, knowledge about prediagnostic dietary factors influencing colorectal cancer survival beyond the already known prognostic factors of short and long-term clinical outcomes as malnutrition is limited and inconsistent.

Out of several potentially modifiable dietary factors suggested to be associated with survival among CRC patients, our study focused on selenium [5, 6].

Selenium (Se) is a trace element essential for optimal body functioning [7, 8]. As a part of selenoproteins, it has enzymatic functions and participates in oxidoreduction, redox signaling, antioxidant defence, thyroid hormone metabolism, and immune response [8, 9, 10]. Although well-described protective physiological mechanisms of selenium against colorectal cancer, the study results are inconclusive. For example, the preventive role of selenium in colorectal cancer carcinogenesis was noticed in some observational studies in which Se was measured in diet [11, 12] and in serum [13, 14]. Those findings, however, were not confirmed in some other observational research [15, 16]. Furthermore, colorectal cancer was prevented by selenium supplementation neither in the largest trial carried out so far, namely the SELECT study [17], nor in the last Cochrane meta-analysis encompassing observational and experimental studies [18]. Therefore, it is not entirely clear whether selenium, which is involved in several major metabolic pathways, affects survival and in what direction, although some studies reported that selenoproteins are thought to improve CRC survival through their role in regulating programmed cell death and inhibiting angiogenesis [19]. Moreover, some recent studies suggested that selenoproteins might not only counteract but also favor the development of colorectal cancer [20, 21]. Imbalances in multiple signaling pathways, in which selenoproteins participate and various SNPs in selenoprotein genes have been linked to CRC risk [20]. There is evidence from human clinical trials, while also in vitro and in vivo studies that there is a strong association between several selenoproteins and the development or progression of CRC. Thus, selenoproteins could provide targets for cancer treatment [20].

The relationship between selenium dietary intake and survival in patients diagnosed with CRC has not been extensively studied. To our knowledge, only one study – the ecological study published in the 1970s [22] has examined the association between dietary selenium and mortality from cancer of colon and rectum among populations from 27 countries, showing a high negative correlation. Further studies (cohort ones) on the association between selenium intake and mortality or survival analyzed mainly breast cancer [23, 24] and cancer in general [25]. The results of those studies were inconclusive [23, 24, 25] (see electronic supplementary material [ESM] 1).

Other studies on the association between colorectal cancer and selenium considered selenium measured in serum [26, 27, 28, 29]. The results of those studies were inconsistent. In contrast, the findings from observational studies on the relationship between serum selenium concentration and survival from other tumor types (like breast cancer [30, 31, 32, 33], renal cancer [34], laryngeal cancer [35], and lung cancer [36]) presented consistent results supporting the association of higher selenium status with better survival.

To date, there have been no studies reported (except the aforementioned one) aimed at evaluating the role of dietary selenium and colorectal cancer prognosis. Therefore, the purpose of the presented study was to assess the association between selenium content in habitual diet assessed before diagnosis and survival among CRC patients.

Materials and methods

Sample

This paper investigates the impact of selenium intake on survival among CRC cases. The dietary data were collected during the case-control study carried out between 2000 and 2012 in Cracow. A group of 683 incident colorectal cancer patients (a group of patients-cases from the primary case-control study) was included in our prospective investigation. The design of the primary study has been described elsewhere [37]. The incident CRC cases were recruited from patients diagnosed and referred to surgery treatment at the Ist Chair of General Surgery and Department of Gastroenterological Surgery, Jagiellonian University Medical College. All the included cases were histologically confirmed sporadic adenocarcinomas either of colon (ICD-X: C18) or rectum (ICD-X: C20). Only sporadic cancers were eligible, therefore all CRC cases suspected to be hereditary were excluded. The following exclusion criteria were used: age over 75, communication problems (including cognitive limitations making it difficult to do an interview), the presence of secondary cancer (distant metastasis), or CRC being a metastasis in colon or rectum, recurrent cancer, any type of surgery of gastrointestinal tract in the past, present or past diagnosis of chronic disease of the gastrointestinal tract (diverticulitis, irritable bowel syndrome, gastric ulcer, pancreatitis) and any of the following: diagnosis of diabetes, renal failure, hepatic insufficiency, and additionally, the presence of prolonged gastrointestinal symptoms. Additionally, in order to limit the possibility of genetically determined CRC for the current study, cases diagnosed before 40 years of age were also excluded.

The vital status was checked in 683 CRC cases, out of which the status of 12 was not identified due to no exact matching in the country database. Deaths were verified throughout 2017 using a National Vital Registry. There were 338 deaths identified by the registry. The study design is presented in Figure 1.

