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FOOD IN HEALTH AND DISEASE

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DIETARY HABITS OF COLORECTAL CANCER PATIENTS – COMPARISON BETWEEN SLAVONIA AND DALMATIA

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Summary

Diet plays crucial role in colorectal cancer (CRC), from incidence to progression. It is the second cause of death due to carcinoma in Croatia, with significant regional differences. The aim of this observational study was to determine dietary habits of CRC patients, and whether their diet differs by region. A total of 60 patients with non-metastatic CRC, 30 from Slavonia and 30 from Dalmatia participated in the study. Two thirds of patients from both regions changed their diet for better after CRC diagnosis. However, one third of patients do not get any physical activity. Patients do not differ in their energy intake or intake of vitamins or minerals. Still, high contribution of fats (>40%) and low contribution of carbohydrates in the total daily energy intake was found. Contribution of proteins is higher in Slavonia (p=0.040). More patients from Dalmatia have intake of calcium <700 mg/day (43.3% vs 33.3%). Alcohol is consumed more often by patients from Dalmatia (p<0.001) and higher consumption of alcohol correlates with the high risk diet profile which was found in 66.7% of patients from Dalmatia in comparison to 36.7% patients from Slavonia (p=0.020). The results point out some regional differences in the diet which need further analysis.

Keywords: colorectal cancer; diet; regional differences

Introduction

In Europe, 4.4 million people annually are diagnosed with cancer, with 1.96 million cancer-related deaths, 12.5% of which are attributed to colorectal cancer (CRC) (WHO, 2020). Globally, CRC is the third most common cancer (WCRFI, 2020). The toll of cancer is experienced by the entire society, either directly or indirectly. For example, the global annual healthcare allocation for cancer patients is around € 900 billion (EC, 2020). The burden of cancer in 27 countries of the European Union (EU) in 2020 has risen up to 2.7 million new cases and 1.3 million deaths consequently. Colorectal cancer is the second most common cancer (11.8% of all new cases), and the second cause of death (12.5% of all cancer deaths) with high mortality rates especially in Eastern countries (ECIS, 2020). Early CRC diagnosis is crucial for survival (WCRFI, 2020).

The incidence of CRC is significantly higher in men (10.6% vs. 9.2%) (Ferlay et al., 2019), while women have a longer survival (58.7% vs. 59.2%) and lower mortality rates (6.3% vs. 8.8%). This, however, changes in women over 50 years (Yang et al., 2017), probably because of the changes in the sex hormones level in menopause (Majek et al., 2013). In addition, women are more likely to have the so-called right (proximal) CRC which is more aggressive in relation to the left (distal) CRC which is more common in men (Yang et al., 2017).

The majority of CRC cases (70%) are spontaneous and the remaining 10 to 30% are of hereditary origin (Banjari and Hjårtaker, 2018). For spontaneous CRC the most important risk factors are diet and physical activity (Banjari and Fako, 2013). Poor diet and lifestyle habits can overcome positive genetic family history or diagnosis of some of the inflammatory bowel diseases (Johnson et al., 2013). The strongest correlation was found for the consumption of processed and red meat, that is, heme iron (Abid et al., 2014), while for the total dietary intake of iron, the results are inconsistent (Ashmore et al., 2016; Fonseca-Nunes et al., 2013; Bastide et al., 2011).

Daily consumption of 50 g of processed meat (salted and smoked meat, e.g. sausages, kulen, dry cured ham or bacon) increases the risk of CRC by 18% (Abid et al., 2014). Red meat (beef, pork and game meat) increases the risk by 12% (Zhao et al., 2013). Diet plays crucial role in survival too (Banjari, 2018), along with pre-existence of obesity and lack of physical activity.

Diet is very diverse across Croatian regions, from Hungarian-Turkish-like in the eastern regions, Austrian-like in the northern parts to the Mediterranean type in the coastal regions. Culinary diversity is not solely restricted to Croatia and can be seen in many countries across

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Europe and world (Anderson et al., 2016; Mertens et al., 2019). Yet, these regional differences become evident once CRC incidence and mortality are compared (Banjari and Kožić, 2018).

The traditional dietary patterns in continental (Eastern) Croatia can be characterized as the high-risk diet for CRC (due to significant consumption of processed and red meat, more saturated fats and the preference for spicy foods) (Banjari and Kožić, 2018). On the other hand, diet in the coastal region can be described as the Mediterranean type of diet or the CRC low-risk diet, because of the well-proven beneficial effects on the CRC risk (Farinetti et al., 2017). Still, even though nutrition has the strongest impact on CRC risk (Johnson et al., 2013; WCRFI and AICR, 2018), latest incidence rates per 100 000 population from 2019, for C18 (colon cancer excluding rectum) show that CRC is more common in Dalmatia than in Slavonia (43.3 in Osijek-Baranja County (Eastern Croatia) and 60.0 in Zadar and 69.9 in Split-Dalmatia County (coastal regions)) (HZJZ, 2021).

The aim of this study was to compare dietary pattern of CRC patients from Slavonia and Dalmatia.

Participants and methods

Study type and participants

We conducted an observational study encompassing non-metastatic CRC patients, diagnosed with either colon or rectal cancer for at least 6 months, both gender, at least 40 years old. The recruitment was done through patient registry of General hospital Zadar (N=30) and University Hospital Centre Osijek (N=30). In every region, 16 men and 14 women participated in the study.

Study was approved by ethics committee of General hospital Zadar and University Hospital Centre Osijek. After patients gave written consent to participate in the study, they were interviewed via telephone to complete all questionnaires.

Questionnaires

Study specific questionnaire included general questions (e.g. age, gender), basic socio-demographic data (e.g. education level, employment, income, household members), health information (e.g. when was CRC diagnosed, constipation, sleep weight change, medications, supplement use), and general diet and lifestyle habits (e.g. number of meals per day, meal skipping, smoking, alcohol consumption, physical activity, preference of foods). Study subjects also completed one 24-hour dietary recall, which was used to calculate macro- and micro-nutrient consumption. Calculations were done by MeDietetic Software (MeDietetic, 2022), which uses national food composition database. These calculations were later compared with referent values for adults for particular nutrients (EFSA, 2019).

Based on the self-reported weight and height, Body Mass Index was calculated and CRC patients were categorized according to their nourishment status (WHO, 2010).

Statistical analysis

Software package Statistica 14.0 was used for statistical analysis, with selected level of significance at 0.05. Graphic analysis was conducted with MS Office Excel 2016 package.

The normality of data distribution was tested using the non-parametric Kolmogorov-Smirnov test, along with the comparison of medians, the comparison of the arithmetic means and by creating histograms. Given that all values are normally distributed, parametric statistical tests were used.

Pearson's correlation test and student's t-test for independent variables was used, along with Chi square test for the comparison of categorical data.

Results and discussion

Patients' general characteristics are shown in Table 1. Patients from Slavonia were significantly younger in comparison to patients from Dalmatia. Age is one of the risk factors for CRC (WCRF and AICR, 2018). People who are 50 years or older have 5% higher risk for CRC (HZJZ, 2018), but globally, CRC incidence is rising among people who are younger than 50 years (Voigtländer et al., 2022). In this research, only three patients were younger than 50 years. Still, younger people tend to have a more aggressive form of CRC, but better survival rates in comparison to patients who are 50+ years old (Steele et al., 2014).

Table 1. General characteristics of CRC patients from Slavonia (n=30) and Dalmatia (n=30)

Characteristics	**Slavonia** (n=30)		**Dalmatia** (n=30)		**p**
	Mean ± SD	**Min - Max**	**Mean ± SD**	**Min - Max**	
Age (years)	61 ± 5	51 – 69	67 ± 11	43 - 82	0.010*
BMI (kg/m^2)	26.3 ± 4.3	20.7 – 36.6	27.6 ± 4.4	18.6 – 39.5	0.272
Time from CRC diagnosis (months)	11 ± 3	1 - 16	39 ± 38	6 – 192	<0.001*
Symptoms prior the diagnosis (months)	6 ± 13	0 - 72	4 ± 6	0 - 24	0.303
Weight loss (kg)	-10.6 ± 10.0	-40 – 6	-8.6 ± 7.9	-25 – 0	0.378

BMI – Body Mass Index, SD – standard deviation, Min – minimum value, Max – maximum value; T-test for independent variables; *statistically significant at p<0.05

There was no significant difference in the average BMI (Table 1), but more patients from Dalmatia are overweight in comparison to patients from Slavonia (50% vs 33%, Figure 1). Between 30 and 70% of CRC has been linked to obesity and overweight, and the risk seem to be more pronounced in men (Duraiyarasan et al., 2022).

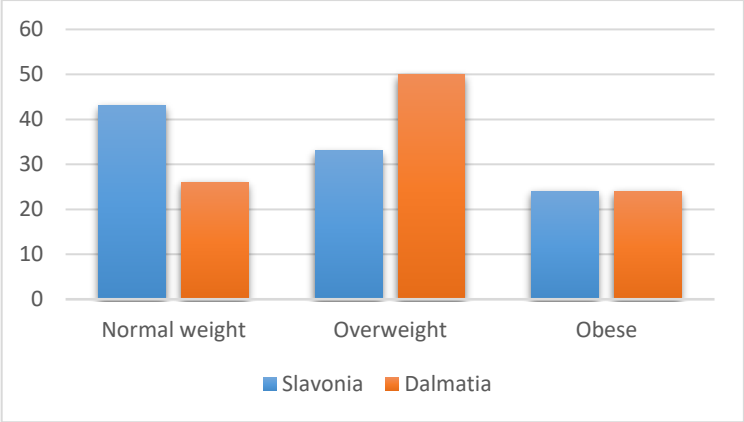

Figure 1. Distribution of CRC patients from Slavonia (n=30) and Dalmatia (n=30) according to their nourishment status

Patients do not differ in the time when the first symptoms appeared prior to the diagnosis (Table 1). Blood in stool and frequent diarrhoea-like stool are the most common symptoms patients mentioned to have appeared before the diagnosis. Some patients also reported feeling tired, bloating, constipation, significant weight loss, iron deficiency anaemia and abdominal pain. Also, there was no difference in weight loss (Table 1). Patients with significant weight loss need close monitoring since it was shown that with every 5 kg weight loss, survival is lower by 25% (Kocarnik et al., 2017). In other words, weight loss is an independent risk factor for survival in CRC patients (Cong et al., 2018; Kuo et al., 2018), while weight gain after the diagnosis did not show to correlate with either poor outcome or survival (Meyerhardt et al., 2017; Cong et al., 2018).

Patients do not differ in their energy or macronutrient consumption (Table 2). Patients from Slavonia consume more complex carbohydrates in comparison to patients from Dalmatia (based on the ratio mono/poly) which is supported by the daily fibre consumption (23.2 ± 17.7 g in comparison to 19.3 ± 9.7 g). On the other hand, ratio between plant and animal proteins shows that patients from Slavonia consume more animal foods (Table 2). Patients from Dalmatia consume significantly more alcohol in comparison to patients from Slavonia (p=0.013, Table 2). Alcohol consumption >50 g/day for men and >25 g/day for women significantly increase the risk for CRC and CRC mortality (Rossi et al., 2018). Alcohol restriction is especially important for obese men who almost double the risk for CRC (Banjari, 2018). However, alcohol consumption in moderation has protective effect in CRC patients who are also diagnosed with diabetes (Walter et al., 2017). Alcohol changes folate metabolism in the liver and is a possible cause of liver metastases in CRC patients (Rossi et al., 2018).

Table 2. Average daily energy and macronutrient intake among CRC patients from Slavonia (n=30) and Dalmatia (n=30)

	Slavonia		**Dalmatia**		**p**
	Mean ± SD	Min - Max	Mean ± SD	Min - Max	
Energy (kJ)	9921 ± 4071	5253 - 20176	9522 ± 3094	4308 - 17614	0.670
Energy (Kcal)	2372 ± 974	1256 - 4825	2276 ± 739	1029 - 4209	0.667
Carbohydrates(g)	264.0 ± 148.3	112.8 – 856.7	229.0 ± 75.7	114.4 – 411.3	0.255
Ratio Mono/Poly	0.6 ± 0.4	0.1 – 1.8	0.8 ± 1.4	0.2 – 8.2	0.305
Total fats (g)	107.9 ± 57.8	52.6 – 267.5	112.2 ± 55.0	34.3 – 255.5	0.771
SFA (g)	34.3 ± 22.8	13.7 – 104.0	33.5 ± 19.0	3.9 – 86.7	0.885
MUFA (g)	39.3 ± 28.0	28.0 -124.9	47.2 ± 33.2	10.1 – 132.2	0.325
PUFA (g)	27.9 ± 15.3	10.3 – 74.6	24.1 ± 13.4	6.8 – 56.06	0.313
Cholesterol (mg)	353.4 ± 483.0	24.8 – 2782.0	480.7 ± 1360.0	0.0 – 7609.6	0.631
Proteins (g)	88.8 ± 36.3	34.5 – 204.1	76.9 ± 39.3	30.5 -39.3	0.226
Ratio Plant/Animal	0.9 ± 0.7	0.1 – 3.5	1.5 ± 4.6	0.0 – 25.8	0.452
Fibre (g)	23.2 ± 17.7	9.6 – 102.3	19.3 ± 9.7	1.8 – 47.8	0.291
Alcohol (g)	1.4 ± 5.3	0.0 – 21.5	8.7 ± 14.7	0.0 – 53.5	0.013*

Min – minimum value, Max – maximum value; Ratio Mono/Poli – ratio between mono- and polysaccharides, SFA – saturated fatty acids, MUFA – mono-unsaturated fatty acids, PUFA– poly-unsaturated fatty acids, Ratio Plant/Animal – ratio between plant and animal proteins

T-test for independent variables; *statistically significant at p<0.05

In comparison to recommended nutrient intake (EFSA, 2019) patients from both regions have much higher contribution of fats to the total daily energy intake (over 30%), while contribution of carbohydrates is lower from the recommended (50 – 55%). Lower death risk, regardless of the cause is related to daily contribution of carbohydrates to the total energy intake between 50 and 55% (Seidelmann et al., 2018). Also, low (< 40%), and high (> 70%) contribution of carbohydrates increase the risk of death by 20% and 23% respectively (Seidelmann et al., 2018).

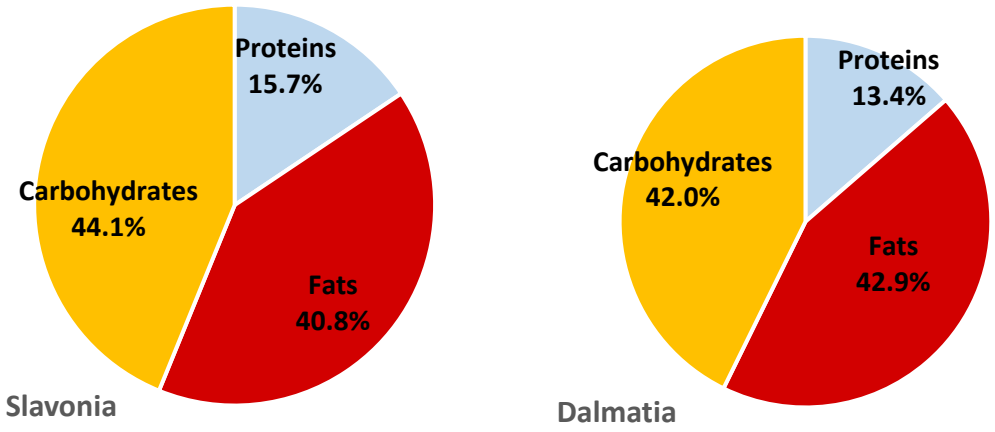

Figure 2. Contribution (%) of proteins, fats and carbohydrates to the total daily energy intake among CRC patients from Slavonia (n=30) and Dalmatia (n=30)

Average daily consumption of vitamins (Table 3) and minerals (Table 4) except for niacin and selenium do not differ significantly among CRC patients from Slavonia and Dalmatia. Vitamin D consumption is slightly higher in Dalmatia in comparison to Slavonia (1.363 ± 4.580 µg vs 1.348 ± 1.855 µg) while more vitamin B_{12} is consumed by patients from Slavonia (3.5 ± 4.9 mg vs 2.5 ± 4.5 mg). On the other hand, more calcium (706 ± 401 mg vs 651 ± 517 mg) and iron (12.9 ± 6.7 mg vs 12.0 ± 7.1 mg) is consumed by patients from Dalmatia. In comparison to recommendations (EFSA, 2019), both groups of patients consume more iron and vitamin B_{12} while vitamin D consumption is well below the recommended intake of 15 µg/day, as well as calcium consumption for which the recommended intake is 1000 mg/day. The strongest protective effect in CRC was found for calcium consumption exceeding 700 mg/day (Banjari, 2018). Calcium consumption below 700 mg/day was found in 10 patients from Slavonia and 13 patients from Dalmatia (not statistical significance).

Table 3. Average daily consumption of vitamins among CRC patients from Slavonia (n=30) and Dalmatia (n=30)

Vitamins	Slavonia		Dalmatia		p
	Mean ± SD	Min - Max	Mean ± SD	Min - Max	
Vitamin A (µg)	569 ± 1143	0 - 6196	688 ± 1033	0 - 4206	0.676
Vitamin D (µg)	1.348 ± 1.855	0.000 – 7.036	1.363 ± 4.580	0.000 – 25.274	0.987
Vitamin E (mg)	2.70 ± 3.45	0.32 – 17.37	4.68 ± 5.47	0.18 – 20.21	0.099
Vitamin K (µg)	142 ± 140	0 - 546	205 ± 254	0 - 1047	0.239
Vitamin C (mg)	111 ± 222	0 - 1228	96 ± 92	5 - 397	0.746
Vitamin B_1 (mg)	0.92 ± 0.73	0.32 – 3.45	0.80 ± 0.42	0.27 – 2.10	0.443
Vitamin B_2 (mg)	1.02 ± 0.61	0.41 – 2.96	0.94 ± 0.78	0.38 – 4.88	0.642
Niacin (mg)	15.1 ± 8.4	4.4 – 38.2	10.0 ± 6.9	3.0 – 35.5	0.012*
Vitamin B_6 (mg)	1.28 ± 0.79	0.18 – 3.34	1.01 ± 0.59	0.15 – 2.34	0.141
Biotin (µg)	23.99 ± 17.43	2.63 – 86.47	27.16 ± 64.88	0.60 – 365.91	0.797
Folates (µg)	159 ± 152	55 – 900	127 ± 83	10 – 378	0.993
Vitamin B_{12} (mg)	3.5 ± 4.9	0.0 – 24.5	2.5 ± 4.5	0.0 – 24.6	0.792

Min – minimum value, Max – maximum value; T-test for independent variables; *statistically significant at p<0.05

Table 4. Average daily consumption of minerals among CRC patients from Slavonia (n=30) and Dalmatia (n=30)

Minerals	Slavonia		Dalmatia		p
	Mean ± SD	Min - Max	Mean ± SD	Min - Max	
Sodium (g)	6906 ± 4999	2109 - 24844	5139 ± 3778	1040 - 21421	0.128
Potassium (g)	3201 ± 1797	966 - 9633	2702 ± 1069	1171 - 5663	0.197
Calcium (mg)	651 ± 517	101 - 2727	706 ± 401	110 - 2306	0.653
Magnesium (mg)	230 ± 149	16 - 603	218 ± 132	49 - 495	0.742
Phosphorus (mg)	1341 ± 526	583 - 3024	1304 ± 681	636 - 4551	0.815
Iron (mg)	12.0 ± 7.1	5.1 – 34.2	12.9 ± 6.7	5.2 – 37.9	0.635
Zinc (mg)	4.46 ± 2.86	0.00 – 13.83	3.24 ± 2.33	0.69 - 10,55	0.075
Copper (μg)	1.08 ± 1.02	0.05 – 5.55	0.76 ± 0.49	0.08 – 2.38	0.120
Manganese (mg)	797 ± 1158	0 - 5221	1142 ± 1212	0 - 5695	0.265
Selenium (μg)	148 ± 70	68 - 361	103 ± 63	13 - 298	0.010*

Min – minimum value, Max – maximum value; T-test for independent variables; *statistically significant at $p<0.05$

When all dietary characteristics are observed in relation to CRC effect (WCRF and AICR, 2018), we found that 11 patients from Slavonia and 20 patients from Dalmatia have diet which can be characterized as the "high-risk" diet (p=0.020; Chi square test). Patients from Slavonia have slightly better distribution of macronutrients in the daily energy intake, their consumption of dietary fibre is higher and they have lower alcohol consumption in comparison to patients from Dalmatia.

Conclusions

The results point out some regional differences in diet between Slavonia and Dalmatia that need more thorough examination in order to determine their role in the progression and survival of CRC patients. Nutrition education programs and/or provision of nutrition information (in a form of pamphlet or booklets) to CRC patients within hospitals is necessary to improve patients' knowledge and behaviour related to diet. That could have important implications in patients' treatment success, recovery and quality of life.

References

Abid, Z., Cross, A.J., Sinha, R. (2014): Meat, dairy, and cancer. *Am J Clin Nutr.* 100 (Suppl 1), 386S-93S.

Anderson, L., Merle Benbow, H., Manzin, G. (2016): Europe on a Plate: Food, Identity and Cultural Diversity in Contemporary Europe. *Australian & New Zealand Journal of European Studie.* 8 (1), 2-15.

Ashmore, J.H., Rogers, C.J., Kelleher, S.L., Lesko, S.M., Hartman, T.J. (2016): Dietary iron and colorectal cancer risk: a review of human population studies. *Crit Rev Food Sci Nutr.* 56 (6), 1012-1020.

Banjari, I. (2018): Kolorektalni karcinom i prehrana - što kažu dokazi?. *Znanstveno-stručni časopis za nutricionizam i dijetetiku Hrana u zdravlju i bolesti*, specijalno izdanje povodom 10. međunarodnog simpozija Štamparovi dani "Zdravi stilovi života" 58-63.

Banjari, I., Fako, J. (2013): The importance of an up-to-date evidence based diet planning for colorectal cancer patients. *Arch Oncol.* 21 (3/4), 160-162.

Banjari, I., Hjårtaker, A. (2018): Dietary sources of iron and vitamin B12: Is this the missing link in colorectal carcinogenesis? *Med Hypotheses* 116, 105-110.

Banjari, I., Kožić, S. (2018): Dietary intake of vitamin B12 in relation to diet and lifestyle characteristics in a population at high risk for CRC. *Central Eur J Pub Health* 26 (4), 253-259.

Bastide, N.M., Pierre, F.H.F., Corpet, D.E. (2011): Heme iron from meat and risk of colorectal cancer: a meta-analysis and a review of the mechanisms involved. *Cancer Prev Res.* 4 (2), 177-184.

Cong, Z., Wang, D., Cao, Y. (2018): The relationship between body mass index changes during chemotherapy and prognosis of patients with advanced colorectal cancer: A retrospective cohort study. *Medicine (Baltimore)* 97 (22), 18-43.

Duraiyarasan, S., Adefuye, M., Manjunatha, N., Ganduri, V., Rajasekaran, K. (2022): Colon Cancer and Obesity: A Narrative Review. *Cureus.* 14 (8), e27589.

EC, European Commission. Europe's Beating Cancer Plan: Let's strive for more. Published 4 February 2020. https://ec.europa.eu/health/non_communicable_diseases/cancer_en

ECIS, European Cancer Information System. Estimates of cancer incidence and mortality in 2020, for all countries. https://ecis.jrc.ec.europa.eu/index.php

Farinetti, A., Zurlo, V., Manenti, A., Coppi, F., Mattioli, A.V. (2017): Mediterranean diet and colorectal cancer: A systematic review. *Nutrition* 43-44, 83-88.

EFSA, European Food Safety Authority: DRV Finder. https://multimedia.efsa.europa.eu/drvs/index.htm

Ferlay, J., Colombet, M., Soerjomataram, I., Mathers, C., Parkin, D.M., Piñeros, M., et al. (2019): Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 144 (8), 1941-1953.

Fonseca-Nunes, A., Jakszyn, P., Agudo, A. (2013): Iron and cancer risk—a systematic review and meta-analysis of the epidemiological evidence. *Cancer Epidemiol Biomarkers Prev.* 23 (1), 12-31.

HZJZ, Croatian Institute of Public Health (2018): Croatian National Cancer Registry. Cancer Incidence in Croatia in 2015. Bulletin No: 40. Zagreb: Croatian Institute of Public Health.

HZJZ, Croatian Institute of Public Health (2021): Croatian National Cancer Registry. Cancer Incidence in Croatia 2019. Bulletin No. 44. Zagreb: Croatian Institute of Public Health.

Johnson, C.M., Wei, C., Ensor, J.E., Smolenski, D.J., Amos, C.I., Levin, B., Berry, D.A. (2013): Meta-analyses of colorectal cancer risk factors. *Cancer Causes Control* 24 (6), 1207-1222.

Kocarnik, J.M., Hua, X., Hardikar, S., Robinson, J., Lindor, N.M., Win, A.K., et al. (2017): Long-term weight loss after colorectal cancer diagnosis is associated with lower survival: The Colon Cancer Family Registry. *Cancer* 123 (23), 4701-4708.

Kuo, Y.-H., Shi, C.-S., Huang, C.Y., Huang, Y.-C., Chin, C.-C. (2018): Prognostic significance of unintentional body weight loss in colon cancer patients. *Mol Clin Oncol.* 8 (4), 539-543.

Yang, Y., Wang, G., He, J., Ren, S., Wu, F., Zhang, J., Wang, F. (2017): Gender differences in colorectal cancer survival: A meta-analysis. *Int J Cancer*. 141 (10), 1942-1949.

Majek, O., Gondos, A., Jansen, L., Emrich, K., Holleczek, B., Katalinic, A., et al. (2013): Sex differences in colorectal cancer survival: population-based analysis of 164,996 colorectal cancer patients in Germany. *PLoS One* 8 (7), e68077.

MeDietetic Software, 2021. https://nutrition.medietetic.com/

Mertens, E., Kuijsten, A., Dofková, M., Mistura, L., D'Addezio, L., Turrini, A., et al. (2019): Geographic and socioeconomic diversity of food and nutrient intakes: a comparison of four European countries. *Eur J Nutr.* 58 (4), 1475-1493.

Meyerhardt, J.A., Kroenke, C.H., Prado, C.M., Kwan, M.L., Castillo, A., Weltzien, E., et al. (2017): Association of Weight Change after Colorectal Cancer Diagnosis and Outcomes in the Kaiser Permanente Northern California Population. *Cancer Epidemiol Biomarkers Prev.* 26 (1), 30-37.

Rossi, M., Anwar, M.J., Usman, A., Keshavarzian, A., Bishehsari, F. (2018): Colorectal Cancer and Alcohol Consumption—Populations to Molecules. *Cancers* 10 (2), 38.

Seidelmann, S.B., Claggett, B., Cheng, S., Henglin, M., Shah, A., Steffen, L.M. et al. (2019): Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. *Lancet Public Health* 3 (9), e419-e428.

Steele, R.S., Park, E.G., Johnson, K.E., Stojadinović, A., Causey, W.M. (2014): The Impact of Age on Colorectal Cancer Incidence, Treatment, and Outcomes in an Equal-Access Health Care System. *Dis Colon Rectum* 57 (3), 303-310.

Voigtländer, S., Hakimhashemi, A., Grundmann, N., Rees, F., Meyer, M., Algül, H., Müller-Nordhorn, J. (2022): Trends of colorectal cancer incidence according to age, anatomic site, and histological subgroup in Bavaria: A registry-based study. *Front Oncol.* 12, 904546.

Zhao, Z., Feng, Q., Yin, Z., Shuang, J., Bai, B., Yu, P., et al. (2017) Red and processed meat consumption and colorectal cancer risk: a systematic review and meta-analysis. *Oncotarget* 8 (47), 83306-83314.

Walter, V., Jansen, L., Ulrich, A., Roth, W., Bläker, H., Chang-Claude, J., et al. (2017): Alcohol consumption and survival of colorectal cancer patients: a population-based study from Germany. *Am J Clin Nutr* 103 (6), 1497-1506.

WCRF, World Cancer Research Fund/ AICR, American Institute for Cancer Research (2018): Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018. https://www.wcrf.org/sites/default/files/Colorectal-cancer-report.pdf

WCRFI, World Cancer Research Fund International (2020): Continous Update Project – Colorectal Cancer Statistics. https://www.wcrf.org/dietandcancer/cancer-trends/colorectal-cancer-statistics

WHO, World Health Organization (2010): A healthy lifestyle - WHO recommendations. https://www.who.int/europe/news-room/fact-sheets/item/a-healthylifestyle---who-recommendations

WHO, World Health Organization. International Agency for Research on Cancer (2020): GLOBOCAN Cancer Today Data. https://gco.iarc.fr/today/home

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THE INFLUENCE OF VITAMIN D ON THE PREVENTION AND TREATMENT OF MALIGNANT DISEASES

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review paper

Summary

Vitamin D has long been recognized for its essential role in maintaining healthy bones and teeth. In recent years, there has been increasing research into the potential influence of vitamin D on malignant diseases. It is estimated that more than 10 million people die from cancer each year, making it one of the leading causes of death globally. While many factors contribute to cancer development, including genetic and environmental factors, research has suggested that vitamin D may play a role in reducing the risk of certain types of cancer. Vitamin D has numerous physiological functions, such as anti-inflammatory, immunomodulatory, proapoptotic, and antiangiogenic effects. Preclinical studies have shown that it could inhibit carcinogenesis, slowing tumor progression by stimulating cell differentiation and inhibiting cancer cell proliferation. Several types of cancer have been studied concerning vitamin D. While more research is needed, some evidence suggests that vitamin D may play a role in reducing the risk of certain types of cancer. Maintaining adequate vitamin D levels through sunlight exposure, diet, or supplementation may be essential in promoting overall health and reducing the risk of malignant diseases.

Keywords: cancer prevention, malignant diseases, vitamin D

Introduction

Malignant diseases are the leading cause of mortality in the world. They are responsible for 10 million deaths in 2020 and cause every sixth death. The most common cancer sites are breast, lung, colon, and prostate. Risk factors for most malignancies include smoking, high body mass index, alcohol consumption, reduced fruit and vegetable intake, and lack of physical activity (Global Cancer Observatory, 2022). One out of three people in Croatia will be diagnosed with cancer during their lifetime. Fortunately, progress in diagnosing and treating malignant diseases has led to a decrease in mortality and an increasing number of people who survive many years after diagnosis. In most developed European countries, the death rate from cancer decreases yearly. In Croatia, mortality from cancer reduces by 2% on average every year (Croatian Institute for Public Health, 2023). In the prevention and treatment of cancer, there are currently no clear guidelines on the additional compensation of specific vitamins and minerals (Harvie, 2014).

Vitamin D

Sources of Vitamin

Ergocalciferol and cholecalciferol are two different forms of vitamin D, and they differ in their natural sources and production pathways. Ergocalciferol (Vitamin D2) is derived from plant sources; certain fungi, including yeast and mushrooms, synthesize it when exposed to ultraviolet (UV) light. Plants, such as some types of algae, can also produce ergosterol, which can be converted into ergocalciferol through a similar UV light-mediated process. Cholecalciferol (Vitamin D3) is primarily derived from animal sources, such as fatty fish (e.g., salmon, mackerel) and fish liver oils (Benedik, 2022) (Table 1). It is synthesized in the skin of animals, including humans, when 7-dehydrocholesterol, a compound present in the skin, is exposed to UV-B radiation from sunlight. Regarding supplementation, both ergocalciferol (D2) and cholecalciferol (D3) are used to address vitamin D deficiency. However, cholecalciferol (D3) is the most commonly used form for supplementation due to its greater effectiveness in raising and maintaining vitamin D levels in the body. Cholecalciferol is also considered the more bioavailable and potent form of vitamin D. It closely resembles the natural form of vitamin D produced in the skin, making it more readily utilized by the body. Ergocalciferol (D2) is still used in some cases, such as for vegans who prefer a plant-based source or for patients with specific medical conditions (Dominguez et al., 2021; Cashman et al., 2014).

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Table 1. Foods rich in vitamin D

Food	Amount	Vitamin D (IU)
Egg yolk	1	42
Salmon	100 g	360
Swoldfish	300 g	566
Sardine	50 g	250
Milk	1 cup	98
Cod liver oil	1 soup spoon	1360
Tuna	300 g	154

Vitamin D metabolism

Vitamin D obtained from food, supplements, or sun exposure is biologically inactive and must undergo two hydroxylations to be activated. In the blood, it is transported by vitamin D-binding protein (VDBP) to the liver, where it is hydroxylated to produce 25-hydroxyvitamin D3 (25(OH)D3), i.e., calcidiol, the primary circulating form of vitamin D with a half-life of about 2-3 weeks. The final step of hydroxylation occurs in the renal proximal convoluted tubules, where CYP27B1 metabolizes 25 (OH)D3 into calcitriol, 25(OH)2D3, the functional and hormonally active form of vitamin D. The half-life of calcitriol is about 6 - 8 hours, which is why it is not a good indicator of vitamin D status in the body. To determine the concentration of vitamin D, the calcidiol level is monitored. In the kidney, CYP27B1 is regulated by parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and calcitriol itself. 25(OH)D3 can also be converted to 24.25(OH)2D3 by CYP24A1, limiting the amount of calcitriol when its circulating level is high (Christakos et al., 2015; Peixoto et al., 2022).

VDBP is a multifunctional protein primarily known for transporting vitamin D and its metabolites in the bloodstream. However, emerging research suggests that VDBP may have additional biological functions, including anti-inflammatory and immunomodulatory effects, independent of its role as a vitamin D transporter. VDBP inhibits the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), in various cell types. VDBP has also been suggested to influence the maturation and function of immune cells, including dendritic cells, macrophages, and T cells. It also exhibits antimicrobial properties by binding to microorganisms, such as bacteria and viruses, and enhancing their clearance by immune cells. It can facilitate the opsonization and phagocytosis of pathogens, contributing to the innate immune response (Chun et al., 2010).

The recommended intake of vitamin D

Vitamin D promotes calcium absorption in the intestines, enables normal bone mineralization by maintaining the concentration of calcium and phosphate in the serum, is needed for bone remodeling, and promotes the reduction of inflammation. Vitamin D is important in preventing the onset and alleviating the clinical picture of multiple sclerosis, rheumatoid arthritis and inflammatory bowel diseases. Vitamin D deficiency is also associated with schizophrenia, depression and lung diseases. Recommended values of 25(OH)D are 30-50 ng/mL (75-125 nmol/L). Mild insufficiency refers to a relatively low vitamin D level but still within a suboptimal range. This stage may be characterized by serum 25-hydroxyvitamin D levels between 20 and 30 ng/mL (50-75 nmol/L). There may not be significant clinical symptoms or complications at this stage, but it indicates that vitamin D levels are not at an ideal class for optimal health. Moderate insufficiency indicates a further decline in vitamin D levels. This stage may be defined by serum 25-hydroxyvitamin D levels between 10 and 20 ng/mL (30-50 nmol/L). Severe insufficiency or deficiency represents significantly low vitamin D levels. This stage may be characterized by serum 25-hydroxyvitamin D levels below 10 ng/mL (30 nmol/L) (Vranešić et al., 2016; Holick et al., 2011). Observational studies have shown that over 40% of Europeans have vitamin D deficiency (Amrein et al., 2020). In the elderly, the numbers are much more dramatic, and some studies have shown that only 15% of older adults have optimal vitamin D status (Kweder et al., 2018). Inadequate vitamin D status is associated with muscle weakness, functional impairment, depression, and increased risk of falls and fractures. Hazards for the appearance of a deficit include a dark complexion, too little sun exposure, older age, obesity, and certain types of pharmacotherapy (antiepileptics, metformin, bisphosphonates, cytostatics, thiazolidinediones, diuretics, calcium channel blockers, ACE inhibitors) (Gröber et al., 2012). The

recommended dietary vitamin D intake for adults over 18 is 600 IU, increasing to 800 IU after age 71. However, to raise serum 25(OH)D levels continuously above 30 ng/mL (75 nmol/L), it is recommended to take at least 1500 – 2000 IU/day of vitamin D. In adults with known vitamin D deficiency, treatment with 50 000 IU of vitamin D2 or vitamin D3 once weekly for eight weeks or 6000 IU of vitamin D2 or D3 daily to achieve a serum 25(OH)D level above 30 ng/mL, followed by maintenance of 1500–2000 IU /day is recommended. In obese patients, patients with malabsorption syndrome, and patients taking medications that affect vitamin D metabolism, a two to three times higher dose (at least 6000-10 000 IU/day) of vitamin D is recommended to treat vitamin D deficiency until reaching a level of 25(OH)D above 30 ng/mL, and after that maintenance of 3000–6000 IU/day (Holick et al., 2011). Vitamin D supplementation has both calcemic and non-calcemic effects. Low-dose supplementation maintains calcium levels and supports bone health, while high-dose supplementation can increase serum calcium levels, potentially affecting organs. In addition, adequate vitamin D levels may reduce the risk of autoimmune diseases and respiratory infections, improve muscle strength and reduce fall risk, positively impact mood and mental well-being, and play a role in preventing and managing conditions like cardiovascular disease, diabetes, and certain cancers (Holick et al.,2011; Ross et al., 2011).

Liver diseases can contribute to vitamin D deficiency through multiple mechanisms. The liver plays a crucial role in the synthesis and activation of vitamin D. In liver diseases such as cirrhosis, impaired liver function can lead to reduced production of 25-hydroxyvitamin D, the primary circulating form of vitamin D. This can result in lower overall vitamin D levels in the body. Furthermore, liver diseases can disrupt the metabolism of vitamin D and its binding proteins, affecting its availability and utilization. As a result, individuals with liver diseases are at an increased risk of developing vitamin D deficiency (Kitson et al., 2012; Arteh et al., 2010). Also, certain gastroenterological diseases can interfere with the absorption and metabolism of vitamin D, leading to reduced biological availability. Conditions such as Crohn's, celiac, and inflammatory bowel disease (IBD) can impair the absorption of fat-soluble vitamins, including vitamin D, due to intestinal inflammation, malabsorption, or surgical interventions. Additionally, conditions affecting the bile acid metabolism or the bile ducts, such as primary biliary cholangitis, can disrupt the enterohepatic circulation of vitamin D and impair its absorption and utilization. Consequently, individuals with these gastroenterological conditions may experience reduced levels of biologically active vitamin D (Ardizzone et al., 2011; Lin et al., 2016). Kidney diseases can lead to vitamin D deficiency due to impaired renal function and decreased synthesis of active vitamin D metabolites. The kidneys are crucial in converting inactive vitamin D (calcidiol) into its active form (calcitriol). In conditions such as chronic kidney disease (CKD) or end-stage renal disease (ESRD), there is a decline in renal function, resulting in reduced production of calcitriol. This can lead to inadequate activation of vitamin D and subsequent deficiency. Moreover, kidney diseases can cause urinary losses of vitamin D-binding protein, further contributing to lower vitamin D levels (Wolf et al, 2007; Isakova et al, 2011).

Vitamin D and cancer

Observational studies have established an association between low vitamin D concentrations and an increased prevalence of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease. Many studies indicate a connection between low vitamin D concentrations and certain cancers (Wang et al., 2017). It has been shown that patients with a higher level of circulating vitamin D in the blood have a significantly lower risk of death, especially in the case of colorectal cancer. Such optimistic results support the concept of targeted intervention with vitamin D (Jeon et al., 2018). Vitamin D has numerous physiological functions, such as anti-inflammatory, immunomodulatory, proapoptotic, and antiangiogenic effects. Preclinical studies have shown that it could inhibit carcinogenesis, slowing tumor progression by stimulating cell differentiation and inhibiting cancer cell proliferation. Vitamin D can therefore inhibit tumor invasiveness and its propensity to metastasize, potentially reducing cancer mortality (Bouillon et al., 2006; Bouillon et al., 2008).

Colorectal cancer

According to the World Health Organization, colorectal cancer is the most frequently diagnosed cancer in men and the second in order in women (Global Cancer Observatory, 2022). Although the incidence of colorectal cancer has decreased in the total population over the last decades, it has increased in the population under 50. Many studies have shown how diet and lifestyle have a significant influence on the development of the disease. A diet rich in red meat and poor in fiber, fruits, and vegetables increases the risk of colorectal cancer, as does insufficient physical activity. The impact of low calcium intake and vitamin

D hypovitaminosis on the risk of disease and worse clinical outcomes in patients with colorectal cancer is also known (Thanikachalam et al., 2019). Several meta-analyses have reported an association between lower vitamin D levels and increased colorectal cancer risk. In a study that collected data from 17 cohorts, including 5706 patients with colorectal cancer and 7107 controls, it was demonstrated that higher levels of circulating vitamin D lead to a statistically significant reduction in the risk of colorectal cancer in women and a non-statistically significant reduction in men (McCullough et al., 2017).

The biological action of calcitriol is mediated by the vitamin D receptor (VDR), which is a member of the steroid hormone receptor family. VDR was first identified in the small intestine and was later found in almost all tissues, while the intestine is the organ with the highest expression of VDR. Altered expression of VDR and other essential proteins in the synthesis and catabolism of vitamin D has been observed in many different tumors. CYP27B1 and VDR are strongly expressed during the early progression of colorectal cancer in well-differentiated tumors. They are downregulated in poorly differentiated tumors, while CYP24A1 is upregulated, suggesting an autocrine/paracrine growth control by active metabolites of vitamin D in colorectal tissue as a restriction against tumor progression (Christakos et al., 2015; Peixoto et al., 2022). VDR expression increases in hyperplastic polyps and the early stages of tumorigenesis but decreases in the late stages of poorly differentiated tumors and is absent in associated metastases. Colorectal cancer with higher expression of VDR responds better to the addition of calcitriol, but regulation of VDR in tumor cells by some transcription factors reduces its anticancer effect (Matusiak et al., 2005; Christakos et al., 2015).

Vitamin D has been shown to play a significant role in preventing colon cancer by regulating the homeostasis of the intestinal epithelium through multiple mechanisms. It exerts its effects by modulating the oncogenic Wnt signaling pathway and inhibiting tumor-promoting inflammation. Vitamin D acts as a negative regulator of the Wnt signaling pathway, which plays a crucial role in the development and progression of colon cancer. The Wnt pathway regulates the growth and differentiation of intestinal epithelial cells: and interacts with Wnt signaling components, such as β-catenin and the Wnt co-receptor LRP5/6, to suppress aberrant activation of the pathway. This modulation helps maintain the balance between cell proliferation and differentiation, preventing the uncontrolled growth of colon cancer cells (Palmer et al, 2011; Larriba el al., 2014).

Vitamin D also possesses anti-inflammatory properties that help inhibit tumor-promoting inflammation in the colon. Chronic inflammation is a risk factor for colon cancer development and progression. Vitamin D exerts its anti-inflammatory effects by modulating the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while promoting the production of anti-inflammatory cytokines. This modulation helps create an environment that discourages tumor growth and progression. (Byers et al., 2012; Bharti et al., 2002).

Growing evidence shows that vitamin D is crucial in regulating the gut microbiota and promoting a healthy gut environment. Dysbiosis, or an imbalance in gut microbiota, has been linked to colorectal cancer (CRC) development and progression. Vitamin D has been shown to exert indirect antitumor effects in CRC by modulating the gut microbiota. Studies have demonstrated that vitamin D deficiency is associated with changes in the composition and function of the gut microbiota, with a reduction in beneficial bacteria such as Bifidobacterium and Lactobacillus and an increase in potentially harmful bacteria such as Fusobacterium and Enterobacteriaceae. In addition, vitamin D supplementation has been shown to improve gut microbial diversity and promote the growth of beneficial bacteria in animal models of CRC (Song et al., 2020; Sukik et al., 2023).

One study examined the association between pre-diagnosis plasma 25-hydroxyvitamin D levels and survival outcomes in patients with stage I-IV CRC. Higher vitamin D levels were associated with improved overall survival and disease-free survival in patients with stage III CRC, but no significant association was observed in patients with other stages (Ng et al., 2008). Other study investigated the association between preoperative serum vitamin D levels and survival outcomes in patients with CRC. Higher vitamin D levels were associated with improved overall survival and disease-free survival, particularly in patients with stage III CRC (Mezawa et al., 2010).

Breast cancer

Breast cancer is the most common cancer in women. Every year, 2 million women worldwide fall ill with this disease. Numerous risk factors for breast cancer have been identified, including race, ethnicity, family history of cancer, genetic traits, and modifiable exposures such as increased alcohol consumption, physical inactivity, and exogenous hormones. Parity, older age at first pregnancy may influence breast cancer risk through long-term effects on sex hormone

levels or other biological mechanisms (Coughlin et al., 2019). Many studies have examined the association between vitamin D concentration and breast cancer risk, but the results are inconsistent. One meta-analysis showed that women with the highest quantile of circulating 25(OH)D had a 45% reduced risk of breast cancer compared to women with the lowest quantile (Chen et al., 2010). Another meta-analysis showed a gradual inverse association above the threshold of 27 ng/mL, but with flattening of the effects above 35 ng/mL in postmenopausal women but not in premenopausal women (Bauer et al., 2013). A randomized trial of over 25 000 men and women found no significant effect of vitamin D (2000 IU) with or without omega-3 supplementation on breast cancer incidence (Manson et al., 2020).

In breast cancer tissue, VDR expression has been reported to be inversely correlated with breast cancer aggressiveness. In benign breast lesions, VDR is significantly more pronounced than in breast cancer lesions (in situ and invasive). Also, VDR expression is higher in luminal A BC than in triple-negative breast cancer, which is the most aggressive type. Higher overall VDR expression in breast cancer is associated with tumor characteristics such as lower grade, smaller size, ER/PR positivity, lower Ki67 expression, and lower mortality risk. Previous studies have shown that VDR expression in breast cancer tissue decreased during tumor progression. Further research is needed on whether VDR expression can be a potential biomarker for breast cancer progression. (Vanhevel et al., 2022; Lopes et al., 2012).