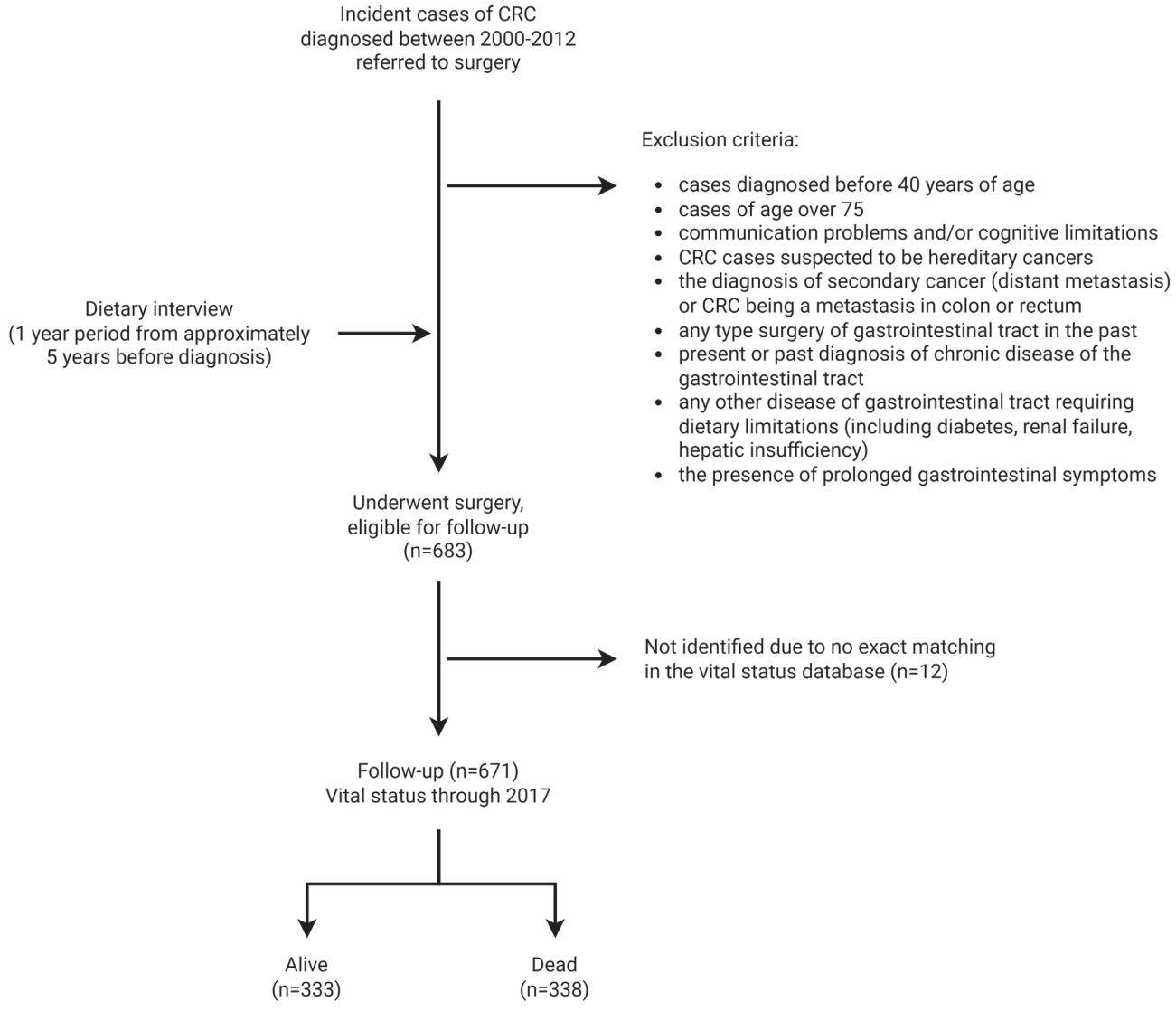

Figure 1. Study flow chart.

Tools and data collections

All participants were asked to sign a consent concerning participation in the study. When the written consent had been obtained, data about dietary habits, sociodemographic characteristics, alcohol consumption, smoking, physical activity, and some other health behaviors were gathered (using a standardized questionnaire) by trained interviewers during a face-to-face interview. This interview was carried out after hospital admission but before surgery. The study design was approved by the Bioethical Committee of Jagiellonian University, Krakow, Poland (IRB no 1072.6120.347.2020).