Prostate cancer

About 1 in 8 men will be diagnosed with prostate cancer during their lifetime. About 6 out of 10 cases are diagnosed in men who are 65 or older, and it is rare in men under 40. Risk factors include age, family history, insulin-like growth factor, sexually transmitted diseases, obesity, smoking, alcohol consumption, vasectomy, and diet (Perdana et al., 2016). Studies investigating the association between 25(OH)D levels and cancer still did not answer the requested questions. A meta-analysis showed that men with elevated serum 25(OH)D levels have a higher risk of developing prostate cancer than men with lower serum 25(OH)D levels (Xu et al., 2014). One study found that the relationship varied by aggressiveness; higher levels of 25(OH)D increase the risk of low-grade prostate cancer (Gleason score 2-6) but reduce the risk of high-grade disease (Gleason score 8-10) (Schenk et al., 2014). A study involving 7808 participants showed that higher vitamin D levels could reduce the risk of death in prostate cancer patients, concluding that vitamin D is an essential protective factor in the progression and prognosis of prostate cancer (Song et al., 2018).

Bladder cancer

Bladder cancer occurs three times more often in men than women, and the frequency increases with age. The most significant risk factor is smoking, which increases the risk of cancer by a minimum of 3 times. Over 50% of people with bladder cancer are smokers. Several studies have investigated the association between 25 (OH)D3 and bladder cancer. One study examined the effect of vitamin D supplementation on the effectiveness of cisplatin therapy used to treat bladder cancer. The results showed that low serum 25(OH)D3 levels were significantly associated with a worse response to cisplatin. Pretreatment of 25(OH)D3-deficient mice reduced tumor volume compared to cisplatin monotherapy (Bunch et al., 2019). The results of another study showed that a concentration of 25(OH)D3 ≥74 nmol/L is associated with a 60% lower risk of bladder cancer (Zhao et al., 2016). One study revealed that lower levels of vitamin D were associated with an increased risk of bladder cancer. Furthermore, the study examined the role of VDBP, a protein involved in vitamin D transport, and its association with bladder cancer risk. Interestingly, the findings suggested that higher VDBP levels were associated with a decreased risk of bladder cancer. This indicates that VDBP may play a significant role in the vitamin D pathway and its potential impact on bladder cancer development. These findings emphasize the importance of considering both vitamin D and VDBP levels in assessing the risk of bladder cancer. Further research is warranted to elucidate the underlying mechanisms by which vitamin D and VDBP exert their effects and to explore potential preventive strategies and therapeutic interventions targeting this pathway (Hektoen et al., 2021)

Lung cancer

Lung cancer is the most common cause of death from cancer. Smoking is known as the most critical risk factor, but there is still not much evidence about dietary supplements that would serve as lung cancer prevention. So far, several studies have been conducted that have examined the connection between vitamin D and lung cancer. One meta-analysis showed a significant reduction in lung cancer risk by 5% for every ten nmol/L increase in 25(OH)D3 concentration (Chen et al., 2015). Another study showed that vitamin D supplementation could improve survival in patients with early-stage lung adenocarcinoma (Akiba et al.,

2018). Another meta-analysis showed that the combination of vitamin D and calcium supplementation significantly reduced the incidence of lung cancer. Further studies are needed to examine whether a higher concentration of 25(OH)D in the serum could have a preventive role in lung cancer (Sun et al., 2021). Several studies have shown that vitamin D plays a crucial role in preventing lung cancer tumor growth, migration, and proliferation. One of the mechanisms through which vitamin D exerts its anticancer effects is by downregulating Histidine-rich calcium-binding protein (HRC). HRC is a protein involved in calcium homeostasis and is overexpressed in several types of cancer, including lung cancer. In one study, it was demonstrated that vitamin D treatment significantly inhibited lung cancer cell growth, migration, and proliferation in vitro and in vivo. The authors showed that vitamin D downregulated HRC expression in lung cancer cells, leading to a decrease in intracellular calcium concentration and subsequently inhibiting cancer cell growth (Liu et al., 2020).

Ovarian cancer

Ovarian cancer is called the "silent killer" because it is usually diagnosed late when the chances of a cure are already meager. Most cancers are diagnosed in stage III (51%) or IV (29%), where the five-year survival rate is only 42% and 26%, respectively. The risk is higher in women who have not given birth, who have given birth late, and those with later menopause. Pregnancy and oral contraceptives reduce the risk of cancer. The connection with environmental factors has not been proven with certainty (Piatek et al., 2022; Roett et al., 2009). A meta-analysis with almost a million participants concluded that vitamin D intake could not reduce the risk of ovarian cancer (Xu et al., 2021). On the other hand, a study conducted in Australia concluded that exposure to ambient ultraviolet radiation could reduce the risk of epithelial ovarian cancer (Tran et al., 2012). In another cohort study from Australia, higher serum 25(OH)D levels at diagnosis were shown to correlate significantly with more prolonged survival in women diagnosed with invasive ovarian cancer (Webb et al., 2015).

Pancreatic cancer

Pancreatic cancer is an insidious disease because, at the time of diagnosis, in 85% of cases, it has already spread to local structures or has metastasized to the liver and lungs. Risk factors include smoking, obesity, a positive personal or family history of diabetes or chronic pancreatitis, and various genetic syndromes (e.g., MEN1, Lynch, VHL) (Klein et al.,2021). One study showed that people with the highest concentrations of 25 (OH)D have twice the risk of pancreatic cancer (Stolzenberg-Solomon et al.,2010). On the other hand, another study showed that higher levels of 25(OH)D were associated with a lower risk of pancreatic cancer (Wolpin et al., 2012). One meta-analysis studied the impact of vitamin supplementation and the risk of pancreatic cancer. It showed that vitamin D reduces the risk of pancreatic cancer by 25% and vitamin B 12 by 27% (Liu et al., 2018). A meta-analysis of 1 206 011 participants concluded that circulating 25(OH)D concentration is not associated with pancreatic cancer risk (Liu et al., 2013). Given the inconsistency of these studies, further studies are needed to determine whether there is an association between 25(OH)D concentration with this cancer.

Conclusion

Cancer is a complex and heterogeneous disease with different risk factors and etiology depending on the specific location and underlying biology. Research has shown that vitamin D may protect against certain types of cancer, such as colorectal, bladder, and lung cancer, while potentially increasing the risk for others, including prostate and pancreatic cancer. However, the evidence regarding vitamin D supplementation for cancer prevention is still insufficient and inconsistent. High-dose vitamin D supplementation is not recommended for cancer prevention at this time. The risks of bone loss, osteoporosis, and fractures are well-known in patients with malignant disease. Therefore, assessing and addressing vitamin D deficiency in these patients is essential. Monitoring 25(OH)D levels and providing appropriate replacement therapy for vitamin D deficiency can be beneficial. Patients undergoing treatments that negatively affect bone health, such as ovarian suppression/ablation, aromatase inhibitors, and androgen deprivation therapy, are advised to follow a calcium-rich diet, moderate exercise, and take daily vitamin D supplementation of 1000-2000 IU. In addition to vitamin D supplementation, maintaining a healthy lifestyle and practicing cancer prevention strategies are crucial. This includes maintaining a healthy weight, avoiding tobacco and excessive alcohol consumption, and participating in regular cancer screenings.

References

Akiba, T., Morikawa, T., Odaka, M., Nakada, T., Kamiya. N., Yamashita, M., Yabe, M., Inagaki, T., Asano, H., Mori, S., Tsukamoto, Y., Urashima, M. (2018): Vitamin D Supplementation and Survival of Patients with Non-small Cell Lung Cancer: A Randomized, Double-Blind, Placebo-Controlled Trial. *Clin Cancer Res*. 24(17), 4089-4097.

Amrein, K., Scherkl, M., Hoffmann, M., Neuwersch-Sommeregger, S., Köstenberger, M., Tmava Berisha, A., Martucci, G., Pilz, S., & Malle, O. (2020): Vitamin D deficiency 2.0: an update on the current status worldwide. *European journal of clinical nutrition* 74(11), 1498–1513.

Ardizzone, S., Cassinotti, A., Bevilacqua, M., Clerici, M., & Porro, G. B. (2011): Vitamin D and inflammatory bowel disease. *Vitamins and hormones* 86, 367–377.

Arteh, J., Narra, S., & Nair, S. (2010): Prevalence of vitamin D deficiency in chronic liver disease. *Digestive diseases and sciences* 55(9), 2624–2628.

Bauer, S. R., Hankinson, S. E., Bertone-Johnson, E. R., & Ding, E. L. (2013): Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies. *Medicine* 92(3), 123–131.

Benedik E. (2022): Sources of vitamin D for humans. *International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal international de vitaminologie et de nutrition* 92(2), 118–125.

Bharti, A. C., & Aggarwal, B. B. (2002): Nuclear factor-kappa B and cancer: its role in prevention and therapy. *Biochemical pharmacology* 64(5-6), 883–888.

Bouillon, R., Carmeliet, G., Verlinden, L., van Etten, E., Verstuyf, A., Luderer, H. F., Lieben, L., Mathieu, C., & Demay, M. (2008): Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocrine reviews* 29(6), 726–776.

Bouillon, R., Eelen, G., Verlinden, L., Mathieu, C., Carmeliet, G., & Verstuyf, A. (2006): Vitamin D and cancer. *The Journal of steroid biochemistry and molecular biology* 102(1-5), 156–162.

Bunch, B. L., Ma, Y., Attwood, K., Amable, L., Luo, W., Morrison, C., Guru, K. A., Woloszynska-Read, A., Hershberger, P. A., Trump, D. L., & Johnson, C. S. (2019): Vitamin D_3 enhances the response to cisplatin in bladder cancer through VDR and TAp73 signaling crosstalk. *Cancer medicine* 8(5), 2449–2461.

Byers, S. W., Rowlands, T., Beildeck, M., & Bong, Y. S. (2012): Mechanism of action of vitamin D and the vitamin D receptor in colorectal cancer prevention and treatment. *Reviews in endocrine & metabolic disorders* 13(1), 31–38.

Cashman, K. D., & Kiely, M. (2014): Recommended dietary intakes for vitamin D: Where do they come from, what do they achieve and how can we meet them?. *Journal of human nutrition and dietetics : the official journal of the British Dietetic Association* 27(5), 434–442.

Chen, G. C., Zhang, Z. L., Wan, Z., Wang, L., Weber, P., Eggersdorfer, M., Qin, L. Q., & Zhang, W. (2015): Circulating 25-hydroxyvitamin D and risk of lung cancer: a dose-response meta-analysis. *Cancer causes & control : CCC* 26(12), 1719–1728.

Chen, P., Hu, P., Xie, D., Qin, Y., Wang, F., & Wang, H. (2010): Meta-analysis of vitamin D, calcium and the prevention of breast cancer. *Breast cancer research and treatment* 121(2), 469–477.

Christakos, S., Dhawan, P., Verstuyf, A., Verlinden, L., & Carmeliet, G. (2016): Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. *Physiological reviews* 96(1), 365–408.

Chun, R. F., Lauridsen, A. L., Suon, L., Zella, L. A., Pike, J. W., Modlin, R. L., Martineau, A. R., Wilkinson, R. J., Adams, J., & Hewison, M. (2010): Vitamin D-binding protein directs monocyte responses to 25-hydroxy- and 1,25-dihydroxyvitamin D. *The Journal of clinical endocrinology and metabolism* 95(7), 3368–3376.

Coughlin S. S. (2019): Epidemiology of Breast Cancer in Women. *Advances in experimental medicine and biology* 1152, 9–29.

Croatian Institute for Public Health. World Cancer Day 2023. Available on: https://www.hzjz.hr/aktualnosti/svjetski-dan-raka-2023/5/ (Accessed on February 25, 2023).

Dominguez, L. J., Farruggia, M., Veronese, N., & Barbagallo, M. (2021): Vitamin D Sources, Metabolism, and Deficiency: Available Compounds and Guidelines for Its Treatment. *Metabolites* 11(4), 255.

Global Cancer Observatory. International Agency for Research on Cancer. World Health Organization. Available at: https://gco.iarc.fr/ (Accessed on February 23, 2023).

Gröber, U., & Kisters, K. (2012): Influence of drugs on vitamin D and calcium metabolism. *Dermato-endocrinology* 4(2), 158–166.

Harvie M. (2014): Nutritional supplements and cancer: potential benefits and proven harms. *American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Annual Meeting* e478–e486.

Hektoen, H. H., Robsahm, T. E., Stenehjem, J. S., Axcrona, K., Babigumira, R., Mondul, A. M., Gislefoss, R. E., & Andreassen, B. K. (2021): Vitamin D and Vitamin D-binding protein and risk of bladder cancer: A nested case-control study in the Norwegian Janus Serum Bank Cohort. *Cancer medicine* 10(12), 4107–4116.

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., Murad, M. H., Weaver, C. M., & Endocrine Society (2011): Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism* 96(7), 1911–1930.

Isakova, T., Xie, H., Barchi-Chung, A., Vargas, G., Sowden, N., Houston, J., Wahl, P., Lundquist, A., Epstein, M., Smith, K., Contreras, G., Ortega, L., Lenz, O., Briones, P., Egbert, P., Ikizler, T. A., Jueppner, H., & Wolf, M. (2011): Fibroblast growth factor 23 in patients undergoing peritoneal dialysis. *Clinical journal of the American Society of Nephrology : CJASN* 6(11), 2688–2695.

Jeon, S. M., & Shin, E. A. (2018): Exploring vitamin D metabolism and function in cancer. *Experimental & molecular medicine* 50(4), 1–14.

Kitson, M. T., & Roberts, S. K. (2012): D-livering the message: the importance of vitamin D status in chronic liver disease. *Journal of hepatology* 57(4), 897–909.

Klein AP. (2021): Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. *Nat Rev Gastroenterol Hepatol* 18(7), 493-502.

Kweder, H., & Eidi, H. (2018): Vitamin D deficiency in elderly: Risk factors and drugs impact on vitamin D status. *Avicenna journal of medicine* 8(4), 139–146.

Larriba, M. J., González-Sancho, J. M., Bonilla, F., & Muñoz, A. (2014): Interaction of vitamin D with membrane-based signaling pathways. *Frontiers in physiology* 5, 60.

Lin, Z., & Li, W. (2016): The Roles of Vitamin D and Its Analogs in Inflammatory Diseases. *Current topics in medicinal chemistry* 16(11), 1242–1261.

Liu, N., Li, X., Fu, Y., Li, Y., Lu, W., Pan, Y., Yang, J., & Kong, J. (2020): Inhibition of lung cancer by vitamin D depends on downregulation of histidine-rich calcium-binding protein. *Journal of advanced research* 29, 13–22.

Liu, S. L., Zhao, Y. P., Dai, M. H., You, L., Wen, Z., & Xu, J. W. (2013): Vitamin D status and the risk of pancreatic cancer: a meta-analysis. *Chinese medical journal* 126(17), 3356–3359.

Liu, Y., Wang, X., Sun, X., Lu, S., & Liu, S. (2018): Vitamin intake and pancreatic cancer risk reduction: A meta-analysis of observational studies. *Medicine* 97(13), e0114.

Lopes, N., Carvalho, J., Durães, C., Sousa, B., Gomes, M., Costa, J. L., Oliveira, C., Paredes, J., & Schmitt, F. (2012): 1Alpha,25-dihydroxyvitamin D3 induces de novo E-cadherin expression in triple-negative breast cancer cells by CDH1-promoter demethylation. *Anticancer research* 32(1), 249–257.

Manson, J. E., Bassuk, S. S., Buring, J. E., & VITAL Research Group (2020): Principal results of the VITamin D and OmegA-3 TriaL (VITAL) and updated meta-analyses of relevant vitamin D trials. *The Journal of steroid biochemistry and molecular biology* 198, 105522.

Matusiak, D., Murillo, G., Carroll, R. E., Mehta, R. G., & Benya, R. V. (2005): Expression of vitamin D receptor and 25-hydroxyvitamin D3-1{alpha}-hydroxylase in normal and malignant human colon. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 14(10), 2370–2376.

McCullough, M. L., Zoltick, E. S., Weinstein, S. J., Fedirko, V., Wang, M., Cook, N. R., Eliassen, A. H., Zeleniuch-Jacquotte, A., Agnoli, C., Albanes, D., Barnett, M. J., Buring, J. E., Campbell, P. T., Clendenen, T. V., Freedman, N. D., Gapstur, S. M., Giovannucci, E. L., Goodman, G. G., Haiman, C. A., Ho, G. Y. F., … Smith-Warner, S. A. (2019): Circulating Vitamin D and Colorectal Cancer Risk: An International Pooling Project of 17 Cohorts. *Journal of the National Cancer Institute* 111(2), 158–169.

Mezawa, H., Sugiura, T., Watanabe, M., Norizoe, C., Takahashi, D., Shimojima, A., Tamez, S., Tsutsumi, Y., Yanaga, K., & Urashima, M. (2010): Serum vitamin D levels and survival of patients with colorectal cancer: post-hoc analysis of a prospective cohort study. *BMC cancer* 10, 347.

Mondul, A. M., Weinstein, S. J., Layne, T. M., & Albanes, D. (2017): Vitamin D and Cancer Risk and Mortality: State of the Science, Gaps, and Challenges. *Epidemiologic reviews* 39(1), 28–48.

Ng, K., Meyerhardt, J. A., Wu, K., Feskanich, D., Hollis, B. W., Giovannucci, E. L., & Fuchs, C. S. (2008): Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 26(18), 2984–2991.

Pálmer, H. G., González-Sancho, J. M., Espada, J., Berciano, M. T., Puig, I., Baulida, J., Quintanilla, M., Cano, A., de Herreros, A. G., Lafarga, M., & Muñoz, A. (2001): Vitamin D(3) promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of beta-catenin signaling. *The Journal of cell biology* 154(2), 369–387.

Peixoto, R. D., Oliveira, L. J. C., Passarini, T. M., Andrade, A. C., Diniz, P. H., Prolla, G., Amorim, L. C., Gil, M., Lino, F., Garicochea, B., Jácome, A., & Ng, K. (2022): Vitamin D and colorectal cancer - A practical review of the literature. *Cancer treatment and research communications* 32, 100616.

Perdana, N. R., Mochtar, C. A., Umbas, R., & Hamid, A. R. (2016): The Risk Factors of Prostate Cancer and Its Prevention: A Literature Review. *Acta medica Indonesiana* 48(3), 228–238.

Piatek, K., Schepelmann, M., & Kallay, E. (2022): The Effect of Vitamin D and Its Analogs in Ovarian Cancer. *Nutrients* 14(18), 3867.

Roett, M. A., & Evans, P. (2009): Ovarian cancer: an overview. *American family physician* 80(6), 609–616.

Ross, A. C., Manson, J. E., Abrams, S. A., Aloia, J. F., Brannon, P. M., Clinton, S. K., Durazo-Arvizu, R. A., Gallagher, J. C., Gallo, R. L., Jones, G., Kovacs, C. S., Mayne, S. T., Rosen, C. J., & Shapses, S. A. (2011): The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *The Journal of clinical endocrinology and metabolism* 96(1), 53–58.

Schenk, J. M., Till, C. A., Tangen, C. M., Goodman, P. J., Song, X., Torkko, K. C., Kristal, A. R., Peters, U., & Neuhouser, M. L. (2014): Serum 25-hydroxyvitamin D concentrations and risk of prostate cancer: results from the Prostate Cancer Prevention Trial. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 23(8), 1484–1493.

Song, M., Chan, A. T., & Sun, J. (2020): Influence of the Gut Microbiome, Diet, and Environment on Risk of Colorectal Cancer. *Gastroenterology* 158(2), 322–340.

Song, Z. Y., Yao, Q., Zhuo, Z., Ma, Z., & Chen, G. (2018): Circulating vitamin D level and mortality in prostate cancer patients: a dose-response meta-analysis. *Endocrine connections* 7(12), R294–R303.

Stolzenberg-Solomon, R. Z., Jacobs, E. J., Arslan, A. A., Qi, D., Patel, A. V., Helzlsouer, K. J., Weinstein, S. J., McCullough, M. L., Purdue, M. P., Shu, X. O., Snyder, K., Virtamo, J., Wilkins, L. R., Yu, K., Zeleniuch-Jacquotte, A., Zheng, W., Albanes, D., Cai, Q., Harvey, C., Hayes, R., … Kolonel, L. N. (2010): Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *American journal of epidemiology* 172(1), 81–93.

Sukik, A., Alalwani, J., & Ganji, V. (2023): Vitamin D, Gut Microbiota, and Cardiometabolic Diseases-A Possible Three-Way Axis. *International journal of molecular sciences* 24(2), 940.

Sun, K., Zuo, M., Zhang, Q., Wang, K., Huang, D., & Zhang, H. (2021): Anti-Tumor Effect of Vitamin D Combined with Calcium on Lung Cancer: A Systematic Review and Meta-Analysis. *Nutrition and cancer* 73(11-12), 2633–2642.

Thanikachalam, K., & Khan, G. (2019): Colorectal Cancer and Nutrition. *Nutrients* 11(1), 164.

Tran, B., Jordan, S. J., Lucas, R., Webb, P. M., Neale, R., & Australian Ovarian Cancer Study Group (2012): Association between ambient ultraviolet radiation and risk of epithelial ovarian cancer. *Cancer prevention research (Philadelphia, Pa.)* 5(11), 1330–1336.

Vanhevel, J., Verlinden, L., Doms, S., Wildiers, H., & Verstuyf, A. (2022): The role of vitamin D in breast cancer risk and progression. *Endocrine-related cancer* 29(2), R33–R55.

Vranešić Bender, D., Giljević, Z., Kušec, V., Laktašić Žerjavić, N., Bošnjak Pašić, M., Vrdoljak, E., ... Krznarić, Ž. (2016): SMJERNICE ZA PREVENCIJU, PREPOZNAVANJE I LIJEČENJE NEDOSTATKA VITAMINA D U ODRASLIH. *Liječnički vjesnik* 138 (5-6), 0-0.

Wang, H., Chen, W., Li, D., Yin, X., Zhang, X., Olsen, N., & Zheng, S. G. (2017): Vitamin D and Chronic Diseases. *Aging and disease* 8(3), 346–353.

Webb, P. M., de Fazio, A., Protani, M. M., Ibiebele, T. I., Nagle, C. M., Brand, A. H., Blomfield, P. I., Grant, P., Perrin, L. C., Neale, R. E., & Australian Ovarian Cancer Study Group (2015): Circulating 25-hydroxyvitamin D and survival in women with ovarian cancer. *The American journal of clinical nutrition* 102(1), 109–114.

Wolf, M., Shah, A., Gutierrez, O., Ankers, E., Monroy, M., Tamez, H., Steele, D., Chang, Y., Camargo, C. A., Jr, Tonelli, M., & Thadhani, R. (2007): Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney international* 72(8), 1004–1013.

Wolpin, B. M., Ng, K., Bao, Y., Kraft, P., Stampfer, M. J., Michaud, D. S., Ma, J., Buring, J. E., Sesso, H. D., Lee, I. M., Rifai, N., Cochrane, B. B., Wactawski-Wende, J., Chlebowski, R. T., Willett, W. C., Manson, J. E., Giovannucci, E. L., & Fuchs, C. S. (2012): Plasma 25-hydroxyvitamin D and risk of pancreatic cancer. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 21(1), 82–91.