Dietary habits were assessed using a semi-quantitative food frequency questionnaire (SFFQ). In detail, the SFFQ was prepared in cooperation with the German Cancer Research Centre in Heidelberg, Germany, during the preparation phase for the European Prospective Investigation into Cancer and Nutrition study (EPIC). The SFFQ was validated showing good validity properties [38, 39]. The questionnaire consisted of 148 dietary items, including questions about consumption of cereals, dairy products, bread, type and portions of meat and fish, fresh fruit (separately during summer and winter), salads, fresh and cooked vegetables, rice or pasta or groats, while also soup, sweets, drinks, and others. For each food or beverage item, the average portion size was used (for food and vegetables and beverages – the categories of the half, 1, 2 or 3 standard portion sizes were presented; for dishes – standardized photographs of different portion sizes and frequency were assigned; frequency categories used: once a month or less, 2 to 3 times a month, once a week, 2 to 3 times a week,

4 to 6 times a week, once a day, twice a day, 3 to 4 times a day, 5 times a day or more). Subsequently, respondents were asked to provide information about the usual diet they used to have 5 years before the beginning of the diagnosis. Then, dietary data were recalculated using Polish food consumption tables to obtain information about the average consumption of dietary macro- and micronutrients. Additionally, the selenium content in each food and beverage item was calculated using literary data. The selenium concentrations for each dietary item assessed are presented in the additional materials (see ESM 2).

Covariates

Covariates used in the analysis included factors known or suspected to affect colorectal carcinoma survival. The following were considered: age, sex, body mass index calculated from the weight and height obtained by measurements, years of cigarette smoking (how many years the patient had smoked cigarettes at the time he or she was 20, 30, 40, and 50 years old), education (categorized as primary school or less, vocational school, secondary/high school, university or higher), cardiovascular diseases (categorized yes/no). As some patients had been identified during hospitalization as having glucose intolerance issues (GII), this information had been additionally used as covariate. Additionally, there were also dietary variables used, such as dietary selenium intake (presented as a continuous variable or categorized considering the median as <48.8 μg/day/≥48.8 μg/day), protein intake [g/day], energy intake [kcal/day], intake of vitamins C and E [mg/day], alcohol consumption [g/week], the average number of portions of fruit and vegetables consumed daily in the summer and winter season, taking mineral supplements (categorized yes/no). The last group of covariates was assessed at the time of colorectal cancer diagnosis and was extracted from medical records. These included: the tumor stage (categorized as 1st [0, A]/2nd [B1, B2]/3rd [C1, C2]/4th stage [D]), radical surgery (categorized yes/no), chemotherapy after the surgery (categorized yes/no).

Statistical analysis

Patients were assigned to one of two categories of selenium intake based on the median (first group: <48.8 μg/day; second group: ≥48.8 μg/day). The lower selenium intake group was selected as the reference. The assessed endpoint was colorectal cancer survival. The multivariable Cox regression model was used to assess the impact of dietary selenium intake on survival. The proportionality assumption for each covariate was tested by an analysis of the interaction term between the variable of interest and time to event, whether it has a significant impact. The proportionality was violated for the Dukes' staging, therefore in the sensitivity analyses we ran a proportional hazard Cox regression model for each Duke category separately. Additionally, in the sensitivity analyses part we applied models which excluded patients in whom radical surgery was not performed, and also patients in whom glucose intolerance issues (GII) had been identified during hospitalization. P values below the level of 0.05 were considered statistically significant. All analyses were conducted using the statistical program IBM SPSS Statistics version 27.

Results

In total, 683 CRC cases were eligible for the study, out of which 12 were excluded due to no exact matching in the country database. Finally, 671 CRC subjects were included in the study analysis. Among them, 338 deaths were identified by a National Vital Registry throughout 2017. The characteristics of the 671 study participants categorized by their vital status are presented in Table 1. The mean age was 59 years for both groups, 57.1% were men, and 42.9% were women (in both groups). 84.6% of patients who died underwent radical surgery, whereas in the survivors' group – 97.9%. Chemotherapy after surgery was administered to 278 (82.2%) patients from the group of patients who died and 185 (55.6%) patients from the group of patients who survived. Considering comorbidities, newly identified glucose intolerance issues (GII) were identified in 11.8% of patients from the group of patients who died and 6.3% of patients from the group of patients who survived, whereas the frequency of cardiovascular diseases did not differ between groups. Similarly, the distribution of cancer staging (Dukes' system for colorectal cancer), duration of smoking, education level, total energy intake, pure alcohol consumption, body mass index (BMI), taking mineral supplements, vegetables and fruit intake, protein intake, vitamin C and E intake did not differ between groups.

The mean selenium intake was 50.4 μg/day in the group of patients who died and 52.0 μg/day in the group of patients who survived, whereas the median level of Se intake was 48.3 μg/day in the group of patients who died and 49.1 μg/day in the group of patients who survived.

After a median follow-up of 1692 days (4.6 years), 338 of the 671 patients had died (50.4%). The multivariable Cox regression model was used to assess the impact of selenium intake on survival. The decrease in the risk of death associated with an increase in selenium by 10 μg was 15% (HR=0.85; 95% CI: 0.75–0.96) after standardization for key confounding variables such as radical surgery, chemotherapy, tumor stage, glucose intolerance issues, cardiovascular diseases, smoking, age, sex, education, energy intake, alcohol consumption, BMI, use of supplements,

Table 1. Basic characteristic of the study group, by the survival status after approximately 4.6 years of follow-up

	Alive [n=333]	Dead [n=338]	p-value
Dietary selenium [μg/day]			
Mean (SD)	52.0 (18.6)	50.4 (16.3)	p^{MW}=0.441
Median, Q1–Q3	49.1 (39.3–59.8)	48.3 (39.0–58.4)	
Radical surgery [N, (%)]			
Yes	326 (97.9%)	286 (84.6%)	p^{chi2}<0.001
No	7 (2.1%)	52 (15.4%)	df=1
Chemotherapy after surgery [N, (%)]			
Yes	185 (55.6%)	278 (82.2%)	p^{chi2}<0.001
No	148 (44.4%)	60 (17.8%)	df=1
Dukes'* and TNM** system for staging colorectal cancer [N, (%)]			
None: 0 and A (T1, N0, M0)	43 (13.6%)	2 (0.6%)	p^{KS}=0.779
B1 (T2, NO, MO), B2 (T3–4, NO, MO)	182 (57.6%)	75 (23.6%)	
C1 (T2, N1–3, MO), C2 (T3–4, N1–3, MO)	74 (23.4%)	86 (27.0%)	
D (Tx–4, Nx–3, M1)	17 (5.4%)	155 (48.7%)	
Glucose intolerance issue (GII) [N, (%)]			
Yes	21 (6.3%)	40 (11.8%)	p^{chi2}=0.013
No	312 (93.7%)	298 (88.2%)	df=1
Cardiovascular diseases [N, (%)]			
Yes	31 (9.3%)	39 (11.5%)	p^{chi2}=0.345
No	302 (90.7%)	299 (88.5%)	df=1
Duration of smoking [in years]			
Mean (SD)	16.0 (16.0)	16.0 (18.0)	p^{MW}=0.678
Median, Q1–Q3	16.0 (0.00–30.0)	6.00 (0.00–32.0)	
Age			
Mean (SD)	59.0 (8.00)	59.0 (8.00)	p^{MW}=0.697
Median, Q1–Q3	59.0 (53.0–65.0)	60.0 (53.0–66.0)	
Gender [N, (%)]			
Men	190 (57.1%)	193 (57.1%)	p^{chi2}=0.991
Women	143 (42.9%)	145 (42.9%)	
Education [N, (%)]			
Primary school or less	41 (17.2%)	50 (16.2%)	p^{KS}=0.525
Vocational school	93 (39.1%)	145 (47.1%)	
Secondary school/high school	41 (17.2%)	48 (15.6%)	
University or higher	63 (26.5%)	65 (21.1%)	
Total energy [kcal/day]			
Mean (SD)	2207 (740)	2229 (770)	p^{MW}=0.577
Median, Q1–Q3	2007 (1697–2558)	2112 (1713–2530)	
Pure alcohol[1] [g/week]			
Mean (SD)	5.08 (10.7)	4.50 (8.50)	p^{MW}=0.466
Median, Q1–Q3	1.28 (0.41–4.89)	1.02 (0.36–4.43)	
BMI [kg/m^2]			
Mean (SD)	27.0 (4.08)	27.7 (4.43)	p^{MW}=0.129
Median, Q1–Q3	26.8 (24.3–29.4)	27.1 (24.6–30.1)	
Taking mineral supplements [N, (%)]			
Yes	57 (17.1%)	44 (13.0%)	p^{chi2}=0.138
No	276 (82.9%)	294 (87.0%)	df=1
Vegetables and fruit intake [servings/day]			
Mean (SD)	3.51 (2.20)	3.54 (2.23)	p^{MW}=0.805
Median, Q1–Q3	2.98 (2.07–4.48)	2.88 (1.87–4.70)	

Table 1. Basic characteristic of the study group, by the survival status after approximately 4.6 years of follow-up (Continued)

	Alive [n=333]	Dead [n=338]	p-value
Protein intake [g/day]			
Mean (SD)	86.2 (33.6)	88.2 (35.1)	p^{MW}=0.353
Median, Q1–Q3	77.7 (64.2–103)	83.0 (65.5–99.4)	
Vitamin C intake [mg/day]			
Mean (SD)	92.7 (49.5)	92.9 (52.8)	p^{MW}=0.813
Median, Q1–Q3	80.1 (58.5–113)	76.3 (56.8–122)	
Vitamin E intake [mg/day]			
Mean (SD)	9.70 (4.76)	9.97 (4.97)	p^{MW}=0.703
Median, Q1–Q3	8.58 (6.70–11.4)	8.93 (6.66–11.6)	