Xu, J., Chen, K., Zhao, F., Huang, D., Zhang, H., Fu, Z., Xu, J., Wu, Y., Lin, H., Zhou, Y., Lu, W., Wu, Y., & Xia, D. (2021): Association between vitamin D/calcium intake and 25-hydroxyvitamin D and risk of ovarian cancer: a dose-response relationship meta-analysis. *European journal of clinical nutrition* 75(3), 417–429.

Xu, Y., Shao, X., Yao, Y., Xu, L., Chang, L., Jiang, Z., & Lin, Z. (2014): Positive association between circulating 25-hydroxyvitamin D levels and prostate cancer risk: new findings from an updated meta-analysis. *Journal of cancer research and clinical oncology* 140(9), 1465–1477.

Zhao, Y., Chen, C., Pan, W., Gao, M., He, W., Mao, R., Lin, T., & Huang, J. (2016): Comparative efficacy of vitamin D status in reducing the risk of bladder cancer: A systematic review and network meta-analysis. *Nutrition (Burbank, Los Angeles County, Calif.)* 32(5), 515–523.

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KARCINOM GUŠTERAČE – UTJECAJ GENETSKIH I OKOLIŠNIH ČIMBENIKA

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Sažetak

Karcinom gušterače spada u rjeđe oblike karcinoma probavnog sustava. Kasno uzrokuje smetnje, a kada se otkrije najčešće je već u uznapredovalom stadiju. Više od 95 % oboljelih umire unutar 2 godine od postavljanja dijagnoze. Najčešći faktori rizika su: starija životna dob, pušenje, prehrana bogata mastima, a siromašna voćem i povrćem, debljina, smanjena tjelesna aktivnost te ranije bolesti kao što su pankreatitis, šećerna bolest i ciroza jetre. Kod općih smjernica vezanih uz prehranu kao prevenciju razvoja karcinoma gušterače naglasak je na više manjih obroka tijekom dana, pravilnoj kombinaciji nutrijenata unutar obroka i kontroli glikemije. Ovim radom obuhvatit će se preventivne mjere razvoja karcinoma gušterače.

Ključne riječi: gušterača, karcinom, prehrana, autofagija, pretilost

Uvod

Pankreas ili gušterača je neparna žlijezda s endokrinom i egzokrinom funkcijom čiji egzokrini dio čini oko 80 % njenog ukupnog tkiva te izlučuje dvadesetak enzima koji sudjeluju u probavi nutrijenata. Egzokrino žljezdano tkivo gušterače izlučuje enzime nužne za odvijanje probave, a enzimi se pankreasnim sekretom izlijevaju u izvodne kanaliće te potom u akcesorni i glavni pankreatični kanal koji se zajedno s glavnim žučnim kanalom izlijeva u lumen dvanaestnika (duodenuma) gdje se dotad inaktivni enzimi iz proenzimskog transformiraju u aktivni enzimski oblik.
Endokrini dio gušterače tvore Langerhansovi otočići s četiri glavna tipa stanica.
B-stanice koje izlučuju inzulin, α-stanice koje izlučuju glukagon s djelovanjem na glukozu u plazmi (GUP), δ-stanice koje izlučuju somatostatin koji inhibira izlučivanje prethodno navedenih hormona te pankreasni polipeptid (PP) stanice čiji produkt regulira crijevni motilitet, sekreciju nekih gastrointestinalnih (GI) enzima i drugo.
Osim navedenih gušterača posjeduje još dva tipa stanica, a to su D1 koje izlučuju vazoaktivni intestinalni polipeptid (VIP) te enterokromafine stanice u kojima se sintetizira serotonin, a imaju bitnu ulogu u nastanku tumora gušterače.
Karcinom gušterače u najvećem broju slučaja podrazumijeva adenokarcinom spomenutih izvodnih kanala. Uz adenokarcinom postoje i klinički rjeđe viđani oblici tumora gušterače kojih je oko 2 % svih neuroendokrinih tumora gušterače, a koje čine skupine inzulinom, gastrinom, vipom, glukagonom te somatostatinom. Više od trećine ovdje navedenih tumora su nefunkcionalni tumori odnosno bez endokrine funkcije tako da ne dovode do prekomjernog izlučivanja hormona i s njima povezanih simptoma. Karcinom gušterače je među karcinomima sedmi uzročnik smrtnosti. Incidencija u značajnoj mjeri varira od države do države, a vodeće po incidenciji su Europa i Sjeverna Amerika, dok najnižu pojavnost karcinoma gušterače ima Afrika i dijelovi Azije tako da je u zemljama s većim razvojem veća i incidencija ovog karcinoma kod osoba oba spola (Wong i sur., 2017). Značajan nesrazmjer pojavnosti karcinoma gušterače u različitim državama govori o značaju rizičnih čimbenika.
Rizični čimbenici koji dovode do karcinoma gušterače su oni na koje je moguće utjecati te čimbenici na koje nije moguće utjecati kao što su dob, spol, etnička pripadnost, krvna grupa, crijevna mikrobiota, pojavnost karcinoma u obitelji, ali i genske predispozicije kao i šećerna bolest. Tako se karcinom gušterače drži za bolest uglavnom starijih osoba relativno jednako raspoređen na oba spola (Wahi i sur., 2009). Češća je pojavnost u Afro Amerikanaca, a ta činjenica se pripisuje uglavnom promjenjivim faktorima (Midha i sur., 2016) za razliku od nepromjenjive pripadnosti određenoj krvnoj grupi gdje je krvna grupa 0 u nižem riziku za pobol od ove bolesti zahvaljujući alteracijama glikoziltransferaze među različitim krvnim grupama (Wolpin i sur., 2009). Istraživanja crijevne mikrobiote pokazuju kako različite razine crijevnih bakterija imaju utjecaj na različite ishode u pojavnosti ovog karcinoma.

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S druge strane osobe čiji su članovi obitelji iz prve linije srodstva oboljeli od karcinoma gušterače imaju devet puta uvećan rizik za obolijevanje (McGuigan i sur., 2018) kao i osobe oboljele od šećerne bolesti. Ipak treba biti svjestan da šećerna bolest sama po sebi može biti i rana prezentacija karcinoma gušterače tako da je HbA1c potencijalan marker u ranom otkrivanju ovog karcinoma (Grote i sur., 2011).

Od promjenjivih čimbenika u nastanku karcinoma gušterače je najznačajnije pušenje cigareta (Iodice, 2008), uz to svoje mjesto ima prekomjerna konzumacija alkohola i kronični pankreatitis. Uz navedeno, svoje mjesto pri povećanju rizika uz nutritivne čimbenike drži i pretilost - za svakih 5 jedinica indeksa tjelesne mase (ITM) rizik pojave karcinoma gušterače povećava se za 10 % podjednako u oba spola (Pancreatic cancer statistics, 2022).

Broj osoba koje prežive pet godina nakon potvrđivanja dijagnoze karcinoma gušterače je približno 6 %, no glavni razlog za ovako nisko petogodišnje preživljenje jest stadij bolesti i postojanje metastaza u udaljenim organima u trenutku dijagnoze. Iako umjetna inteligencija otvara mogućnosti za pomoć u ranijem otkrivanju karcinoma gušterače (Lin i sur., 2022), ovaj karcinom se zbog nespecifičnih simptoma najčešće prezentira vrlo kasno i samo je 20 % pacijenata podobno za uspješnu kiruršku resekciju (Ilic i sur., 2016) kao potencijalnu opciju za izlječenje u slučaju adenokarcinoma kao najčešćeg tipa karcinoma pankreasa.

Uloga gušterače u metabolizmu hrane

Gušterača igra važnu ulogu u probavi hrane jer proizvodi enzime i inzulin koji pomažu razgraditi hranu. Hranjive tvari iz hrane tada se mogu apsorbirati u krv i tijelo ih može iskoristiti. Različiti enzimi gušterače pomažu razgraditi hranu koja sadrži masti, proteine i ugljikohidrate. Karcinom gušterače može smanjiti broj enzima koje gušterača proizvodi. Također može spriječiti enzime da dođu do crijeva, gdje su potrebni za probavu. Na primjer, karcinom može blokirati kanal gušterače, koji prenosi enzime iz gušterače u tanko crijevo (Diet and pancreatic cancer, 2020).

Povezanost skupina pojedinih namirnica u prevenciji i nastanku karcinoma gušterače

Dobro je poznato da voće, povrće, cjelovite žitarice i orašasti plodovi sadrže povećane količine fitokemikalija, bioaktivnih spojeva koji mogu pružiti zaštitu od niza kroničnih bolesti i karcinoma uopće, a koji se klasificiraju kao karotenoidi, fenoli, alkaloidi, spojevi koji sadrže dušik i organosumporni spojevi (Falasca, 2014). Iako njihovi mehanizmi djelovanja tek trebaju biti u potpunosti razjašnjeni, otkriveno je da fitokemikalije posjeduju aditivno i sinergijsko djelovanje, što bi moglo objasniti njihova antikancerogena svojstva. Neki od mehanizama predloženih za objašnjenje antikancerogenih svojstava fitokemikalija uključuju:

- antioksidativno i protuupalno djelovanje;
- inhibicija stanične proliferacije, diferencijacije, adhezije i invazije;
- antibakterijsko i antivirusno djelovanje i stimulacija imunoloških funkcija;
- popravak oštećenja DNK;
- regulacija metabolizma steroidnih hormona i estrogena;
- regulacija putova prijenosa signala;
- regulacija enzima;
- inhibicija supresije onkogena i indukcija ekspresije gena supresije tumora;
- aktivacija G zaustavljanja staničnog ciklusa;
- indukcija stanične diferencijacije i apoptoze (Liu i sur., 2013).

Voće, povrće, orašari i cjelovite žitarice

Osim uloge fitokemikalija, prehrambena vlakna, jedna od glavnih komponenti voća, povrća, cjelovitih žitarica i orašastih plodova, otkrivena su u obrnutoj korelaciji s rizikom od pojavnosti karcinoma. Studija kontrole slučaja provedena na 326 bolesnika s karcinomom gušterače u Italiji otkrila je da su topiva i netopiva vlakna i vlakna iz voća obrnuto povezana s karcinomom gušterače, iako nije utvrđena povezanost između vlakana žitarica i rizika od karcinoma gušterače (Bolling i sur., 2023). Nasuprot tome, u studiji o mediteranskoj prehrani i riziku od razvoja karcinoma utvrđeno je da cjelovite žitarice imaju zaštitni učinak protiv nekoliko vrsta karcinoma, uključujući karcinom gušterače. U prospektivnoj studiji koja je uključivala 75 680 žena koje su konzumirale porciju orašastih plodova od 28 g dva ili više puta tjedno ista je povezana sa značajno smanjenim rizikom od razvoja karcinoma gušterače (Bao i sur., 2013). Studija kontrole slučaja unutar kohortne studije EPIC (Europsko prospektivno istraživanje karcinoma i prehrane) izvijestila je o obrnutoj korelaciji između razina beta-karotena u plazmi (sadržanog u narančastom voću i povrću i tamnozelenom lisnatom povrću), zeaksantina (sadržanog u paprici, kukuruzu i šafranu) i alfa-tokoferola (sadržan u zelenom i narančastom povrću i rajčicama) u odnosu na rizik od karcinoma gušterače (Jeurnink i sur., 2015). Štoviše, neki izotiocijanati, spojevi sadržani u povrću iz skupine krucifernog

povrća (tj. brokula, cvjetača, kupus i prokulice), kao što su sulforafan, benzil izotiocijanat i fenetil izotiocijanat, pokazali su inhibicijski učinak na stanice karcinoma gušterače u in vitro i studijama na životinjama (Sahu i sur., 2009).

Meso i riba

Neka su istraživanja pokazala da prerađeno crveno meso ili meso kuhano na vrlo visokim temperaturama metodama poput prženja, pečenja na žaru ili roštilja treba ograničiti kako bi se smanjio rizik od karcinoma gušterače. Moguća zaštitna uloga ribe protiv karcinoma gušterače mogla bi biti potkrijepljena hipotezom da bi dugolančane (n-3) polinezasićene masne kiseline (LC-PUFA) kojih ima u izobilju u ribi, mogle biti korisne protiv onkogenosti gušterače zbog protuupalnih svojstava ove hranjive tvari, s obzirom na činjenicu da kronična upala može igrati ulogu u karcinogenezi gušterače. U nedavnoj meta-analizi, koja je uključivala devet prospektivnih kohortnih i 10 studija slučaja-kontrole, nije pronađena inverzna povezanost konzumacije ribe ili LC-PUFA s rizikom od karcinoma gušterače i to je bilo u skladu s drugim objavljenim studijama (Pericleous i sur., 2014).

Masti i šećeri

Čim lipidi uđu u duodenum, oslobađa se kolecistokinin koji potiče lučenje enzima gušterače. Tijekom dugih razdoblja to može dovesti do hipertrofije gušterače i hiperplazije acinusa te posljedično do neoplazije gušterače. Ne postoji izravna veza između konzumacije rafiniranog šećera i pojavnosti karcinoma gušterače, međutim hiperinzulinemija, pretilost, metabolički sindrom i šećerna bolest pozitivno su povezani s rizikom od karcinoma gušterače (Pericleous i sur., 2014).

Restrikcija kalorija

Uz prehranu bogatu voćem, povrćem, orašastim plodovima i cjelovitim žitaricama, restrikcija kalorija još je jedna obećavajuća strategija koja se čini učinkovitom u zaštiti od rizika od karcinoma. Zapravo, kroničnom kontrolom količine unesenih kalorija (u životinjskom modelu obično se provodi smanjenje od 20 % do 40 %), dolazi do smanjene razine inzulina, inzulinu sličnog faktora rasta, leptina, adiponektina, inhibitora aktivatora plazminogena, citokina te se dobije faktor rasta vaskularnog endotela. Ove promjene doprinose smanjenju upale i signaliziranja čimbenika rasta te smanjenju vaskularnih poremećaja, uzrokujući smanjenje rizika od karcinoma i progresije karcinoma. Ovi nalazi jasno pokazuju vezu između visokokalorične prehrane i vjerojatnosti razvoja karcinoma gušterače te sugeriraju plan djelovanja iz preventivne perspektive (Hursting i sur., 2013).

Autofagija kao dio liječenja karcinoma gušterače

Autofagija može imati različite uloge kod karcinoma ovisno o vrsti tumora i kontekstu (Levine i sur., 2008). Doista, tijekom prvih faza progresije tumora autofagija sprječava genomsku nestabilnost i blokira inicijaciju tumora, dok u uznapredovalim stadijima bolesti autofagija, kroz razgradnju i recikliranje staničnih komponenti, doprinosi povećanom zahtjevu za brzim rastom stanica raka. Adenokarcinomi karakteriziraju visoke razine bazalne autofagije, a pokazalo se da farmakološka ili genetska supresija autofagije inhibira rast karcinoma gušterače in vivo i in vitro (Sousa i sur., 2014). Stoga je za rast adenokarcinoma potrebna autofagija, a lijekovi koji inhibiraju ovaj proces predloženi su za kliničko testiranje kod pacijenata s adenokarcinomom gušterače, kao i kod drugih tumora koji pokazuju sličnu ovisnost o autofagiji. Kao posljedica ovog sve većeg interesa za ciljanje ovog procesa, trenutno postoji nekoliko kliničkih ispitivanja koja uključuju inhibitore autofagije, kao što su klorokin i njegovi derivati. Među različitim mehanizmima putem kojih prehrambeni spojevi mogu utjecati na rizik od karcinoma, autofagija se pojavljuje kao važan proces na koji utječe prehrana. To ne iznenađuje s obzirom na to da je dostupnost hranjivih tvari glavni dio autofagije. Nekoliko prehrambenih spojeva pokazalo se da utječu na autofagiju kao što su kvercetin, genistein, kurkumin, sulforafan i resveratrol (Singletary i sur., 2008). Osim toga, pokazalo se da vitamin D utječe na autofagiju i sve više dokaza podupire potencijalnu ulogu vitamina D i njegovih analoga u prevenciji ili liječenju karcinoma gušterače (Barreto i sur., 2015).

Pretilost i karcinom gušterače

Veza između pretilosti (ITM > 30,0 kg/m2), šećerna bolesti tipa 2, kardiovaskularnih bolesti i karcinoma odavno je utvrđena, iako još nisu u potpunosti razjašnjeni mehanizmi kojima dodatne masne naslage povećavaju rizik od karcinoma. Karcinom gušterače trenutno je na popisu karcinoma povezanih s pretilošću, zajedno s karcinomom debelog crijeva, jednjaka, bubrega, endometrija i postmenopauzalnim karcinomom dojke (Azyolinsky i sur., 2014).

Pretilost ili prehrana bogata mastima jedan je od čimbenika koji mogu povećati rizik od razvoja akutnog pankreatitisa (Navina, 2011), mijenjajući ravnotežu probavnih enzima unutar acinarnih stanica i smanjujući lučenje enzima gušterače. Akutni pankreatitis karakterizira upalno stanje gušterače i disfunkcionalna autofagija u stanicama gušterače. Osim toga, povećanjem razine proupalnog hormona leptina i smanjenjem razine protuupalnog hormona adiponektina, pretilost potiče upalu. Dok je normalno upala prirodni odgovor tijela, koje aktivira imunološke stanice pomoću citokina, kemokina i drugih medijatora (Mantovani i sur., 2011), trajna upala može dovesti do nekoliko oštećenja stanica uzrokovanih metaboličkim promjenama i oksidativnim stresom. Autofagija također može posredovati u mehanizmima kemorezistencije stanica raka na lijekove protiv karcinoma. Kao odgovor na metaboličke i terapijske stresove, autofagija inducira staničnu smrt, povećava upalu i potiče tumorigenezu (Gukovsky i sur., 2013). Štoviše, razgradnja prekomjerne masnoće gušterače uzrokovana pretilošću proizvodi višak nezasićenih masnih kiselina koje mogu povećati upalu, nekrozu parenhima i dovesti do oštećenja više organa i smrti (Navina i sur., 2011).

Epidemiološke i eksperimentalne studije dosljedno pokazuju izravnu vezu između pretilosti, visokog ITM-a, debljanja i povećanog rizika od razvoja karcinoma gušterače. Kao posljedica toga, logično je ustvrditi da visokokalorična dijeta i/ili visoka konzumacija masti i šećera, koja s vremenom dovodi do prekomjerne tjelesne mase ili pretilosti, ima negativan utjecaj na rizik od karcinoma gušterače (La Vecchia, 2009).

Literatura

Azvolinsky, A. (2014): Cancer Risk: The Fat Tissue–BMI–Obesity Connection. *J. Natl. Cancer Inst.* 106 (4), dju100.

Bao, Y., Han, J., Hu, F.B., Giovannucci, E.L., Stampfer, M.J., Willett, W.C., Fuchs, C.S. (2013): Association of nut consumption with total and cause-specific mortality. *N. Engl. J. Med.* 369, 2001–2011.

Barreto, S.G., Neale, R.E. (2015): Vitamin D and pancreatic cancer. *Cancer Lett*. 368, 1–6.

Bolling, BW, Aune, D, Noh, H, Petersen, KS, Freisling, H (2023): Dried Fruits, Nuts, and Cancer Risk and Survival: A Review of the Evidence and Future Research Directions. *Nutrient*. 16, 15(6), 1443.

Diet and pancreatic cancer, https://www.pancreaticcancer.org.uk/information/managing-symptoms-and-side-effects/diet-and-pancreatic-cancer/, [posjećeno: 23.03.2023.]

Falasca, M., Casari, I., Maffucci, T. (2014): Cancer chemoprevention with nuts. *J. Natl. Cancer Inst.* 106, 238.

Grote, VA, Rohrmann, S., Nieters, A., Dossus, L., Tjønneland, A,. Halkjær, J., i sur. (2011): Diabetes mellitus, glycated haemoglobin and C-peptide levels in relation to pancreatic cancer risk: a study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Diabetologija* 54 (12), 3037-3046.

Gukovsky, I., Li, N., Todoric, J., Gukovskaya, A., Karin, M. (2013). Inflammation, autophagy, and obesity: Common features in the pathogenesis of pancreatitis and pancreatic cancer. *Gastroenterology* 144, 1199–1209.

Hursting, S.D., Dunlap, S.M., Ford, N.A., Hursting, M.J., Lashinger, L.M. (2013): Calorie restriction and cancer prevention: A mechanistic perspective. *Cancer Metab.* 1, 10.

Ilic, M., Ilic, I. (2016): Epidemiology of pancreatic cancer. *World J Gastroenterol*. 28, 22 (44), 9694-9705.

Iodice, S., Gandini, S., Maisonneuve, P., Lowenfels, AB. (2008): Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch Surg*. 393(4), 535 - 45.

Jeurnink, S.M., Ros, M.M., Leenders, M., van Duijnhoven, F.J., Siersema, P.D., Jansen, E.H., van Gils, C.H., Bakker, M.F, Overvad, K., Roswall, N., et al. (2015) Plasma carotenoids, vitamin C, retinol and tocopherols levels and pancreatic cancer risk within the European Prospective Investigation into Cancer and Nutrition: A nested case-control study: Plasma micronutrients and pancreatic cancer risk. *Int. J. Cancer* 136, E665–E676.

La Vecchia, C. (2009): Association between Mediterranean dietary patterns and cancer risk. *Nutr. Rev*. 67, S126–S129.

Levine, B., Kroemer, G. (2008): Autophagy in the pathogenesis of disease. *Cell* 132, 27–42.

Lin, K.W., Ang, T.L., Li, J.W. (2022): Role of artificial intelligence in early detection and screening for pancreatic adenocarcinoma. *Artif Intell Med Imaging.* 3(2), 21-32.

Liu, R.H. (2013): Dietary bioactive compounds and their health implications. *J. Food Sci.* 78, A18 – A25.

Mantovani, A., Cassatella, M.A., Costantini, C., Jaillon, S. (2011): Neutrophils in the activation and regulation of innate and adaptive immunity. *Nat. Rev. Immunol*. 11, 519–531.

McGuigan, A., Kelly, P., Turkingtn, R.C., Jones, C., Coleman, H.G., McCain, RS. (2018): Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol*. 24(43), 4846–4861.

Midha, S., Chawla, S., Garg, P.K. (2016): Modifiable and non-modifiable risk factors for pancreatic cancer: A review. *Cancer Lett*. 10, 381(1), 269-77.

Navina, S., Acharya, C., DeLany, J.P., Orlichenko, L.S., Baty, C.J., Shiva, S.S., Durgampudi, C., Karlsson, J.M., Lee, K., Bae, K.T., i sur. (2011): Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. *Sci. Transl. Med.* 3 (107), 107ra110.

Pancreatic cancer statistics, https://www.wcrf.org/cancer-trends/pancreatic-cancer-statistics/, [posjećeno: 15.04.2023.]

Pericleous, M., Rossi, R.E., Mandair, D., Whyand, T., Caplin, M.E. (2014): Nutrition and Pancreatic Cancer. *Anticancer Research*. 34(1), 9 - 21.

Sahu, R.P., Zhang, R., Batra, S., Shi, Y., Srivastava, S.K. (2009): Benzyl isothiocyanate-mediated generation of reactive oxygen species causes cell cycle arrest and induces apoptosis via activation of MAPK in human pancreatic cancer cells. *Carcinogenesis* 30, 1744–1753.

Singletary, K., Milner, J. (2008): Diet, autophagy, and cancer: A review. *Cancer Epidemiol. Biomarkers Prev*. 17, 1596–1610.

Sousa, C.M., Kimmelman, A.C. (2014): The complex landscape of pancreatic cancer metabolism. *Carcinogenesis* 35, 1441–1450.

Wahi, M.M., Shah, N., Schrosk, C.E., Rosemungy, A.S., Goldin, S.B. (2009): Reproductive factors and risk of pancreatic cancer in women: a review of the literature. *Ann Epdemiol*. 19(2), 103 - 11.

Wolpin, B.M., Chan, A.T., Hartge, P., Chanock, S.J., Kraft, P., Hunter, D.J., Giovannucci, E.L., Fuchs, C.S. (2009): ABO blood group and the risk of pancreatic cancer. *J. Natl. Cancer Inst*. 18, 101(6), 424 - 431.

Wong, M.C.S., Jiang, J.Y., Liang, M., Fang, Y., Yeung, M.S., Sung, J.J.Y. (2017): Global temporal patterns of pancreatic cancer and association with socioeconomic development. *Scientific Reports* 7, 3165.

PANCREATIC CANCER - IMPACT OF GENETIC AND ENVIRONMENTAL FACTORS

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review paper

Summary

Pancreatic cancer is considered as a rare form of gastrointestinal malignancy and one of its characteristics is a late presentation. Usually, when the patient is diagnosed with pancreatic cancer, illness is in its advanced form which leads to more than 95% death rate within first two years from the moment of diagnosis. Most common risk factors for developing pancreatic cancer include old age, cigarette smoking, diet rich in fats but lacking fruits and vegetables. Among important risk factors there are obesity, sedentary lifestyle and previous medical conditions such as pancreatitis, diabetes and liver cirrhosis. Dietary guidelines for prevention of pancreatic cancer include eating several smaller meals throughout the day, choosing optimal nutrient combination within meals and blood glucose control. In this paper, preventive measures for pancreatic cancer development will be covered.

Keywords: pancreas, carcinoma, nutrition, autophagy, obesity

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THE USE OF VITAMIN D IN ASSISTED REPRODUCTIVE TECHNOLOGY PROCEDURES (*ART*) - CAN THE OCCURRENCE OF BREAST CANCER BE REDUCED?

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review paper

Summary

Introduction: Vitamin D has crucial biological activity and antioxidative function involved in human reproduction. Lots of infertility patients worldwide have their children through assisted reproductive technology. Beside endogenous synthesis, it is possible and important to supplement vitamin D with diet. Vitamin D insufficiency is strongly connected with severe diseases, cancers, infertility. Studies have reported vitamin D insufficiency in up to 75% of women with diagnosed breast cancer and improvements in survival after diagnosis in women with higher level of vitamin D.
Aim: The purpose of this narrative review was to elucidate the role of vitamin D in assisted reproductive technology (*ART*) procedures, prevention and reduction of breast cancer incidence providing current evidence from human studies.
Materials and methods: The Medline database was searched using keywords *vitamin D, breast cancer, fertility, supplementation, in vitro fertilization*. The search was made as of April 10, 2023.
Results and discussion: Majority of papers analysed show that vitamin D is important in achieving good quality embryos in procedures of medically assisted reproduction and through effects that are noticeable in endometrium vitamin D supplementation facilitates successful implantation of embryos. Research also shows that there is some elevated risk in developing breast cancer after those procedures, but some papers also show that there is no notable risk, so the results are inconclusive. We found that there is a general agreement that normal serum concentrations of vitamin D acts oncoprotective against breast cancer and may facilitate treatment on already developed cancer.
Conclusion: For women with elevated risk for breast cancer, supplementation with vitamin D after medically assisted reproduction seem to have protective effect.

Keywords: vitamin D, breast cancer, fertility, supplementation, in vitro fertilization

Introduction

Worldwide, infertility affects 123 million women, therefore medically assisted reproductive technology represent important mean to improve fertility rates globally. *In vitro* fertilization with embryo transfer at the end of the procedure is one of the most effective techniques for treating infertility (Tian et al., 2022). Vitamin D is fat-soluble secosteroid which has pivotal role in increasing intestinal absorption of calcium, magnesium and phosphate. Vitamin D is synthesized in the skin from 7-dehydrocholesterol, metabolized within the body to the form $1,25(OH)_2D_3$ and transported by vitamin D-binding protein into the blood (Laganà et al., 2017). The 7-dehydrocholesterol that is produced from cholesterol and stored under the skin, can be converted into vitamin D3 after being exposed to ultraviolet radiation (Wang et al., 2021). Parathyroid hormone, FGF23, calcium and phosphate are the major regulators of the renal 1-hydroxylase (the enzyme producing 1,25(OH)2D), the major enzyme that catabolizes 25(OH)D and 1,25(OH)2D is the 24-hydroxylase (Bikle, 2017). Most actions of 1,25(OH)2D are mediated by the vitamin D receptor (VDR) which is a transcription factor that is coupled with retinoid X receptor that when bound to 1,25(OH)2D regulates gene transcription either positively or negatively (Bikle, 2017). Vitamin D receptor is found in most cells in human body (Bikle, 2017). Along with endogenous synthesis, it is possible and important, in case of insufficiency, to supplement vitamin D with diet. Main sources of vitamin D3 (cholecalciferol) are sea fish fat and cod liver oil, and sources of vitamin D2 (ergocalciferol) are plants and mushrooms (Laganà et al., 2017). The World Health Organization (WHO) defined 'vitamin D insufficiency' as serum level of 25OHD below 20 ng/ml (50 nmol/L) (Skowrońska et al., 2016). Fat-soluble vitamins have crucial biological activity, antioxidative function involved in, for example, human reproduction. There are association between levels of fat-soluble vitamin in follicular fluid, quality of oocytes and consequently embryo development (Skowrońska et al., 2020). Vitamin D plays an important role in maintaining the normal development of the uterus and ovaries, 25(OH)D levels have a significant impact on the

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fertility, which suggest that 25(OH)D may affect the fertility of patients with infertility (Tian et al., 2022). Paffoni et al. (2014) concluded that vitamin D insufficiency negatively affects clinical pregnancy rate in women undergoing *in vitro* fertilization (*IVF*) procedure. In male infertility, insufficiency or high level of vitamin D in serum have negative impact on spermatozoa number, their progressive motility and sperm morphology (Nikolac Gabaj et al., 2020). Vitamin D insufficiency is strongly connected with severe diseases pointing out cancers and pregnancy complications including infertility. Studies have reported vitamin D insufficiency in up to 75% of women with diagnosed breast cancer and improvements in survival after diagnosis in women with higher level of vitamin D. It affects approx. 200 genes connected with cellular proliferation, apoptosis and terminal differentiation of normal and cancer cells. Vitamin D receptors have been found in up to 80% of breast cancers (Hines et al., 2010).

The purpose of this review was to elucidate the role of vitamin D in assisted reproductive technology procedures, prevention and reduction of breast cancer incidence providing current evidence from human studies.

Materials and methods

The Medline database was searched using keywords *vitamin D, breast cancer, fertility, supplementation, in vitro fertilization*. The search was made up to April 20, 2023. After the extraction of all papers, they were compared to each other for duplicates and related studies, so two authors separately analysed the inclusion of studies according to the set criteria. We analysed 18 papers that included 14 reviews, 2 clinical trials and 2 randomized controlled trials. Results are shown in form of narrative review.

Results and discussion

Role of vitamin D in medically assisted reproduction

Vitamin supplementation is present worldwide as a form of preparation for pregnancy or IVF procedures and vitamin D is an important part. When analysing publications, we found confirmation that this vitamin plays an important part for oocyte and embryo quality. Polycystic ovary syndrome patients are characterized with insulin resistance, metabolic and reproductive functions that make achieving pregnancy difficult and often seek fertility counselling or require fertility procedures, they are sometimes deficient in vitamins such as vitamin D, chromium and omega-3 (Fagfoori et al., 2017). Ozyurt and Karakus (2022) show that both serum and FF 25-hydroxyvitamin D level of women with PCOS at the time of oocyte retrieval are like non-PCOS controls and that follicular fluid 25-hydroxyvitamin D levels correlate with total and MII oocyte counts, positive pregnancy test and clinical pregnancy rate but do not correlate with miscarriage and live birth rates. Paffoni et al. (2014) recruited 154 women with serum 25(OH)D <20 ng/mL and 181 women with serum 25(OH)D ≥20 ng/mL and found that clinical pregnancy rates were 20% (30/154) and 31% (56/181 and subgroup analyses showed that the group of women with the highest serum levels (>30 ng/mL) had the highest chances of pregnancy. Vitamin D influences embryo cleavage and implantation in patients with repeated implantation failure by affecting the expression pattern and regulatory modifications of the progesterone receptors in the endometrial stromal cells (Hosseinirad et al., 2020).

Kermack et al. (2020) showed that increased dietary intake of omega-3 fatty acids, vitamin D, and olive oil for 6 weeks before in vitro fertilization (IVF) or IVF–intracytoplasmic sperm injection (ICSI) altered the rate of embryo cleavage. Possible explanation is that vitamin D alters AMH signalling, FSH sensitivity, and progesterone production and release in human granulosa cells, indicating a possible physiologic role for vitamin D in ovarian follicular development (Irani and Merhi, 2014). Not only that vitamin D influences embryo quality, but vitamin D supplementation regulates local immune response of natural killer cells for optimization of maternal tolerance for implantation in women with repeated implantation failure (Chen et al, 2020).

Vitamin D is also having an impact on cycles with donated oocyes and recipients with nonreplete vitamin D status [25(OH)D<30 ng/mL] were associated with lower pregnancy rates suggesting that the effects of vitamin D may be mediated through the endometrium (Rudick et al., 2014).

Grzechocinska et al. (2013) conclude that results in patients without calciferol insufficiency are explained by reports about high concentration of vitamin D and its metabolites in human in decidua collected in the 1st trimester of pregnancy which suggests its contribution in proper implantation and local immunological preference of the embryo.

There are some papers that haven not found a positive link between vitamin D levels and fertilization success or embryo development (Skowronska et al., 2020) and that neither free nor total 25(OH) vitamin D seems to play a major role in human embryo implantation (Tian et al., 2022).

Vitamin D is also important in sperm quality and male fertility. The vitamin D receptor and the vitamin D inactivating enzyme CYP24A1 are co-expressed in

high quality sperm and research results provide proof of principle for a CYP24A1-based sperm test to improve fertility outcome for infertile patients referred for IUI and supports a role for vitamin D metabolites during fertilization (Hansen et al., 2019).
Vitamin D serum concentrations depend not only on supplementation but on environmental factors. There were significant differences in 25-hydroxyvitamin D (25(OH)D) concentrations in different seasons and vitamin D deficiencies are lowest in summer when levels of vitamin D are highest due to sunlight exposure and these vitamin D concentrations significantly correlated with female infertility (Wang et al., 2021). Rogenhofer et al. (2022) show that highest anti Muller hormone concentrations were found between August and October when vitamin D has highest concentrations. Research of Aerfi et al. (2018) showed that concealing dress code is an independent risk factor for vitamin D deficiency due to a lack of skin exposure to sunlight and it may play a crucial role in reduced ovarian reserve in infertile female Iranian population.

Link between breast cancer and medically assisted reproduction

Medically assisted reproduction includes the use of gonadotropins, clomiphene citrate or letrozole as inductors of ovulation and these medications can influence estrogene levels in female body. Breast cancer is sensitive on estrogene levels and there is a concern that ovarian stimulation may alter the risk of developing breast cancer after such treatments. Some research show that women who received six or more IVF cycles did not have an increased risk of breast cancer, there was no excess breast-cancer risk associated with clomiphene, human chorionic gonadotropin, gonadotropin analogues and progesterone and there was no significant association between fertility treatment and excess breast-cancer risk in patients with more than 10 years' follow-up (Cullinane et al., 2022). Also, there was no significant increase in the risk of breast cancer among women treated with any ovarian stimulation drug for infertility compared with that in unexposed controls from the general population and the infertile population (Beebeejaun et al., 2021). Among women undergoing fertility treatment in the Netherlands between 1980 and 1995, IVF treatment compared with non-IVF treatment was not associated with increased risk of breast cancer after a median follow-up of 21 years (Belt-Dousebout et al., 2016). Gronwald et al. (2016) show that there was no significant relationship between the use of any fertility medication or IVF and the subsequent risk of ovarian cancer among women with a BRCA mutation.
In contrast some research shows that there is a positive link between fertility treatment and risk of breast cancer. Age 40 or more at IVF treatment, hormonal infertility and 4 or more IVF cycles were found to be risk factors to develop breast cancer compared to the general population and 29% of women in IVF treatments had positive family history of breast cancer (Pappo et al., 2008). Women exposed to ART had an elevated risk of breast and research findings show increased risk in the study population warrant continued monitoring of women treated with ART as this population advances into more typical cancer age ranges (Reigstad et al., 2015).
Women who have been exposed to fertility drugs with IVF seem to have a transient increase in the risk of having breast or uterine cancer diagnosed in the first year after treatment, though the incidence overall is no greater than expected and unexplained infertility was associated with an increased risk of a diagnosis of ovarian or uterine cancer (Venn et al., 1999).
In a review paper Impicciatore and Tiboni (2006) report an increased risk was recently observed in women giving birth after in vitro fertilization (IVF), but it appeared to be consequential to the infertile status rather than the effect of fertility drugs and there is a possible trend towards an increased risk has been reported by some authors for endometrial cancer. Kessous et al. (2016) show that patients with a history of IVF treatments had a significantly increased risk of being diagnosed with ovarian and uterine cancer, but a history of IVF treatment remained independently associated with ovarian and uterine cancer.

Role of vitamin D supplementation in breast cancer

When analysing papers on relationship between vitamin D concentrations we found that vitamin D has mostly anticancerogenic properties in relation to breast cancer. Some studies strongly suggest that vitamin D deficiency increases the risk of developing cancer and that avoiding deficiency and adding vitamin D supplements might be an economical and safe way to reduce cancer incidence and improve cancer prognosis and outcome (Feldman et al., 2014). Preclinical data have indicated that vitamin D affects up to 200 genes that influence cellular proliferation, apoptosis, angiogenesis, terminal differentiation of normal and cancer cells and that vitamin D receptors have been found in up to 80% of breast cancers influencing patient survival (Hines et al., 2010).
Among premenopausal women, high intake of low-fat dairy foods containing vitamin D as a component was associated with reduced risk of breast cancer (Shin et al., 2002).

Women with serum 25(OH)D levels less than 20 ng/ml and calcium levels less than 10.5 mg/dl had higher odds of having breast cancer (Sofi et al., 2018) and vitamin D supplements appear protective against breast cancer development (Rossi et al., 2014).

Merchan et al. (2018) conclude that vitamin D and its receptor show oncoprotective actions and vitamin D presents oncoprotective actions through modulation of inflammation, cell proliferation, cell differentiation, angiogenesis, invasive and metastatic potential, apoptosis, miRNA expression regulation and modulation of the Hedgehog signalling pathway.

25(OH)D deficiency was directly related to breast cancer incidence while total vitamin D and supplemental vitamin D intakes had an inverse relationship with this outcome (Hossain et al, 2019). In another study the combination of ω-3 free fatty acids (ω-3 FFAs) and 1α, 25-dihydroxy-vitamin D dramatically enhances cell apoptosis among three subtypes of breast cancer cell lines (Yang et al., 2017).

Vitamin D may inhibit the transformation of normal mammary progenitors into breast cancer stem cells that initiate and sustain the growth of breast tumours through modulation of long chain RNAs that are important for breast cancer pathogenesis (Blasiak et al., 2022).

Conclusions

Women with elevated risk for developing breast cancer going through medically assisted reproduction, could benefit from supplementation with vitamin D to reduce the risk of developing breast cancer.

References

Arefi, S., Khalili, G., Iranmanesh, H., Farifteh, F., Hosseini, A., Fatemi, H.M., Lawrenz, B. (2018): Is the ovarian reserve influenced by vitamin D deficiency and the dress code in an infertile Iranian population? *J Ovarian Res.* 11(1), 62.

Bandera Merchan, B., Morcillo, S., Martin-Nuñez, G., Tinahones, F.J., Macías-González, M. (2017): The role of vitamin D and VDR in carcinogenesis: Through epidemiology and basic sciences. *J Steroid Biochem Mol Biol.* 167, 203-218.

Beebeejaun, Y., Athithan, A., Copeland, T.P., Kamath, M.S., Sarris, I., Sunkara, S.K. (2021): Risk of breast cancer in women treated with ovarian stimulation drugs for infertility: a systematic review and meta-analysis. *Fertil Steril.* 116 (1), 198-207.

Bikle, D.D. (2017): Vitamin D: Production, Metabolism, and Mechanisms of Action. [Updated 2021 Dec 31]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278935/

Blasiak, J., Chojnacki, J., Pawlowska, E., Jablkowska, A., Chojnacki, C. (2022): Vitamin D May Protect against Breast Cancer through the Regulation of Long Noncoding RNAs by VDR Signaling. *Int J Mol Sci.* 23 (6), 3189.

Chen, X., Diao, L., Lian, R., Qi, L., Yu, S., Liu, S., Lin, S., Xue, Z., Zeng, Y. (2020): Potential impact of maternal vitamin D status on peripheral blood and endometrium cellular immunity in women with recurrent implantation failure. *Am J Reprod Immunol.* 84 (1), e13243.

Cullinane, C., Gillan, H., Geraghty, J., Evoy, D., Rothwell, J., McCartan, D., McDermott, E.W., Prichard, R.S. (2022): Fertility treatment and breast-cancer incidence: meta-analysis. *BJS Open.* 6 (1), zrab149.

Faghfoori, Z., Fazelian, S., Shadnoush, M., Goodarzi, R. (2017): Nutritional management in women with polycystic ovary syndrome: A review study. *Diabetes Metab Syndr.* 11 Suppl 1, S429-S432.

Feldman, D., Krishnan, A.V., Swami, S., Giovannucci, E., Feldman, B.J. (2014): The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer.* 14 (5), 342-357.

Gronwald, J., Glass, K., Rosen, B., Karlan, B., Tung, N., Neuhausen, S.L., Moller, P., Ainsworth, P., Sun, P., Narod, S.A., Lubinski, J., Kotsopoulos, J., Lynch, H.T., Cybulski, C., Kim-Sing, C., Friedman, S., Senter, L., Weitzel, J., Singer, C., Eng, C. (2016): Treatment of infertility does not increase the risk of ovarian cancer among women with a BRCA1 or BRCA2 mutation. *Fertil Steril.* 105 (3), 781-785.

Grzechocinska, B., Dabrowski, F.A., Cyganek, A., Wielgos, M. (2013): The role of vitamin D in impaired fertility treatment. *Neuro Endocrinol Lett.* 34 (8), 756-762.

Hansen, L., Lorenzen, M., Bentin-Ley, U., Nielsen, J., Krog, H., Berg, A.H., Bonnie Sofie Håkansson, Astrid Munk Pedersen, T. Høst, Juul, A., Bach Jensen, M. (2019): Presence of the vitamin D inactivating enzyme CYP24A1 in human sperm and prediction of the success of intrauterine insemination: A prospective study. *J Steroid Biochem Mol Biol.* 191, 105353.

Hines, S.L., Jorn, H.K.S., Thompson, K.M., Larson, J.M. (2010): Breast cancer survivors and vitamin D: A review. *Nutrition* 26 (3), 255-262.

Hossain, S., Beydoun, M.A., Beydoun, H.A., Chen, X., Zonderman, A.B., Wood, R.J. (2019): Vitamin D and breast cancer: A systematic review and meta-analysis of observational studies. *Clin Nutr ESPEN.* 30, 170-184.

Hosseinirad, H., Novin, M., G., Hosseini, S., Nazarian, H., Amidi, F., Paktinat, S., Azizi, E., Mofarahe, Z., S. (2020): Effect of 1,25(OH)2-vitamin D3 on expression and phosphorylation of progesterone receptor in cultured endometrial stromal cells of patients with repeated implantation failure. *Acta Histochem.* 122 (2), 151489.

Impicciatore, G.G., Tiboni, G.M. (2011): Ovulation inducing agents and cancer risk: review of literature. *Curr Drug Saf.* 6 (4), 250-258.

Irani, M., Merhi, Z. (2014): Role of vitamin D in ovarian physiology and its implication in reproduction: a systematic review. *Fertil Steril.* 102 (2), 460-468.e3.

Kermack, A.J., Lowen, P., Wellstead, S.J., Fisk, H.L., Montag, M., Cheong, Y., Osmond, C., Houghton, F.D., Calder, P.C., Macklon, N.S. (2020): Effect of a 6-week 'Mediterranean' dietary intervention on in vitro human embryo development: the Preconception Dietary Supplements in Assisted Reproduction double-blinded randomized controlled trial. *Fertil Steril.* 113 (2), 260-269.

Kessous, R., Davidson, E., Meirovitz, M., Sergienko, R., Sheiner, E. (2016): The risk of female malignancies after fertility treatments: a cohort study with 25-year follow-up. *J Cancer Res Clin Oncol.* 142 (1), 287-293.

Laganà, A.S., Vitale, S.G., Ban Frangež, H., Vrtačnik-Bokal, E., D'Anna, R. (2017): Vitamin D in human reproduction: the more, the better? An evidence-based critical appraisal. *Eur Rev Med Pharmacol Sci.* 21 (18), 4243-4251.

Nikolac Gabaj, N., Unic, A., Miler, M., Pavicic, T., Culej, J., Bolanca, I., Herman Mahecic, D., Milevoj Kopcinovic, L., Vrtaric, A. (2020): In sickness and in health: pivotal role of vitamin D. *Biochem Med (Zagreb).* 30 (2), 020501.

Ozyurt, R., Karakus. C. (2022): Follicular fluid 25-hydroxyvitamin D levels determine fertility outcome in patients with polycystic ovary syndrome. *Taiwan J Obstet Gynecol.* 61 (4), 620-625.

Paffoni, A., Ferrari, S., Viganò, P., Pagliardini, L., Papaleo, E., Candiani, M., Tirelli, A., Fedele, L., Somigliana, E. (2014): Vitamin D Deficiency and Infertility: Insights From in vitro Fertilization Cycles. *J Clin Endocrinol Metab.* 99 (11), E2372- E2376.

Paffoni, A., Somigliana, E., Sarais, V., Ferrari, S., Reschini, M., Makieva, S., Papaleo, E., Viganò, P. (2019): Effect of vitamin D supplementation on assisted reproduction technology (ART) outcomes and underlying biological mechanisms: protocol of a randomized clinical controlled trial. The 'supplementation of vitamin D and reproductive outcome' (SUNDRO) study. *BMC Pregnancy Childbirth.* 19 (1), 395.

Pappo, I., Lerner-Geva, L., Halevy, A., Olmer, L., Friedler, S., Raziel, A., Schachter, M., Ron-El, R. (2008): The possible association between IVF and breast cancer incidence. *Ann Surg Oncol.* 15 (4), 1048-1055.

Reigstad, M.M., Larsen, I.K., Myklebust, T.Å., Robsahm, T.E., Oldereid, N.B., Omland, A.K., Vangen, S., Brinton, L.A., Storeng, R. (2015): Risk of breast cancer following fertility treatment-A registry based cohort study of parous women in Norway. *Int J Cancer.* 136 (5), 1140-1148.