SD: standard deviation; Q1–Q3: quartile 1 to quartile 3; chi^2: chi-square test; MW: the U-Mann-Whitney test; KS: the Kolmogorov-Smirnov test; df: degrees of freedom; GII: glucose intolerance issue; BMI: body mass index; μg/day: micrograms per day; g/day: grams per day; mg/day: milligrams per day; servings/day: servings per day; g/week: grams per week; kcal/day: kilocalories per day; kg/m^2: kilograms per square meter.
[1]Participants reported their consumption expressed in "standard" drinks, which is an equivalent of 12fl of regular beer of about 5% alcohol or 5fl of wine (approximately 12% alcohol) or 1.5fl of distilled spirits (gin, rum, vodka, whiskey, 40% alcohol). Each "standard" drink contains roughly 14g of pure alcohol.
*Dukes' staging: is a pathological staging based on resection of the tumor and measures the depth of invasion through the mucosa and bowel wall.
**TNM: TNM system for staging cancer (T-refers to the size and extent of the primary tumour, N-refers to the number of nearby lymph nodes that have cancer, M-refers to whether the cancer has metastasized).
Explanation of abbreviations for CRC stages on the basis published by Butorovic S. [54]:

Stage			
Dukes	TNM	Pathological description	5-year survival
A	T1, N0, M0	Cancer limited to the mucosa and submucosa	>90%
B1	T2, N0, M0	Cancer extending to the muscularis	85%
B2	T3, N0, M0	Cancer extending to serosa and beyond serosa	70–80%
C (C1, C2)	Tx, N1, M0	Cancer affects to regional lymph nodes (C1-tumor spread to 1–4 regional lymph nodes; C2-tumor spread to more than 4 regional lymph nodes)	35–65%
D	Tx, Nx, M1	Distant metastases (liver, lungs...)	5%

vegetables and fruit intake, protein intake, vitamin C and E intake (Table 2).

The Cox regression model adjusted for the aforementioned confounders, when taking selenium as a categorized variable, showed that patients with higher dietary selenium intake (≥48.8 μg/day) had a 27% lower risk of death compared to patients with lower dietary selenium intake (<48.8 μg/day) (HR=0.73; 95% CI: 0.54–0.98) (Table 2). To verify the stability of estimates we ran some sensitivity analyses which include: 1) a model which excluded patients newly diagnosed with glucose intolerance issues during hospitalization, 2) a model (adjusted for the aforementioned confounders) excluding very ill patients with advanced cancer in whom radical surgery could not be performed (a model with GII as a confounding variable: HR=0.72; 95% CI: 0.52–0.99; and a model without patients identified as GII: HR=0.72; 95% CI: 0.52–0.99 for higher vs. lower dietary Se intake group), 3) separate models for each Dukes' category (Table 3).

Discussion

In this prospective cohort study, among 671 cases of colorectal cancer, dietary selenium was inversely associated with the risk of death. As was mentioned in the introduction, the results in this area are not consistent. The presented results are in line with the Cancer Mortality Correlation Studies by Schrauzer et al. The authors published there a high negative statistically significant correlation between dietary selenium intake and mortality from both colon and rectal cancer (correlation coefficient for colon cancer: r=−0.74 for males; r=−0.72 for females; for rectal cancer: r=−0.58 for males; r=−0.55 for females) [22]. Another cohort study published by Psathakis et al. showed colorectal cancer patients with serum selenium level <70 μg/L having significantly lower mean survival time and a lower cumulative cancer-related survival rate than patients with the concentration >70 μg/L [26].

There is also a recent study published by Baker et al. on blood selenium status and mortality among patients with colorectal cancer, which suggested an inverse association between prediagnostic Se status and CRC-specific mortality among CRC patients in Western Europe [29]. Serum selenium concentration was not available in our study, so in order to obtain some comparability of our results to the results on serum selenium, we additionally implemented a formula for the conversion of selenium from the diet to selenium in plasma or blood serum [$C_{Se\text{-}plasma}$=($1.12\times i_{se\text{-}diet}$)+23] as published by Haldimann et al. [40].

Table 2. Selenium dietary intake and hazard ratios (HRs) for colorectal cancer

	Model 1			Model 2		
	HR	95% CI	p-value	HR	95% CI	p-value
Dietary selenium intake (continuous)						
For and each increase by 10 μg/day	0.96	0.90–1.02	.200	0.85	0.75–0.96	.009
Dietary selenium intake (categorized, reference group <48.8 μg/day)						
<48.8 μg/day	1			1		
≥48.8 μg/day	0.88	0.71–1.09	.231	0.73	0.54–0.98	.037

Model 1: univariable proportional hazard Cox regression.
Model 2: adjusted for age [years], sex, BMI [kg/m^2], pure alcohol consumption [g/week], an average intake of energy [kcal/day], smoking duration [years], radical surgery [yes/no], chemotherapy after surgery [yes/no], Dukes' staging [A/B1, B2/C1, C2/D], glucose intolerance issue [yes/no], cardiovascular diseases [yes/no], education [primary school or less/vocational school/secondary school or high school/university or higher], taking mineral supplements [yes/no], vegetables and fruit intake [servings/day], protein intake [g/day], intakes of vitamin C [mg/day] and vitamin E [mg/day].
HR: hazard ratio; CI: confidence interval.

Table 3. Sensitivity analyses: hazard ratios (HRs) associated with dietary selenium intake across different analytical models

	HR	95% CI	p-value
Sample limited to patients without GII			
Dietary selenium intake (continuous) for and each increase by 10 μg/day	0.85[a]	0.75–0.96	.009
Dietary selenium intake (categorized, reference group <48.8 μg/day) ≥48.8 μg/day	0.73[a]	0.54–0.98	.036
Sample limited to patients who underwent radical surgery			
Dietary selenium intake (continuous) for and each increase by 10 μg/day	0.85[b]	0.74–0.98	.021
Dietary selenium intake (categorized, reference group <48.8 μg/day) ≥48.8 μg/day	0.72[b]	0.52–0.99	.045
Sample limited to patients who underwent radical surgery and had no GII			
Dietary selenium intake (continuous) for and each increase by 10 μg/day	0.85[c]	0.74–0.97	.019
Dietary selenium intake (categorized, reference group <48.8 μg/day) ≥48.8 μg/day	0.72[c]	0.52–0.99	.043
Subgroups by Dukes' staging			
Duke 2nd stage (B1, B2)			
Dietary selenium intake (continuous) for and each increase by 10 μg/day	0.98[d]	0.78–1.23	.878
Dietary selenium intake (categorized, reference group <48.8 μg/day) ≥48.8 μg/day	0.83[d]	0.44–1.56	.561
Duke 3rd stage (C1, C2)			
Dietary selenium intake (continuous) for and each increase by 10 μg/day	0.61[d]	0.45–0.84	.002
Dietary selenium intake (categorized, reference group <48.8 μg/day) ≥48.8 μg/day	0.49[d]	0.25–0.93	.030
Duke 4th stage (D)			
Dietary selenium intake (continuous) for and each increase by 10 μg/day	0.85[d]	0.69–1.04	.109
Dietary selenium intake (categorized, reference group <48.8 μg/day) ≥48.8 μg/day	0.90[d]	0.56–1.43	.651

HR: hazard ratio; CI: confidence interval; GII: glucose intolerance issue.
[a]Proportional hazard Cox regression model adjusted for: age [years], sex, BMI [kg/m^2], pure alcohol consumption [g/week], an average intake of energy [kcal/day], smoking duration [years], radical surgery [yes/no], chemotherapy after surgery [yes/no], Dukes' staging [A/B1, B2/C1, C2/D], cardiovascular diseases [yes/no], education [primary school or less/vocational school/secondary school or high school/university or higher], taking mineral supplements [yes/no], vegetables and fruit intake [servings/day], protein intake [g/day], intakes of vitamin C [mg/day] and vitamin E [mg/day].
[b]Model adjusted for covariates as in a and additionally adjusted for GII, but limited to patients who underwent radical surgery.
[c]Model adjusted for covariates as in a, but limited to patients who underwent radical surgery.
[d]Model adjusted for covariates as in a and for GII; the model presented results in subgroups by Dukes' staging; for Dukes' category 1 (0, A) – model cannot reach convergence due to limited number of outcomes (deaths).
B1 (Duke 2nd stage): cancer extending to the muscularis; B2 (Duke 2nd stage): cancer extending to serosa and beyond serosa; C (Duke 3rd stage): cancer affects to regional lymph nodes (C1-tumor spread to 1–4 regional lymph nodes; C2-tumor spread to more than 4 regional lymph nodes); D (Duke 4th stage): distant metastases (i.e. liver, lungs).