Rogenhofer, N., Jeschke, U., von Schönfeldt, V., Mahner, S., Thaler, C.J. (2022): Seasonal dynamic of cholecalciferol (D3) and anti-Muellerian hormone (AMH) with impact on ovarian response and IVF/ICSI. *Arch Gynecol Obstet.* 306 (1), 219–228.

Rosato, V., Bertuccio, P., Bosetti, C., Negri, E., Gross, N.D., Ferraroni, M., Decarli, A., Talamini, R., Dal Maso, L., Falcini, F., Montella, M., Franceschi, S., La Vecchiam C. (2013): Nutritional factors, physical activity, and breast cancer by hormonal receptor status. *Breast.* 22 (5), 887-893.

Rossi, R.E., Pericleous, M., Mandair, D., Whyand, T., Caplin, M.E. (2014): The role of dietary factors in prevention and progression of breast cancer. *Anticancer Res.* 34 (12), 6861-6875.

Rudick, B.J., Ingles, S.A., Chung, K., Stanczyk, F.Z., Paulson, R.J., Bendikson, K.A. (2014): Influence of vitamin D levels on *in vitro* fertilization outcomes in donor-recipient cycles. *Fertil Steril.* 101 (2), 447-452.

Shin, M.-H., Holmes, M.D., Hankinson, S.E., Wu, K., Colditz, G.A., Willett, W.C. (2002): Intake of Dairy Products, Calcium, and Vitamin D and Risk of Breast Cancer. *J Natl Cancer Inst.* 94 (17), 1301-1311.

Skowrońska, P., Kunicki, M., Pastuszek, E., Konieczna, L., Bączek, T., Łukaszuk, K. (2020): Follicular fat-soluble vitamins as markers of oocyte competency. *Syst Biol Reprod Med.* 66 (2), 112-121.

Skowrońska, P., Pastuszek, E., Kuczyński, W., Jaszczoł, M., Kuć, P., Jakiel, G., Wocławek-Potocka, I., Łukaszuk, K. (2016): The role of vitamin D in reproductive dysfunction in women – a systematic review. *Ann Agric Environ Med*. 23(4), 671-676.

Sofi, N.Y., Jain, M., Kapil, U., Seenu, V., R., L., Yadav, C.P., Pandey, R.M., Sareen, N. (2018): Reproductive factors, nutritional status and serum 25(OH)D levels in women with breast cancer: A case control study. *J Steroid Biochem Mol Biol.* 175, 200-204.

Tian, M., Zeng, S., Cai, S., Reichetzeder, C., Zhang, X., Yin, C., Kuang, W., Cheng, K., Jiang, Y., Tao, M., Zeng, Y., Lin, G., Li, J., Gong, F., Hocher, B. (2022): 25(OH)VitD and human endocrine and functional fertility parameters in women undergoing IVF/ICSI. *Front. Endocrinol.* 13, 986848.

van den Belt-Dusebout, A.W., Spaan, M., Lambalk, C.B., Kortman, M., Laven, J.S.E., van Santbrink, E.J.P., van der Westerlaken, L.A.J., Cohlen, B.J., Braat, D.D.M., Smeenk, J.M.J., Land, J.A., Goddijn, M., van Golde, R.J.T., van Rumste, M.M., Schats, R., Józwiak, K., Hauptmann, M., Rookus, M.A., Burger, C.W., van Leeuwen, F.E. (2016): Ovarian Stimulation for In Vitro Fertilization and Long-term Risk of Breast Cancer. *JAMA.* 316 (3), 300-312.

Venn, A., Watson, L., Bruinsma, F., Giles, G., Healy, D. (1999): Risk of cancer after use of fertility drugs with in-vitro fertilisation. *Lancet.* 354 (9190), 1586-1590.

Wang, X., Zhao, S., Zhou, M., Jiang, L. (2021): Factors influencing vitamin D levels in women attending the fertility clinic and the effect on assisted fertility outcomes. *Ann Palliat Med.* 10 (7), 7813-7822.

Yang, J., Zhu, S., Lin, G., Song, C., He, Z. (2017): Vitamin D enhances omega-3 polyunsaturated fatty acids-induced apoptosis in breast cancer cells. *Cell Biol Int.* 41 (8), 890-897.

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ULOGA PREHRANE U PREVENCIJI KARCINOMA

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Sažetak

Karcinom postaje sve veći javnozdravstveni problem današnjice, čija prevalencija je u kontinuiranom porastu diljem svijeta. Među vodećim je uzrocima smrtnosti, a glavni rizični čimbenici su oni na koje zapravo možemo utjecati te time prevenirati od 30 do 50 % različitih vrsta karcinoma. Jedan od ključnih i glavnih koraka u prevenciji je održavanje normalne/zdrave tjelesne mase, pravilnom, uravnoteženom i raznolikom prehranom uz redovnu tjelesnu aktivnost. Ne postoji „super hrana" za koju možemo reći da sprječava razvoj karcinoma, kao niti točno određena hrana koja ga uzrokuje, ali postoje načini prehrane koji mogu doprinijeti prevenciji odnosno razvoju ove bolesti u sklopu prevencije. Preporučuje se općenito dati prednost hrani biljnog podrijetla, što je najbolje obuhvaćeno principima Mediteranske prehrane. Takva prehrana obiluje povrćem (osobito zelenim lisnatim, crvenim i narančastim te krucifernim), voćem (bobičastim, citrusima, crvenim i narančastim), mahunarkama i cjelovitim žitaricama te maslinovim uljem. Od hrane životinjskog podrijetla preporučuje se češća konzumacija ribe i mliječnih proizvoda. S druge strane, preporučuje se izbjegavati konzumaciju industrijski procesirane hrane bogate solju, mastima niske nutritivne kvalitete i dodanim šećerom te ograničiti konzumaciju crvenog mesa i paziti na sam proces pripreme hrane kako ne bi došlo do stvaranja štetnih/kancerogenih spojeva. Preporučuje se izbaciti mesne prerađevine, kao i prekomjernu konzumaciju alkohola. Usvajanje preporuka o promjeni načina života, što uključuje pravilnu prehranu i redovitu tjelesnu aktivnost, važan je dio prevencije razvoja karcinoma.

Ključne riječi: prevencija, hrana biljnog podrijetla, antioksidansi, karcinom, procesirana hrana

Uvod

Karcinom je multifaktorijalna bolest čija je prevalencija diljem svijeta u porastu. U većini zemalja karcinom je drugi među vodećim uzrocima smrtnosti; odmah nakon kardiovaskularnih bolesti. Prema podacima Svjetske zdravstvene organizacije (eng. *World Health Organization,* WHO) u 2020. godini zabilježeno je oko 10 milijuna smrtnih slučajeva kao posljedica različitih vrsta karcinoma, a među najčešćima ubrajaju se karcinomi dojke, prostate, pluća, debelog crijeva i rektuma (Ferlay i sur., 2020). Istraživanja su pokazala da su globalnom porastu karcinoma, u razdoblju od 2010. godine do 2019. godine, doprinijeli metabolički čimbenici rizika koji su rezultirali i visokim postotkom smrtnih ishoda (sa 643 000 umrlih u 2010. godini na 865 000 u 2019. godini (porast za 34,7 %)). Suprotno, u 2019. godini bihevioralni čimbenici rizika imaju sve veću ulogu u nastanku različitih vrsta karcinoma. Općenito, rezultati dosadašnjih provedenih istraživanja pokazali su da smanjena izloženost promjenjivim rizičnim čimbenicima može utjecati na smanjenje nesposobnosti prilagođenih godina života (eng. *Disability-Adjusted Life Years,* DALY) povezanih s nekom bolešću kao i na smrtnost uzrokovanu karcinomima (GBD 2019 Cancer Risk Factors Collaborators, 2022).

Vodeći čimbenici rizika u razdoblju od 2010. godine do 2019. godine uzimajući u obzir DALY prikazani su u tablici 1.

Danas je poznato da se od 30 do 50 % pojedinih vrsta karcinoma može prevenirati provođenjem preventivnih strategija utemeljenih na dokazima koji uključuju i rano otkrivanje te odgovarajuće liječenje u osoba sa postavljenom dijagnozom. Mnoge vrste karcinoma, ukoliko se pravovremeno dijagnosticiraju, imaju veću vjerojatnost pozitivnog ishoda liječenja (WHO, 2019).

Čimbenici koji utječu na prevenciju karcinoma

Poznato je da brojni čimbenici mogu utjecati na razvoj karcinoma. Postoje pojedini na koje ne možemo utjecati kao što su dob i genetski čimbenici te oni na koje možemo, kao što su način života koji uključuje i provođenje tjelesne aktivnosti te pravilna i uravnotežena prehrana (Tablica 2) koja predstavlja jedan od važnijih čimbenika kako u prevenciji, tako i u liječenju različitih vrsta karcinoma (Narimatsu i Yaguchi, 2022; Kerschbaum i Nüssler, 2019).

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Tablica 1. Vodeći čimbenici rizika (bihevioralni, metabolički i okolišni) u razdoblju od 2010. godine do 2019. godine (GBD 2019 Cancer Risk Factors Collaborators, 2022)

	Vodeći čimbenici rizika, 2010. god.	**Vodeći čimbenici rizika, 2019. god.**
1.	Pušenje	Pušenje
2.	Konzumacija alkohola	Konzumacija alkohola
3.	Visok indeks tjelesne mase (ITM)	Visok indeks tjelesne mase (ITM)
4.	Rizični spolni odnosi	Rizični spolni odnosi
5.	Visoke koncentracije glukoze natašte	Visoke koncentracije glukoze natašte
6.	Zagađenje česticama iz okoline	Zagađenje česticama iz okoline
7.	Profesionalna izloženost azbestu	Profesionalna izloženost azbestu
8.	Smanjena konzumacija cjelovitih žitarica	Smanjena konzumacija cjelovitih žitarica
9.	Smanjena konzumacija mlijeka i mliječnih proizvoda	Smanjena konzumacija mlijeka i mliječnih proizvoda
10.	Smanjena konzumacija voća	Pasivno pušenje
11.	Pasivno pušenje	Smanjena konzumacija voća

* BIHEVIORALNI METABOLIČKI OKOLIŠNI

Tablica 2. Uloga pojedine vrste hrane i nutrijenata u prevenciji i nastanku pet najčešćih karcinoma (prilagođeno prema: Chang i Hu, 2023; Herby i sur., 2023; Speciani i sur., 2023; Jin i Je, 2022; He i sur., 2021; Ubago-Guisado i sur., 2021; Sargsyan i Dubasi, 2021; Wajszczyk i sur., 2021; Key i sur., 2020; Nandini i sur., 2020; Rock i sur., 2020; Shin i sur., 2020; WCFR, 2018b; Mori i sur., 2017)

	Hrana i nutrijenti koji doprinose smanjenju rizika	**Hrana i nutrijenti koji doprinose povećanju rizika**	**Hrana za koju su dokazi ograničeni ili ih nema dovoljno**
Karcinom dojke	voće, neškrobno povrće, vlakna iz povrća, masna morska riba	alkohol, crveno i procesirano meso	vlakna iz voća, žitarica i mahunarki, mlijeko i mliječni proizvodi
	β-karoten, riboflavin, tiamin, folat, željezo, kalcij, magnezij, kalij, vitamin C i B6	zasićene masne kiseline, hrana s visokim glikemijskim indeksom, niske koncentracije vitamina D	
Karcinom pluća	voće, neškrobno povrće (osobito kruciferno)	lošija nutritivna kvaliteta prehrane, voda koja sadrži arsen, procesirano meso	crveno meso, riba, alkohol
	vitamin B6, metionin, prehrambeni unos vitamina C i K2, hem željezo, hrana koja sadrži retinol, *β*-karoten i karotenoide	visoke doze *β*-karotena u obliku dodataka prehrani (kod pušača)	izoflavoni
Kolorektalni karcinom	vlakna iz voća i povrća, sjemenke i orašasti plodovi, mlijeko i jogurti, češnjak, mahunarke	alkohol, crveno i procesirano meso	riba
	prehrambeni unos Ca, koncentracija vitamina B2, B6 i retinola u plazmi, prehrambeni unos *β*-karotena i vitamina E	lošija nutritivna kvaliteta prehrane, prehrana s proupalnim učinkom	koncentracija cirkulirajućeg vitamina D, unos vitamina C i karotena
Karcinom prostate	voće i povrće (osobito kruciferno), cjelovite žitarice, riba	procesirano meso, alkohol	mlijeko i mliječni proizvodi
	izoflavoni	niske koncentracije vitamina E i selena u plazmi, zasićene i trans masne kiseline	vitamin D i E, selen, likopen, *β*-karoten
Karcinom želuca	voće i povrće, žitarice	slana hrana, veće količine ukiseljenog povrća, procesirano meso, alkohol	zeleni čaj
	vitamin C, *β*-karoten, selen	infekcija *Helicobacter pylori*	

Pretilost, tjelesna aktivnost i održavanje normalne tjelesne mase

Pretilost se prema Svjetskoj zdravstvenoj organizaciji (eng. *World Health Organization*, WHO) definira kao pretjerano nakupljanje masti koje može imati negativan utjecaj na zdravlje. Općenito, kao jedan od glavnih uzročnika nastanka pretilosti navodi se neravnoteža između unosa i potrošnje energije (WHO, 2018).

Posljedice pretilosti povezane su s razvojem brojnih kroničnih nezaraznih bolesti gdje su najviše izražene šećerna bolest tipa 2 (44 %), ishemijska bolest srca (23 %) te pojedine vrste karcinoma (7 do 41 %) (EASO, 2020), uključujući karcinom kolona, jednjaka, gušterače i bubrega te karcinom dojke u postmenopauznom razdoblju života (Renehan i Soerjomataram, 2016).

Redovita tjelesna aktivnost svojim djelovanjem na više sustava što uključuje imunološki, metabolički i endokrinološki, utječe na smanjenje rizika za razvoj pretilosti, a time i karcinoma osobito kolona, dojke i endometrija (Leitzmann i sur., 2015; Kerschbaum i Nüssler, 2019).

Potencijalan mehanizam djelovanja uključuje povećanje protuupalne razine adiponektina, smanjenje koncentracije spolnih hormona, sistemske upale, inzulinu sličnog faktora rasta (IGF-1), hiperinzulinemije i citokina povezanih sa pretilošću te utječe na raznolikost crijevne mikrobiote (Jurdana, 2021).

Stoga su preporuke WHO-a da bi se tjedno trebalo provoditi najmanje 150 minuta umjerene tjelesne aktivnosti ili 75 minuta tjelesne aktivnosti visokog intenziteta (Kerschbaum i Nüssler, 2019; WHO, 2022).

Uloga prehrane u prevenciji razvoja karcinoma

Do danas je provedeno mnogo istraživanja koja su pokazala da se pravilnom i uravnoteženom prehranom mogu osigurati sve potrebne hranjive tvari, a time i prevenirati razvoj brojnih kroničnih nezaraznih bolesti. Kada govorimo o karcinomima ne postoji „super hrana" koja može spriječiti njihov razvoj, ali su istraživanja pokazala da konzumacija pojedine vrste hrane može smanjiti ili povećati rizik od razvoja pojedinih vrsta karcinoma (Grosso i sur., 2017).

Multicentrično prospektivno istraživanje *The European Prospective Investigation into Cancer and Nutrition* (EPIC study), provedeno u 10 europskih zemalja, istraživalo je povezanost čimbenika rizika povezanih s prehranom i pojave četiri najučestalija karcinoma u Europskoj populaciji (karcinom dojke, pluća, prostate i kolorektalni karcinom). Pokazalo se da odgovarajući unos voća i povrća može djelovati zaštitno na razvoj karcinoma dojke, pluća te debelog crijeva. Jednako je pokazano za unos voća i smanjeni rizik za karcinom prostate. Ujedno, dokazana je povezanost između nižeg unosa crvenog i prerađenog mesa te višeg unosa ribe s manjim rizikom od karcinoma dojke. Unos alkohola povećava rizik od razvoja karcinoma dojke i crijeva, a odgovarajući unos fermentiranih mliječnih proizvoda, odnosno jogurta, a time i kalcija, može imati zaštitni učinak na razvoj karcinoma crijeva i prostate (Ubago-Guisado i sur., 2021).

Hrana koja može pomoći u prevenciji razvoja karcinoma

Hrana biljnog podrijetla

Kada je riječ o prevenciji karcinoma prednost se daje općenito hrani biljnog podrijetla upravo iz razloga jer se na taj način može osigurati odgovarajući unos esencijalnih nutrijenata, mikronutrijenata i antioksidansa (kao vitamina E i C, selena), fitokemikalija, biljnih sterola i vlakana za koje je dokazano da mogu imati zaštitni učinak u razvoju pojedinih vrsta karcinoma (Kerschbaum i Nüssler, 2019; Mentella i sur., 2019).

Brojna provedena istraživanja pokazala su da pojedine vrste povrća (pogotovo kruciferno povrće i češnjak) i voća u svom sastavu sadrže antioksidanse koje štite DNA od oštećenja te stanice od oksidativnog stresa (Mentella i sur., 2019; Aune i sur., 2017). Stoga su i preporuke Svjetskog fonda za istraživanje karcinoma (eng. *World Cancer Research Fund*, WCRF) da bi dnevni unos trebao biti najmanje 400 g raspoređen kroz 5 serviranja. Provedeno prospektivno kohortno istraživanje pokazalo je povezanost između unosa krucifernog povrća (npr. cvjetača, kupus, brokula, rotkvica), kao izvora izotiocijana te smanjenog rizika od razvoja karcinoma pluća u osoba koje su bili nepušači (Mori i sur., 2017). Dodatno provedena meta-analiza prospektivnih kohortnih istraživanja pokazala je kako je općenito unos povrća u pušača značajno povezan sa smanjenjem rizika od razvoja karcinoma pluća. Isto tako umjeren unos voća značajno smanjuje rizik od karcinoma pluća kod pušača, ali iznimno visok unos negativno je povezan s razvojem rizika u osoba koje su bile pušači te u pušača (Wang i sur., 2019), odnosno ne postiže se nikakva daljnja korist povećanjem dnevnog unosa voća iznad ~400 g (Vieira i sur., 2016).

Ovo povrće ujedno je i izvor antioksidansa sulforafana (npr. brokula), iz skupine izotiocijanata, za koje je dokazano da može imati ulogu u prevenciji

i liječenju karcinoma dojke, kože, usne šupljine, debelog crijeva, mokraćnog mjehura i prostate (Nandini i sur., 2020). S druge strane, istraživanja su pokazala da ne postoji značajna povezanost između unosa narančastog i crvenog povrća i voća kao izvora karotenoida (npr. mrkva, rajčica, marelica) sa smanjenim rizikom od razvoja karcinoma (WCFR, 2018a). Poznato je da mogu djelovati na smanjenje karcinogeneze, ali je potrebno provesti dodatna istraživanja kako bi se utvrdio točan mehanizam djelovanja (Rowles i Erdman, 2020).

Citrusi su izvor flavonoida za koje je znanstveno dokazano da imaju antikancerogeno, antioksidatvno, protuupalno i drugo biološko djelovanje (Cirmi i sur., 2017). Posebno se ističe naringerin za kojeg su istraživanja pokazala da može usporiti razvoj pojedinih vrsta karcinoma na način da modificira signalne puteve, inducira apoptozu, djeluje na stanične cikluse i angiogenezu (Motallebi i sur., 2022).

Voće, povrće, cjelovite žitarice i mahunarke smatraju se najboljim izvorom vlakana za koje je znanstveno dokazano da mogu smanjiti rizik za razvoj kolorektalnog karcinoma. Stoga su preporuke da bi dnevni unos vlakana prema WCFR trebao biti oko 30 g (WCFR, 2018b).

Cjelovite žitarice su značajan izvor antioksidansa i brojnih bioaktivnih spojeva kao što su fenolni spojevi, lignani i fitoestrogeni (Motallebi i sur., 2022). Provedene meta-analize pokazale su kako je dnevni unos cjelovitih žitarica od oko 30 g povezan s oko 7 % smanjenim rizikom od ukupne smrtnosti kao posljedica karcinoma, s najjačim dokazima za karcinom jednjaka, želuca, gušterače i debelog crijeva (Gaesser, 2020).

Orašasti plodovi i mahunarke dobar su izvor fitokemikalija, vlakana i antioksidansa. Provedena istraživanja pokazala su povezanost između dnevnog unosa mahunarki od 100 g (1 porcija/dan) te orašastih plodova od 28 g (1 porcija/dan) sa smanjenjem rizika za 21 %, odnosno 33 % za razvoj kolorektalnog karcinoma (Jin i Je, 2022). Ujedno, istraživanja su pokazala kako redoviti unos češnjaka može dodatno doprinijeti smanjenju rizika od razvoja ove vrste karcinoma (Speciani i sur., 2023).

Postoje brojna istraživanja koja su pokazala dobrobit maslinovog ulja na zdravlje. Maslinovo ulje izvor je brojnih antioksidansa među kojima se ističu oleokantal i hidroksitirozol za koje je utvrđeno da imaju antitumorsko djelovanje, a najbolji izvor je ekstra djevičansko maslinovo ulje (Markellos i sur., 2022). Tako je nedavno provedeno istraživanje dokazalo da svakodnevna konzumacija 1,5 žlice maslinova ulja može sniziti ukupnu smrtnost uzrokovanu karcinomima za 17 % (Guasch-Ferré i sur., 2022).

Hrana životinjskog podrijetla

Istraživanja su pokazala da svakodnevni visoki unos mliječnih proizvoda (oko 700 g odnosno 4 serviranja/dan) može smanjiti rizik od razvoja kolorektalnog karcinoma te karcinoma prostate što se pripisuje brojnim prisutnim nutrijentima kao što su kalcij, vitamin D, laktoferin, linolna kiselina i probiotici (Ubago-Guisado i sur., 2021; Motallebi i sur., 2022; Jin i sur., 2020).

Međutim, postoje ograničeni dokazi da ova vrsta hrane može smanjiti rizik od razvoja karcinoma dojke u žena u perimenopauzi. Jednako vrijedi i za prehranu bogatu kalcijem u žena i perimenopauzi i postmenopauzi (He i sur., 2021; Wajszczyk i sur., 2021).

Postoje ograničeni dokazi da konzumacija ribe može smanjiti rizik od kolorektalnog karcinoma i karcinoma jetre. Masna plava riba bogata je omega-3 masnim kiselinama (eikosapentaenskom i dokosaheksaenskom masnom kiselinom) za koje je dokazano da mogu ublažiti oksidativni stres i upalne procese uzrokovane nealkoholnom masnom bolesti jetre (Jump i sur., 2015), dok su provedena eksperimentalna istraživanja pokazala da mogu smanjiti rizik od razvoja kolorektalnog karcinoma (Shin i sur., 2020). Visok unos masne morske ribe je povezan sa značajno smanjenim rizikom od razvoja karcinoma dojke (Ubago-Guisado i sur., 2021).