Consequently, we obtained results suggesting the inverse association between selenium in serum and CRC-specific survival (HR=0.60; 95% CI: 0.33–1.07 for the highest ≥92.9 μg/L vs. the lowest ≤65.0 μg/L quintile); albeit the results were not statistically significant. When comparing our results to the results of the study by Baker et al., it may be noticed that they are similar in a certain sense. Baker suggested an inverse non-significant association between selenium in blood serum and CRC-specific mortality (HR=0.73; 95% CI: 0.52–1.02 for the highest ≥100 μg/L vs. the lowest ≤67.5 μg/L quintile). The approximation conducted in our study, however, should be treated with caution due to the fact that the conversion formula was developed for Switzerland, yet not for the Polish population.

Contrary to the presented findings, there were two other published studies that showed no association between serum selenium and survival from CRC [27, 28]. Some possible explanations were, as the first showed preliminary results from the EPIC study, and it was a report presented during the conference with a limited number of covariates considered, while the second had been done using an ecological design sharing all the limitations associated with this research strategy. Referring to some other research area investigating the role of dietary selenium in cancer survivors, it is worth noting a study by Harris et al. [23] that investigated breast cancer which is similar to colorectal adenocarcinoma in terms of the possible genetic mechanisms of its formation [41]. That study concluded that selenium intake before breast cancer diagnosis might improve breast cancer-specific survival and overall survival. In that study, women in the highest quartile of selenium intake ($\geq$27.7 μg/day) had a multivariable HR of death from breast cancer of 0.69 (95% CI: 0.52–0.92) compared with those in the lowest quartile (<20.5 μg/day). Additionally, a significant trend across quartiles was observed (p^{trend}=0.009). There are also findings from observational studies on selenium in blood and breast cancer which support the association between higher selenium status and better survival outcomes [30–33]. Similarly, studies on serum selenium and other tumor types such as cancers of kidney, larynx and lung also showed the presence of some association [34, 35, 36]. In addition, a publication by Hatfield et al. [42] provided evidence that very high selenium levels may promote neoplastic transformation instead of protective effects (a potential U-shaped association between the selenium status and cancer risk). This would explain the differences in the results obtained across different selenium intakes and would support our findings showing some protective associations 'selenium-cancer survival' in the population characterized by relatively lower dietary selenium intake. Thus, the results obtained may vary worldwide due to the different levels of endogenous selenium. For example, in North America selenium intake ranges from very high levels (approximately 200–724 μg/day) in parts of North America, such as North and South Dakota, Montana and Wyoming to "adequate" levels (100–200 μg/day) in the rest of North America [43]. These values when compared to the values of selenium intakes in eastern European countries (equal to approximately 7–30 μg/day) are clearly higher [43]. As serum selenium concentration correlates with the dietary selenium intake under steady-state conditions, in practice, following Haldimann and co-authors [40] "under steady-state conditions, an increase in the mean daily dietary intake of 1 μg of natural selenium is equivalent to the mean increase in its serum or plasma concentration of about 1.5 μg/L", which provides an implication for individuals identified with low selenium levels.

There is also some body of evidence on molecular mechanisms linking CRC survival with selenium. In a study by Tianhong Li [44], colorectal cancer patients (with stage III) with a low expression of human selenium-binding protein 1 (SBP1) in carcinogenic cells had significantly shorter disease-free and overall survival than patients with high tumor SBP1 expression. A lower expression of SBP1 associated with poor survival was also described in a study by Kim H et al. [45]. In another study by Hughes et al., in the Czech CRC patient cohort, no major association between transcript levels and survival was found, except for an association between higher selenoprotein F (SELENOF) gene expression and a lower disease-free and overall survival [46]. In that study the correlation of gene expression with serum selenium status was also examined and there were no significant correlations with selenium status markers. At this point, additional studies are needed to clarify the association between gene expression and functional Se status better.

Several potential biological mechanisms may link selenium to CRC survival. As a part of selenoproteins, Se has been implicated in regulating several major cell signaling pathways, many of which may control colorectal neoplasm development [20]. In addition, several selenoproteins may prevent cancer progression and thereby decrease mortality due to 1) having well-established functions in redox control and response to oxidative stress and inflammation (hallmark processes in colorectal carcinogenesis), 2) playing an important role in the regulation of programmed cell death and the cell cycle, and inhibition of cellular proliferation [19, 20].

Additionally, Jiang reported that selenium supplementation inhibited angiogenesis by affecting the vascular endothelial growth factor (VEGF) [47]. Furthermore, selenium may play an antimetastatic role due to its ability to downregulate the expression of several genes, i.e., those involved in osteopontin and collagen metabolism [48, 49]. Interestingly, selenium has also been reported to stop energy production in tumor cells by suppressing a reaction of glutaminolysis [50]. However, several studies have shown some selenoproteins such as TXNRD1, SELENOF, and GPx2 to have the potential for both cancer prevention and promotion [42, 51].

Although the observational design used in our study is linked to several limitations, there are several strengths which include a cohort study design, a large sample size, detailed information on a diet, a long follow-up period, a small number of dropouts, and data on many important covariates which were subsequently used for adjustment. In addition, literary data on possible risk factors in survival studies were carefully checked, which facilitated the comprehensive adjustment of confounders. Moreover, we did some additional analyses in the section entitled "sensitivity

analyses" (Table 3). As presented, we ran the following models: 1) after exclusion of patients identified with glucose intolerance issues during hospitalization; 2) after exclusion of severe patients (those who did not undergo radical surgery) – to avoid reverse causation bias; 3) models across Dukes' staging categories, as this was the time-dependent variable in our analyses. All the aforementioned models showed a similar direction for HR point estimates. Some results missed statistical significance due to a decrease in the sample size.

Referring to limitations, firstly, as in epidemiological studies based on data collection by questionnaires, measurement errors in self-reported dietary data introduced by SFFQ are prone to recall bias and may have attenuated estimates for the associations. The purpose of using SFFQ, however, is to assess habitual diet, which is considered to reflect the average exposure to dietary factors. Secondly, because selenium in food may vary between geographic regions due to its content in the soil where the food is produced, a lack of biological measurements weakens our conclusion. The majority of food available on the market in Poland, however, is produced locally, and the use of data about the content of serum published for Polish food strengthens our results. Thirdly, it is hard to confirm that the patient-reported diet at the time of the study exactly corresponds to the diet of 5 years ago. The source of potential errors in the assessment of food consumption using the FFQ questionnaire (concerning food consumption during, for instance, last year or the previous 5 years) is the respondent's long-term memory. Therefore, when validating such questionnaire, the appropriate reference method for assessing the diet is, e.g. a multiple 24-hour interview method or a registration method repeated several times a year over several days because the results of these methods do not depend on the respondent's memory [52]. The FFQ questionnaire used in our study was developed for the German part of the EPIC (European Investigation into Cancer and Nutrition) Project and has been validated. During the validation of this FFQ questionnaire, the reproducibility of the method was checked by reusing this questionnaire 6 months after completing the nutrition assessment for the first time using the first FFQ questionnaire [38]. The results of the repeatability study showed a reproducible estimation of the consumption of individual food groups. During the validation, the relative validity of the method was also assessed (the results of the FFQ method of nutrition were compared with the results obtained with the reference method – 24-hour interviews performed every month) showing good properties [38]. Therefore, the questionnaire applied in our study may be considered to represent a reliable tool providing valuable information on food intake frequencies and amounts. In our study we did not repeat validity procedures used at the time when the SFFQ was developed, and the dietary questionnaire was not specifically validated regarding the content of selenium. Fourthly, the assessment of diet in our participants was obtained as before the diagnosis and we did not examine the post-surgery diet during the follow-up period. This was the consequence of the purpose of our study, which tried to investigate the selenium-related status before surgery as a determinant of post-surgery outcomes. Although Velentzis and co-authors showed in their study that no change in selenium pre-diagnosis to post-diagnosis intake was noted among a cohort of breast cancer patients [53], collecting data before the diagnosis only should be mentioned among the major limitations of our study. And finally, as with other observational studies, there was a possibility of residual confounding, despite controlling for relevant covariates.

In summary, our study suggests selenium as an additional dietary factor which may be associated with survival among colorectal cancer patients referred to surgery. Due to the observational nature of the study, the results should be taken with caution. Lower levels of selenium in food in Poland limit the generalizability of our findings for other populations naturally exposed to higher levels of selenium by food supply. These preliminary findings, however, provide the basis for well-structured clinical trials to verify and elucidate the role of dietary selenium among CRC patients more profoundly.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0300-9831/a000768

ESM 1. Studies on the relationship between selenium (Se intake or selenium measured in serum or plasma) and survival from colorectal cancer, breast cancer and cancer in general (Table E1).

ESM 2. The concentration of selenium, including losses on cooking, by dietary item (Table E2).

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Conflict of interest
The authors declare that there are no conflicts of interest.

Author contributions
Both authors MA and AG contributed to the conception and design of the study, generation, collection, assembly, analysis and interpretation of data, and manuscript drafting.

ORCID
Malgorzata Augustyniak
https://orcid.org/0000-0002-8238-3732
Aleksander Galas
https://orcid.org/0000-0002-9233-4301

Malgorzata Augustyniak (MSc)
Jagiellonian University Medical College
Chair of Epidemiology and Preventive Medicine
Department of Epidemiology
7 Kopernika St
31-034 Krakow, Poland
malgorzata.augustyniak@uj.edu.pl