Hrana koja može doprinijeti razvoju karcinoma

Ne može se reći da određena hrana uzrokuje karcinom, ali svakako postoji dokazana povezanost između prekomjerne konzumacije određene vrste hrane (zbog njihovog utjecaja na organizam, načina njihove pripreme tj. obrade itd.) i povećanja rizika za razvoj karcinoma. Općenito, industrijski procesirana hrana (bogata dodanim šećerima, solju, trans masnim kiselinama, zasićenim masnim kiselinama, a s druge strane siromašna vlaknima) utječe na povećanje rizika za razvoj karcinoma (Rock, 2020). Prospektivno kohortno istraživanje provedeno od strane *UK Biobank*, na gotovo 200 tisuća ispitanika čije je zdravlje praćeno u narednom desetljeću, utvrdila je da konzumacija industrijski procesirane hrane povećava rizik za razvoj 34 različite vrste karcinoma (osobito jajnika i mozga). Povećanje konzumacije industrijski procesirane hrane za 10 % dovodi do 2 %-tnog povećanja rizika za razvoj karcinoma općenito te 19 %-tnog povećanja rizika za razvoj karcinoma jajnika, a povezana je i sa 6 % većom smrtnosti od karcinoma općenito, 16 % većom smrtnosti od karcinoma dojke i 30 % od karcinoma jajnika (Chang i Hu, 2023). Jedan od osnovnih puteva

kojima i šećer utječe na razvoj karcinoma je doprinos razvoju pretilosti i drugih metaboličkih poremećaja (kardiometabolički, inzulinska rezistencija, šećerna bolest tipa 2 itd.), koji dalje predstavljaju čimbenike rizika za razvoj karcinoma (Malik i Hu, 2022). Važno je obratiti pozornost na tzv. „skriveni šećer" u hrani, a to se ponajprije odnosi na: bezalkoholne zaslađene napitke, glukozno-fruktozni te kukuruzni sirup, rafinirane žitarice, pekarske proizvode itd. Kada govorimo o žitaricama, postoje istraživanja čije rezultate je za sad potrebno promatrati s oprezom zbog potrebe za daljnjim istraživanjima, ali ukazuju na povećanje rizika za razvoj karcinoma uslijed konzumacije rafiniranih žitarica (Gaesser, 2020), budući da se u tom procesu rafinacije često dodaje šećer i druge komponente čime se povećava njihov glikemijski indeks i kalorijska vrijednost, a smanjuje se udio vlakana, vitamina i minerala (WCRFc, 2018). Osim toga, žitarice mogu biti kontaminirane mikotoksinima (npr. aflatoksin) od kojih su neki potvrđeni kancerogeni (aflatoksin se povezuje s razvojem karcinoma jetre) (WCRFc, 2018; Mentela i sur., 2019).

Međunarodna agencija za istraživanje karcinoma (eng. *International Agency for Research on Cancer*, IARC), svrstala je procesirano meso u skupinu kancerogena za ljude (skupina 1), a crveno meso u skupinu vjerojatnih kancerogena za ljude (skupina 2A) (Turesky, 2018). Potencijalni mehanizmi koji se najvjerojatnije nalaze u pozadini ovih povezanosti, odnose se zapravo na spojeve koji nastaju prilikom obrade mesa. Primjerice, nitriti i nitrati u prerađenom/sušenom mesu, nitrozamini u crijevima čije stvaranje je katalizirano hem-željezom, a dovode do oksidativnih oštećenja DNA, zatim heterociklički aromatski amini (HAA) i policiklički aromatski ugljikovodici (PAH) koji nastaju prilikom toplinske obrade mesa na visokim temperaturama (prženje, roštiljanje i sl.) (Farvid i sur., 2021; Singh i sur., 2020). Osim toga, prekomjerna konzumacija crvenog (i procesiranog) mesa može poticati upalne procese i oksidativni stres u organizmu, što može inicirati karcinogenezu (Rock i sur., 2020).

Globalno, oko 41 % svih novih slučajeva karcinoma u 2020. godini može se pripisati prekomjernom unosu alkohola (Rumgay i sur., 2021). Američki institut za istraživanje karcinoma (eng. *American institute for cancer research*, AICR) klasificirao je konzumaciju alkohola kao treći glavni promjenjivi čimbenik rizika za razvoj karcinoma (nakon pušenja i pretilosti). Za pojedince koji ipak piju alkohol, preporuka je ograničiti konzumaciju na ne više od 1 pića dnevno za žene i ne više od 2 pića dnevno za muškarce (WCFR, 2018b).

Kada govorimo o mlijeku i mliječnim proizvodima, postoje oprečni rezultati istraživanja vezani uz utjecaj na karcinom dojke i prostate. Ova vrsta hrane je glavni prehrambeni izvor kalcija, čije visoke koncentracije smanjuju regulaciju sinteze biološki aktivnog vitamina D, a postoje ograničeni dokazi da tako utječu na povećanu proliferaciju stanica u prostati, odnosno povećavaju rizik za razvoj karcinoma (Herby i sur., 2023; WCRF, 2018b). Nedavno provedena populacijska istraživanja pokazala su da postoji moguća povezanost između karcinoma dojke i visokog unosa mlijeka (Herby i sur., 2023). Još uvijek nije u potpunosti razjašnjeno utječu li na taj rizik zasićene masne kiseline iz mlijeka ili druge komponente (npr. kalcij, estrogen koji se nalazi u kravljem mlijeku kao posljedica industrijske proizvodnje, povećana koncentracija čimbenika rasta 1 sličnog inzulinu (eng. *insulin-like growth factor* 1, IGF-1)). Osim toga, mlijeko i mliječni proizvodi komponente su tzv. „zapadnjačke prehrane" stoga se to povećanje rizika može pripisati i ukupnom štetnom/kancerogenom utjecaju ovakvog načina prehrane (Sargsyan i Dubsai, 2021) te su svakako potrebna daljnja istraživanja.

Zaključak

Danas je karcinom jedan od vodećih uzročnika smrti diljem svijeta. Ne postoji jedna vrsta hrane koja može spriječiti nastanak karcinoma nego se savjetuje raznovrsna, pravilna i uravnotežena cjeloživotna prehrana koja uključuje visok unos hrane biljnog podrijetla; voća, povrća, cjelovitih žitarica, mahunarki te hrane životinjskog podrijetla koja je izvor visokovrijednih nutrijenata kao što su riba i mliječni proizvodi. Glavni zaštitni učinak krije se u sinergiji hrane, a kao najbolji prehrambeni obrazac kojeg karakterizira unos ove vrste hrane je Mediteranska prehrana za koju je dokazano da može utjecati na prevenciju pojedinih vrsta karcinoma kao i na ukupnu smrtnost uzrokovanu karcinomima (Mentella i sur., 2019). Uz provođenje pravilne prehrane, a kako bi prevenirali razvoj brojnih kroničnih nezaraznih bolesti te pojedinih vrsta karcinoma, savjetuje se provođenje redovite tjelesne aktivnosti i održavanje normalne tjelesne mase.

Literatura

Aune, D., Giovannucci, E., Boffetta, P., Fadnes, L. T., Keum, N., Norat, T., Greenwood, D. C., Riboli, E., Vatten, L. J., Tonstad, S. (2017): Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-

analysis of prospective studies. *Int. J. Epidemiol.* 46 (3), 1029–1056.

Cirmi, S., Maugeri, A., Ferlazzo, N., Gangemi, S., Calapai, G., Schumacher, U., Navarra, M. (2017): Anticancer Potential of Citrus Juices and Their Extracts: A Systematic Review of Both Preclinical and Clinical Studies. *Front. Pharmacol.* 8, 420.

Chang, K., Gunter, M. J., Rauber, F., Levy, R. B., Huybrechts, I., Kliemann, N., Millett, C., Vamos, E. P. (2023): Ultra-processed food consumption, cancer risk and cancer mortality: a large-scale prospective analysis within the UK Biobank. *Eclinicalmedicine* 56, 101840.

European Association for the Study of Obesity (EASO) (2020): OBESITY STATISTICS. Dostupno na: < https://easo.org/media-portal/statistics/>.

Farvid, M.S., Sidahmed, E., Spence, N.D., Mante Angua, K., Rosner, B.A., Barnett, J.B. (2021): Consumption of red meat and processed meat and cancer incidence: A systematic review and meta-analysis of prospective studies. *Eur. J. Epidemiol.* 36, 937-951.

Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D. M., Piñeros, M., Znaor, A., Bray, F. (2021): Cancer statistics for the year 2020: An overview. *Int. J. Cancer* 2021, 10.

GBD 2019 Cancer Risk Factors Collaborators (2022): The global burden of cancer attributable to risk factors, 2010-19:a systematic analysis for the Global Burden of Disease Study 2019. *Lancet (London, England)* 400 (10352), 563– 591.

Gaesser, G. A. (2020): Whole Grains, Refined Grains, and Cancer Risk: A Systematic Review of Meta-Analyses of Observational Studies. *Nutrients* 12 (12), 3756.

Grosso, G., Bella, F., Godos, J., Sciacca, S., Del Rio, D., Ray, S., Galvano, F., Giovannucci, E. L. (2017): Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk. *Nutr. Rev.* 75 (6), 405-419.

Guasch-Ferré, M., Li, Y., Willett, W. C., Sun, Q., Sampson, L., Salas-Salvadó, J., Martínez-González, M. A., Stampfer, M. J., Hu, F. B. (2022): Consumption of Olive Oil and Risk of Total and Cause-Specific Mortality Among U.S. Adults. *J. Am. Coll. Cardiol.* 79 (2), 101–112.

He, Y., Tao, Q., Zhou, F., Si, Y., Fu, R., Xu, B., Xu, J., Li, X., Chen, B. (2021): The relationship between dairy products intake and breast cancer incidence: a meta-analysis of observational studies. *BMC cancer* 21 (1), 1109.

Herby, A. R., Cullimore, J. P., Paul-Quinn, J. L., Crosby, L. M. (2023): Dairy Intake and Incidence of Common Cancers in Prospective Studies: A Narrative Review. *International Journal of Disease Reversal and Prevention* 5(1), 14.

Jin, S., Je, Y. (2022): Nuts and legumes consumption and risk of colorectal cancer: a systematic review and meta-analysis. *Eur. J. Epidemiol*. 37 (6), 569–585.

Jin, S., Kim, Y., Je, Y. (2020): Dairy Consumption and Risks of Colorectal Cancer Incidence and Mortality: A Meta-analysis of Prospective Cohort Studies. *Cancer Epidemiol. Biomarkers Prev.* 29 (11), 2309–2322.

Jump, D. B., Depner, C. M., Tripathy, S., Lytle, K. A. (2015): Potential for dietary ω-3 fatty acids to prevent nonalcoholic fatty liver disease and reduce the risk of primary liver cancer. *Adv. Nutr.* 6(6), 694–702.

Jurdana, M. (2021): Physical activity and cancer risk. Actual knowledge and possible biological mechanisms. *Radiology and oncology* 55 (1), 7–17.

Kerschbaum, E., Nüssler, V. (2019): Cancer prevention with nutrition and lifestyle. *Visc. Med.* 35 (4), 204-209.

Key, T.J., Bradbury, K.E., Perez-Cornago, A., Sinha, R., Tsilidis, K.K., Tsugane, S. (2020): Diet, nutrition, and cancer risk: what do we know and what is the way forward?. *BMJ* 368.

Leitzmann, M., Powers, H., Anderson, A. S., Scoccianti, C., Berrino, F., Boutron-Ruault, M. C., Cecchini, M., Espina, C., Key, T. J., Norat, T., Wiseman, M., Romieu, I. (2015): European Code against Cancer 4th Edition: Physical activity and cancer. *Cancer Epidemiol*. 39 (1), 46-55.

Malik, V.S., Hu, F.B. (2022): The role of sugar-sweetened beverages in the global epidemics of obesity and chronic diseases. *Nat. Rev. Endocrinol*. 18 (4), 205-218.

Markellos, C., Ourailidou, M. E., Gavriatopoulou, M., Halvatsiotis, P., Sergentanis, T. N., Psaltopoulou, T. (2022): Olive oil intake and cancer risk: A systematic review and meta-analysis. *PloS one* 17 (1), e0261649.

Mentella, M.C., Scaldaferri, F., Ricci, C., Gasbarrini, A., Miggiano, G.A.D. (2019): Cancer and Mediterranean Diet: A Review. *Nutrients* 11, 2059.

Mori, N., Shimazu, T., Sasazuki, S., Nozue, M., Mutoh, M., Sawada, N., Iwasaki, M., Yamaji, T., Inoue, M., Takachi, R., Sunami, A., Ishihara, J., Sobue, T., Tsugane, S. (2017): Cruciferous Vegetable Intake Is Inversely Associated with Lung Cancer Risk among Current Nonsmoking Men in the Japan Public Health Center (JPHC) Study. *J. Nutr.* 147 (5), 841–849.

Motallebi, M., Bhia, M., Rajani, H. F., Bhia, I., Tabarraei, H., Mohammadkhani, N., Pereira-Silva, M., Kasaii, M. S., Nouri-Majd, S., Mueller, A. L., Veiga, F. J. B., Paiva-Santos, A. C., Shakibaei, M. (2022): Naringenin: A potential flavonoid phytochemical for cancer therapy. *Life Sci.* 305, 120752.

Nandini, D. B., Rao, R. S., Deepak, B. S., Reddy, P. B. (2020): Sulforaphane in broccoli: The green chemoprevention!! Role in cancer prevention and therapy. *J. Oral Maxillofac. Pathol*. 24 (2), 405.

Narimatsu, H., Yaguchi, Y.T. (2022): The Role of Diet and Nutrition in Cancer: Prevention, Treatment, and Survival. *Nutrients* 14, 3329.

Renehan, A. G., Soerjomataram, I. (2016): Obesity as an Avoidable Cause of Cancer (Attributable Risks). *Recent Results Cancer Res*. 208, 243-256.

Rock, C.L., Thomson, C., Gansler, T., Gapstur, S.M., McCullough, M.L., Patel, A.V., Andrews, K.S., Bandera, E.V., Spees, C.K., Robien, K., Hartman, S., Sullivan, K., Grant, B.L., Hamilton, K.K., Kushi, L.H., Caan, B.J., Kibbe, D., Donze Black, J., Wiedt, T.L., McMahon, C., Sloan, K., Doyle, C. (2020): American Cancer Society guideline for diet and physical activity for cancer prevention. *CA Cancer J. Clin.* 70 (4), 245-271.

Rowles, L., Erdman, J. W. (2020): Carotenoids and their role in cancer prevention. *BBA Mol. Cell Biol. Lipids* 1865 (11), 158613.

Sargsyan, A. i Dubasi, H. B. (2021): Milk consumption and prostate cancer: a systematic review. *WJMH* 39 (3), 419.

Shin, A., Cho, S., Sandin, S., Lof, M., Oh, M. Y., Weiderpass, E. (2020): Omega-3 and -6 Fatty Acid Intake and Colorectal Cancer Risk in Swedish Women's Lifestyle and Health Cohort. *Cancer Res. Treat*. 52(3), 848–854.

Singh, L., Agarwal, T., Simal-Gandara, J. (2020): PAHs, diet and cancer prevention: Cooking process driven-strategies. *Trends Food Sci. Technol*. 99, 487-506.

Speciani, M. C., Gargari, G., Penagini, R., Mutignani, M., Ferraroni, M., Natale, A., Katsoulis, M., Cintolo, M., Leone, P., Airoldi, A., Vecchi, M., Bonzi, R., Ciafardini, C., Oreggia, B., Carnevali, P., Guglielmetti, S., Riso, P., La Vecchia, C., Rossi, M. (2023): Garlic consumption in relation to colorectal cancer risk and to alterations of blood bacterial DNA. *Eur. J. Nutr.* 10.

Turesky, R. J. (2018): Mechanistic evidence for red meat and processed meat intake and cancer risk: a follow-up on the international agency for research on cancer evaluation of 2015. *Chimia* 72 (10), 718.

Ubago-Guisado, E., Rodríguez-Barranco, M., Ching-López, A., Petrova, D., Molina-Montes, E., Amiano, P., Barricarte-Gurrea, A., Chirlaque, M.D., Agudo, A., Sánchez, M. J. (2021): Evidence update on the relationship between diet and the most common cancers from the European Prospective Investigation into Cancer and Nutrition (EPIC) study: a systematic review. *Nutrients* 13 (10), 3582.

Vieira, A. R., Abar, L., Vingeliene, S., Chan, D. S., Aune, D., Navarro-Rosenblatt, D., Stevens, C., Greenwood, D., Norat, T. (2016): Fruits, vegetables and lung cancer risk: a systematic review and meta-analysis. *Ann Oncol.* 27(1), 81–96.

Wajszczyk, B., Charzewska, J., Godlewski, D., Zemła, B., Nowakowska, E., Kozaczka, M., Chilimoniuk, M., Pathak, D. R. (2021): Consumption of Dairy Products and the Risk of Developing Breast Cancer in Polish Women. *Nutrients* 13 (12), 4420.

Wang, C., Yang, T., Guo, X. F., Li, D. (2019): The Associations of Fruit and Vegetable Intake with Lung Cancer Risk in Participants with Different Smoking Status: A Meta-Analysis of Prospective Cohort Studies. *Nutrients* 11(8), 1791.

World Cancer Research Fund (WCRFa), American Institute for Cancer Research (AICR) (2018): Diet, nutrition, physical activity and cancer: a global perspective - the third expert report. Dostupno na: https://www.wcrf.org/dietandcancer.

World Cancer Research Fund (WCRFb), American Institute for Cancer Research (AICR). Continuous Update Project Expert Report 2018. (2018): Recommendations and public health and policy implications. Dostupno na: https://www.wcrf.org/dietandcancer.

World Cancer Research Fund (WCRFc), American Institute for Cancer Research (AICR) (2018): Wholegrains, vegetables and fruit and the risk of cancer - the third expert report. Dostupno na: https://www.wcrf.org/wp-content/uploads/2020/12/Wholegrains-veg-and-fruit.pdf .

World Health Organization (2019): Cancer prevention; 2019. Dostupno na: https://www.who.int/cancer/prevention/en/

World Health Organization (2018): Global Strategy on Diet, Physical Activity and Health Childhood overweight and obesity. Dostupno na: <https://www.who.int/dietphysicalactivity/childhood/en/>.

World Health Organization (2022): Physical activity. Dostupno na: https://www.who.int/news-room/fact-sheets/detail/physical-activity

THE ROLE OF DIET IN CANCER PREVENTION

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review paper

Summary

Cancer is becoming an increasing public health problem today, the prevalence of which is continuously increasing around the world. It is among the leading causes of mortality and the main risk factors are those that we can actually influence and thereby prevent from 30 to 50% of different types of cancer. One of the key and main steps in prevention is maintaining a normal/healthy body mass, with a proper, balanced and varied diet along with regular physical activity. There is no "super food" that can be said to prevent the development of cancer, nor is there a specific food that causes it, but there are protective ways of eating that can contribute to the prevention or development of this disease, as part of overall prevention. It is generally recommended to give preference to food of plant origin, which is best covered by the principles of the Mediterranean diet. Such a diet is rich in vegetables (especially green leafy, red, orange and cruciferous), fruits (berries, citrus, red and orange), legumes, whole grains and olive oil. From foods of animal origin, more frequent consumption of fish and dairy products is recommended. On the other hand, it is recommended to avoid the consumption of industrially processed food rich in salt, fat of low nutritional quality and added sugar, to limit the consumption of red meat and to pay attention to the process of food preparation in order not to create harmful/carcinogenic compounds. It is recommended to exclude processed meat, as well as excessive alcohol consumption. Adopting recommendations on lifestyle changes, which includes proper nutrition and regular physical activity is an important part of preventing the development of cancer.

Keywords: prevention, plant-based foods, antioxidants, cancer, processed foods

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VAŽNOST PROCJENE NUTRITIVNOG STATUSA BOLESNIKA S KOLOREKTALNIM KARCINOMOM

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Sažetak

Kolorektalni karcinom (engl. Colorectal Cancer, CRC) je treći najčešći maligni tumor na svijetu. Procjenjuje se da 10-20 % pacijenata oboljelih od karcinoma umire zbog posljedica pothranjenosti, a ne zbog samog karcinoma. Nutritivni status bolesnika znatno utječe na ishod liječenja bolesnika s CRC-om, bez obzira na to je li riječ o pothranjenosti, gubitku potporne mišićne mase, normalnoj ili prekomjernoj tjelesnoj masi. Problemi s prehranom trebaju se uzeti u obzir i rješavati od vremena postavljanja dijagnoze, kirurškog liječenja te paralelno s antineoplastičnim liječenjem (kemoterapija, imunoterapija i endokrina terapija) i radioterapijom. Pri tom je važno imati multidisciplinarni tim jer postupci uključuju procjenu statusa validiranim probirnim upitnicima na malnutriciju NRS 2002 (engl. Nutritional Risk Screening 2002) i sarkopeniju SARC-F (engl. Strength, assistance with walking, rising from a chair, climbing stairs and falls), mjerenje mišićne snage i funkcije dinamometrijom šake, analizu sastava tijela bioelektričnom impedancijom, procjenu prehrambenih navika i unosa hrane te savjetovanje o prehrani. Studije daju ohrabrujuće rezultate u primjeni fitonutrijenata zelenog čaja, ekstrakta kvercetina, omega-3 masnih kiselina, probiotika, prebiotika, prehrambenih vlakana i orašastih plodova zahvaljujući njihovim protuupalnim i antioksidativnim svojstvima. Osnovni princip perioperativne dijetoterapije je adekvatnim namirnicama smanjiti ili spriječiti pojavu nutritivnih deficita i komplikacija koje se povećavaju promjenom nutritivnog statusa, dok u poslijeoperacijskoj i terapijskoj fazi liječenja pozitivno utjecati na bolesnikov oporavak i povratak svakodnevnim aktivnostima.

Ključne riječi: kolorektalni karcinom, nutritivni status, nutritivna potpora, perioperativna dijetoterapija

Uvod

Kolorektalni karcinom (*engl. Colorectal Cancer, CRC*) je treći najčešći maligni tumor na svijetu, odmah nakon karcinoma prostate i pluća/bronha u muškaraca te dojke i pluća/bronha u žena. Tijekom 2020. godine u svijetu je potvrđeno 1 931 590 novih slučajeva CRC-a (International Agency for Research on Cancer, 2020; Sung i sur., 2021). Prema podacima Hrvatskog zavoda za javno zdravstvo (HZJZ, 2020), karcinom debelog i završnog crijeva najčešći je novo dijagnosticirani karcinom u Republici Hrvatskoj s 3 706 novih slučajeva. CRC je multifaktorska bolest na koju utječu brojni rizični čimbenici. Nepromjenjivi rizični čimbenici su: dob (40 do 50 godina), spol (incidencija je veća u muškarca), upalne bolesti crijeva, nasljedne mutacije (pozitivna obiteljska anamneza), zračenje abdomena, cistična fibroza, kolecistektomija i terapija antiandrogenima (American Cancer Society, 2017).

Promjenjivi rizični čimbenici su: način života, prehrana, nutritivni status, šećerna bolest i inzulinska rezistencija (American Cancer Society, 2017).

Brojna istraživanja dokazuju pozitivne učinke određenih obrazaca prehrane i načina života na prevenciju CRC-a (Thanikachalam i Khan, 2019), dok je malo spoznaja o utjecaju nutritivnog statusa i dijetoterapije na tijek liječenja.

Nutritivni status bolesnika znatno utječe na ishod liječenja bolesnika s CRC-om, bez obzira na to je li riječ o pothranjenosti, gubitku potporne mišićne mase, normalnoj ili prekomjernoj tjelesnoj masi. Pothranjenost negativno utječe na kvalitetu života, a procjenjuje se da 10-20 % pacijenata oboljelih od karcinoma umire zbog posljedica pothranjenosti, a ne zbog samog karcinoma (Muscaritoli i sur., 2021).

U razvijenim zapadnim zemljama s rastućim brojem pretilih ljudi često malnutricija i sarkopenija ostaju neprepoznati, osobito kod novootkrivenih bolesnika s CRC-om. Razlog je tome način procjene nutritivnog statusa i antropometrijskih obilježja (Ryan i sur., 2016).

Naime, od svih antropometrijskih obilježja indeks tjelesne mase (ITM) u najširoj je uporabi za procjenu stanja uhranjenosti, i to kao pokazatelj smanjene ili prekomjerne tjelesne mase. Bolesnici s ITM-om od 18 do 20 kg/m^2 pripadaju kategoriji potencijalno pothranjenih te se kod njih prepoznaje malnutricija i sarkopenija. Međutim, kod bolesnika koji su normalne ili prekomjerne tjelesne mase malnutricija i sarkopenija često su „maskirane“ ITM-om unutar normalnog raspona te se oslanjanjem samo na ITM malnutricija i sarkopenija mogu lako previdjeti (Martinis i Lasić, 2020).

Moghadamyeghaneh i sur. (2015) ističu da gubitak tjelesne mase koji je nastao zbog bolesti u bolesnika koji imaju prekomjernu tjelesnu masu nije nužno povezan sa

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ITM-om. Takav gubitak tjelesne mase, osobito prije operacije bolesnika s CRC-om, rezultira promjenama u sastavu tijela povezanih s gubitkom potporne mišićne mase uz povećanje količine masnog tkiva. Prijeoperacijski gubitak tjelesne mase u bolesnika s CRC-om planiranih za resekciju debelog crijeva povezan je s lošijom prognozom, signifikantnim mortalitetom i produljenom hospitalizacijom. Pregledni radovi potvrđuju da su nenamjerni gubitak tjelesne mase i pad koncentracije serumskog albumina bili glavni prediktori ishoda kirurškog liječenja u bolesnika starijih od 65 godina s operacijama na gornjem dijelu probavnog sustava (Tsaousi i sur., 2017; Weimann i sur., 2017; Martinis i Lasić, 2020; Muscaritoli i sur., 2021).

Prema Ziętarska i sur. (2017) maligni tumori su heterogena skupina bolesti u kojih metaboličke abnormalnosti i prehrambeni problemi mogu biti različiti ovisno o vrsti, položaju i stadiju tumora.

Klinička slika bolesnika s CRC-om ovisi o lokalizaciji tumorske lezije. Većina bolesnika u početnom stadiju karcinoma nema nikakvih simptoma te se kod njih dijagnoza postavlja probirnim testom na okultno krvarenje (Zietarska i sur., 2017). Simptomi mogu biti rektalno krvarenje, promjene u navikama pražnjenja crijeva i bol u abdomenu te promjene u unosu i odabiru hrane. Gubitak na tjelesnoj masi veći od 10 ili 15 % u posljednjih šest mjeseci, umor te anemija sugeriraju da je u pitanju uznapredovala bolest (Melnyk i sur., 2011; Weimann i sur., 2017; Muscaritoli i sur., 2021).

Prevalencija malnutricije u bolesnika s CRC-om je od 30 do 90 %, a ovisi o mjestu karcinoma, stadiju bolesti i načinu liječenja. De van der Schueren i sur. (2018) navode kako malnutricija smanjuje toleranciju na liječenje kemoterapijom te smanjuje kvalitetu života i preživljavanje. Glavni uzroci su metaboličke promjene izazvane karcinomom i/ili simptomi karcinoma koji uzrokuju mučninu i bol, što dovodi do smanjenog unosa hrane (Van Cutsem i Arends, 2005).

Weimann i sur. (2017) te Muscaritoli i sur. (2021) naglašavaju važnost:

- procjene nutritivnog statusa putem obrasca (npr. procjena nutritivnog rizika putem upitnika NRS 2002) pri prijemu na bolničko liječenje ili prvom kontaktu
- praćenje i dokumentaciju oralnog unosa hrane
- praćenje (ITM) ili indeksa nemasne tjelesne mase (FFMI)
- nutricionističko savjetovanje i intervencija

S tim u vezi definirani su kriteriji za uvođenje perioperacijske dijetetičke potpore te Europsko društvo za kliničku prehranu (*engl. The European Society for Clinical Nutrition and Metabolism, ESPEN*) rizičnima smatra:

- gubitak tjelesne mase veći od 10 ili 15 % u posljednjih šest mjeseci
- ITM < 18,5 kg/m^2
- upitnici za procjenu statusa – Subjektivna općenita procjena nutritivnog statusa (*engl. Subjective Global Assessment – SGA*) stupanj C ili NRS 2002 ≥ 3
- prijeoperacijski serumski albumin < 30 g/l (bez dokazane jetrene ili bubrežne disfunkcije)

Zbog svega navedenog nutritivnu procjenu i plan nutritivne njege je važno provesti odmah nakon postavljanja dijagnoze u bolesnika koji nemaju klinički manifestiranu malnutriciju, ali se očekuje da bolesnik neće moći kroz određeni period unijeti potrebnu količinu hrane (Ryan i sur., 2016).

Time se smanjuju rizici od nastanka nutritivnih deficita i komplikacija koje rastu s promjenama nutritivnog statusa. Problemi s prehranom trebaju se uzeti u obzir i rješavati od vremena dijagnoze, kirurškog liječenja te paralelno s antineoplastičnim liječenjem (kemoterapija, imunoterapija i endokrina terapija) i radioterapijom (Lewandowska i sur., 2022).

Istraživanje Daniele i sur. (2017) pokazuje da nutritivna procjena i intervencija bolesnika s CRC-om, bez obzira na stupanj uhranjenosti, može utjecati na bolje perioperacijske ishode te na sniženje stope mortaliteta. Dokazano je da perioperacijska nutritivna intervencija poboljšava perioperacijske ishode, uključujući smanjenje infekcija kirurške rane i ostalih morbiditeta za 20 do 40 % (Zelić i sur., 2014; Weimann i sur., 2017; Gustafsson i sur., 2018).

Procjena nutritivnog statusa bolesnika s CRC-om

Prema relevantnim smjernicama (Weimann i sur., 2017; Gustafsson i sur., 2018; Muscaritoli i sur., 2021) u bolesnika s malignim bolestima koji se pripremaju za elektivni kirurški zahvat već u tijeku dijagnostičke obrade potrebno je procijeniti nutritivni status koristeći validirane dijagnostičke postupke. Pri tom je važno imati multidisciplinarni tim koji uključuju liječnika, medicinsku sestru i nutricionista (Deftereos i sur., 2021, Vaughan i sur., 2021) zbog postupaka koji uključuju procjenu statusa dijetetičkim i antropometrijskim metodama te perioperacijsko savjetovanje o prehrani i plan nutritivne njege (Burden i sur., 2017). Dijetetičke metode uključuju: validirane probirne upitnike na malnutriciju NRS 2002 (*engl. Nutritional Risk Screening 2002)* i sarkopeniju SARC-F (*engl. Strength, assistance with walking, rising from a chair, climbing stairs and falls*) te nutritivnu anamnezu – procjenu prehrambenih navika i unosa hrane. Antropometrijske metode su:

mjerenje mišićne snage i funkcije dinamometrijom šake, mjerenje opsega struka i opsega potkoljenice te analiza sastava tijela putem bioelektrične impedancije.
S obzirom na dobivene rezultate procjene i mjerenja, određuje se stupanj nutritivnog rizika, prijeoperacijsko savjetovanje bolesnika o prehrani i plan nutritivne njege. Svim visokorizičnim i pothranjenim bolesnicima uvodi se visokoenergetska i visokoproteinska oralna nutritivna potpora u trajanju od 7 do 14 dana prije planirane operacije (Weimann i sur., 2017; Gustafsson i sur., 2018; Muscaritoli i sur., 2021). Cilj savjetovanja o prehrani i plana nutritivne njege je smanjiti perioperacijski stres uz što brži oporavak funkcije crijeva te smanjenje učestalosti komplikacija nakon kirurškog liječenja (Burden i sur., 2017, Vanghan i sur., 2021).

Dijetetičke metode

Probirni upitnik NRS 2002

Xie i sur. (2022) zaključuju da u bolesnika s CRC-om procjena nutritivnog statusa prije i tijekom hospitalizacije treba biti dio rutinske kliničke prakse pri čemu je najbolje koristiti NRS 2002 probirni upitnik. U studiji provedenoj na 301 bolesniku s CRC-om utvrdili su da je NRS 2002 točniji u utvrđivanju prisutnosti nutritivnog rizika prilikom prvog pregleda prije hospitalizacije u odnosu na MNA (*eng. Mini Nutritional Assessment*), MUST (*eng. Malnutrition Universal Screening Tool*), NRI (*eng. Nutritional Risk Index*) i MST (*eng. Malnutrition Screening Tool*) upitnike.
Upitnik NRS 2002 je alat kojim se u inicijalnom probiru odgovara na četiri pitanja (ITM < 20,5 kg/m^2, gubitak tjelesne mase u posljednja tri mjeseca, smanjeni unos hrane posljednjeg tjedna i težina bolesti). Pozitivan odgovor na bilo koje od pitanja upućuje ispitivača na završni probir u kojem se procjenjuje odstupanje u nutritivnom statusu.
Kondrup i sur. (2003) navode da ukupan zbroj NRS 2002 ≥ 3 upućuje na nutritivni rizik i potrebu za nutritivnom potporom. Zbroj manji od 3 znači potrebu tjednog ponavljanja probira. U slučaju planiranog operativnog zahvata čak i ako je NRS 2002 < 3, nutritivna potpora je indicirana jer se očekuje da bolesnik neće imati adekvatni unos hrane kroz određeni period.

Probirni upitnik SARC-F

Matsui i sur. (2022) preporučuju SARC-F upitnik za probir sarkopenije u studiji provedenoj na 421 bolesnika s gastrointestinalnim zloćudnim tumorima. Kod tih bolesnika SARC-F se pokazao kao alat koji ima nisku do umjerenu osjetljivost za predviđanje niske mišićne snage. Upitnik sadrži pet pitanja koja se temelje na bolesnikovoj percepciji u ograničenjima snage, sposobnosti hoda, ustajanju sa stolca, penjanju uz stepenice i padovima u posljednjih godinu dana (Malmstrom i sur., 2016).

Procjena nutritivnog unosa

Važan dio procjene nutritivnog statusa čini mjerenje oralnog unosa hrane, što omogućuje prepoznavanje neadekvatnog unosa energije i nutrijenata u perioperacijskom periodu. Metode koje se uobičajeno primjenjuju uključuju 24-satno prisjećanje, dnevnik prehrane te upitnike o učestalosti konzumiranja namirnica kako bi se procijenio unos nutrijenata prije bolničkog i kirurškog liječenja. Ako je unos hrane ili nutrijenata manji od 50 % preporučenog unosa, dodatno se povećava rizik od malnutricije (Martinis i Lasić, 2020). Prema Sun i sur. (2015) niski unos hrane i nutrijenata prije bolničkog kirurškog liječenja bolesnika s CRC-om bolji je prediktor nutritivnog rizika nego sam NRS 2002 upitnik.

Antropometrijske metode

Analiza sastava tijela bioelektričnom impedancijom

Analiza bioelektrične impedancije (BIA) je pouzdana i neinvazivna metoda koja se temelji na mjerenju električnih signala (niske sigurne doze struje od 800 μA) koji prolaze kroz masno tkivo, mišiće i vodu u tijelu, a povezana je s nutritivnim statusom bolesnika i ishodima liječenja (Gupta i sur., 2008; Tsaousi i sur., 2017).
Fazni kut (*engl. phase angle – PhA*) jest linearna metoda mjerenja odnosa između reaktancije (Rc) (otpor koji proizvodi stanična membrana) i električnog otpora (R) (koji pruža protok struje kroz tijelo). Uzimanjem luka tangentne vrijednosti omjera reaktancije u odnosu na električni otpor dobivamo vrijednost faznog kuta (PhA = arctangens reaktancija / električni otpor × 180°/π). PhA se direktno mjeri bioelektričnom impedancijom. PhA je tumačen kao pokazatelj cjelovitosti membrane, tj. distribucije vode između unutarstaničnih i izvanstaničnih prostora. Smatra se parametrom staničnog zdravlja jer mjeri kapacitet stanične membrane te odražava kvalitetu tjelesnih stanica (Martinis i Lasić, 2020).
U studiji provedenoj na 66 bolesnika liječenih u jedinici intenzivnog liječenja Lee i sur. (2015) zaključuju da su rezultati BIA mjerenja uključujući: PhA, izvanstaničnu tekućinu (*engl. extra cellular water*, ECW) i ECW/ukupnu tjelesnu tekućinu (*engl. total body water*, TBW), značajno povezani s nutritivnim statusom. Rezultati su pokazali kako je PhA veći u skupini bolesnika s normalnom tjelesnom masom, dok je indeks edema (ECW/TBW) bio veći u skupini izrazito pothranjenih bolesnika. Kod onih koji nisu preživjeli,

PhA je bio značajno niži, dok ECW/TBW i udio TBW/nemasna masa bili su veći nego kod preživjelih.
Upravo zbog toga PhA se smatra važnim prognostičkim alatom za procjenu kliničkih ishoda ili za praćenje progresije bolesti kod različitih kliničkih stanja kao što su ciroza jetre, hemodijaliza i maligna oboljenja. PhA može biti bolji prediktor od serumskih ili antropometrijskih nutritivnih pokazatelja.
Yasui – Yamada i sur. (2020) su u svom retrospektivnom istraživanju provedenom na 501 bolesniku s gastrointestinalnim (GI) i hepatobilijarnim (HBP) karcinomom pokazali da je najveća incidencija poslijeoperacijskih komplikacija i prevalencija pothranjenosti upravo u skupini ispitanika s niskim vrijednostima PhA. PhA navode kao koristan kratkoročni i dugoročni postlijeoperacijski prognostički marker za bolesnike s GI i HBP karcinomom.
Gomes i sur. (2020) su u 124 onkološka bolesnika zabilježili smanjenje količine unutarstanične tekućine uz povećanje ECW-a zbog narušenog integriteta staničnih membrana. Visoke vrijednosti ECW/TBW omjera može se pronaći u bolesnika na hemodijalizi ili ascitesom te starijih, izrazito pretilih ili pothranjenih. Pothranjenost dovodi do skupljanja mišićnih stanica uz prelazak tekućine iz stanica u ekstracelularni prostor što na kraju dovodi do relativnog povećanja ECW-a te smanjenja PhA (Fan i sur., 2012).

Dinamometrija šake

Metoda za mjerenje mišićne snage (*engl. hand grip strength,* HGS) odnosno statične jakosti mišića šake u izravnoj je korelaciji s nutritivnim statusom te može upućivati na rane promjene mišićne funkcije uzrokovane malnutricijom. Prediktor je komplikacija poslije operacije te gubitka mišićne snage i funkcije (skeletnih mišića) ako je vrijednost manja od 85 % referentne vrijednosti za dob i spol. Rezultati dinamometrije linearno rastu s potpornom mišićnom masom. Za dinamometriju šake može se reći da je vrlo osjetljiva metoda procjene statusa jer može prije detektirati gubitak potporne mišićne mase, kao i njezin oporavak (osobito skeletnih mišića) u odnosu na ostale metode antropometrije (Martinis i Lasić, 2020).
Zhuang i sur. (2020) u retrospektivnoj studiji provedenoj na 8257 bolesnika s malignom bolešću zaključuju kako je nizak HGS snažno povezan sa smrtnošću od karcinoma. Rezultati ukazuju na korisnost HGS mjerenja u rutinskoj kliničkoj praksi za poboljšanje procjene pacijenata, prognoze i intervencije u onkoloških bolesnika.

Promjene u prehrani prije kirurškog liječenja CRC-a

Simptomi CRC-a su posljedica rasta tumora unutar lumena. Promjena crijevnih navika češće se viđa kao simptom u karcinoma lokaliziranih ljevostrano pri čemu karcinom progresivno sužava lumen crijeva uz popratnu dijareju, promjene oblika stolice i moguću crijevnu opstrukciju (Ballinger i Anggiansah, 2007). Opstruktivni simptomi bolesti često zahtijevaju kašastu dijetu. Preporučuju se lako probavljive namirnice koje se mogu lakše pasirati i miksati. U dijetoterapiju se uvodi nemasno meso (piletina, puretina, junetina) i bijela riba (oslić, škarpina i sl.). Izbjegava se povrće koje uzrokuje nadutost (grah, grašak, leća, slanutak, cvjetača, brokula, kelj, poriluk, kupus). Pripremaju se nemasne mesne juhe i juhe od povrća. Voće se priprema u obliku kašica ili se prirodno cijedi u sok. Obroci se pripremaju miksanjem svih namirnica zajedno ili se glavno jelo i prilozi mogu miksati odvojeno kako bi jelo bilo privlačnije.
Prevalencija prijeoperacijske anemije u bolesnika s CRC-om varira s obzirom na lokaciju tumorske lezije. Liu i sur. (2018) ističu da prijeoperacijska anemija povećava rizik poslijeoperacijskog mortaliteta, duljinu hospitalizacije te rizik respiratornih, urinarnih, septičkih komplikacija i infekcije rane.
Opservacijske studije pokazale su da su niske koncentracije 25-hidroksi vitamina D u bolesnika s CRC-om povezane s lošim ishodima uključujući nisku stopu preživljavanja (Ng i sur., 2009; Zgaga i sur., 2014), u takvih bolesnika važna je nadoknada istog.

Dijetoterapija kod gubitka apetita

Gubitak apetita često se javlja prije i/ili nakon kirurškog liječenja. Kod onkoloških bolesnika dolazi i do smanjenog osjeta okusa, otežanog gutanja, upale sluznice usne šupljine, usporenog pražnjenja želuca, mučnine, povraćanja, opstrukcije crijeva i pojave boli.
Liječenje kemoterapijom i radioterapijom te psihička reakcija na bolest također mogu utjecati na gubitak apetita. U poslijeoperacijskom periodu, pojava boli kod gotovo svih bolesnika može utjecati na smanjeni unos hrane. Važno je na vrijeme prepoznati i liječiti problem gubitka apetita. Prema istraživanjima, 2/3 bolesnika s CRC-om dnevno uzima manje od 25 kcal/kg tjelesne mase. To znači da ne pokrivaju minimalne nutritivne potrebe kao i potrebe koje proizlaze iz anaboličkih procesa povezanih s oporavkom (Lewandowska i sur., 2022).

Kod gubitka apetita potrebno je:

- Unos hrane rasporediti na više manjih obroka prema bolesnikovim željama. Dijetoterapija se

mora prilagoditi individualnim potrebama i dijagnozi.
- U slučaju kada bolesnik ne može unositi krutu/formiranu hranu, treba mu davati cijeđene prirodne sokove, kašice od sezonskog voća i povrća kako bi potaknuli apetit ili u prehranu uvesti gotove enteralne napitke (Martinis i Lasić, 2020).

Ukoliko je potrebno, primjenjuju se i stimulator apetita megestrol-acetat u dozi od 400-800 mg/dan (Zelić i sur., 2014; Burden, 2021).

Oralni enteralni pripravci

Nutritivna potpora trebala bi sadržavati visokoenergetske, visokoproteinske enteralne obroke (1-1,2 g proteina/kg tjelesne težine/dan), a uz dodatak imunomodulirajućih enteralnih pripravaka (eikosapentaenoična kiselina, EPA, ≥2 g/dan). Nedavno objavljeno randomizirano kliničko ispitivanje pokazalo je da nakon kirurškog liječenja CRC-a u bolesnika s nutritivnim rizikom uporaba oralnih visokoproteinskih pripravaka može smanjiti gubitak skeletnih mišića i učestalost sarkopenije te dodatno poboljšati toleranciju kemoterapije (Krznarić i sur., 2007; Zelić i sur., 2014).
Prema preporukama ESPEN-a, nutritivna intervencija preporučuje se u bolesnika sa (Weimann i sur., 2017; Muscaritoli i sur., 2021):
- ograničenim unosom hrane (manje od 60 % dnevnih energijskih potreba) dulje od 10 dana,
- normalnim nutritivnim statusom, ali se očekuje da bolesnik neće moći kroz određeni period (najmanje 7 dana) unijeti potrebnu količinu hrane,
- lošim nutritivnim statusom, pothranjenih.

Prema hrvatskim smjernicama (Krznarić i sur., 2007) omega-3 masne kiseline odgovorne su za redukciju imunosupresivnih i proupalnih posrednika u ciklusu arahidonske kiseline (prostaglandin E2, tromboksan A2 i leukotrien B4), a smanjuju i rizik od ishemične ozljede (snižava agregaciju trombocita), a ujedno se smanjuje sinteza i oslobađanje TNF-α (čimbenik nekroze tumora) te interleukina (IL-1, IL-6). Također, EPA poboljšava funkciju limfocita te se tako pojačava imunosni odgovor. Kao lipidi ugrađuju se u fosfolipidni dvosloj membrana stanica i staničnih organela gdje utječu na strukturalni integritet, transportne sustave i fluidnost membrane. Parenteralni i enteralni pripravci obogaćeni omega-3 masnim kiselinama prisutni su u svakodnevnoj kliničkoj primjeni (Zelić i sur., 2014; Burden, 2021).

Plan nutritivne njege i energijske potrebe bolesnika s CRC-om

Dnevni energijski unos bolesnika s CRC-om rijetko je veći od potreba zdravih osoba, uglavnom se kreću između 25-30 kcal/kg/dan s obzirom na to da bolesnici imaju smanjenu tjelesnu aktivnost (Muscaritoli i sur., 2021). Pretjeran unos energije (*engl. overfeeding*) nije poželjan te može biti kontraindiciran (Martinis i Lasić, 2020). Tijekom bolesti, tj. u perioperacijskoj fazi povećane su potrebe za energijom zbog akutne faze i kataboličkih procesa te osnovne bolesti (kronična bolest, tumorski proces). Vrijednost potrebne energije ovisi o težini bolesti, a kreće se od +20 % do +47 % bazalnog metabolizma u usporedbi sa zdravim osobama. S druge strane, kao posljedica kirurškog liječenja, zbog resekcije kolorektalnog karcinoma, oštećen je dio gastrointestinalnog trakta, dok je upotreba kemoterapeutika i radioterapije povezana s oštećenjem mukozne membrane, u obliku prolaznog mukozitisa (Miyano i sur., 2013). Stoga u svrhu regeneracije tkiva, indiciran je veći unos proteina u odnosu na standardni unos, 1 g/kg/dan, ukoliko je potrebno 1,5 g/kg/dan (Muscaritoli i sur., 2021) te unos prebiotika i probiotika. Osobito se ističe važnost unosa aminokiseline glutamina. Glutamin je važna komponenta za održavanje zdrave mukozne membrane budući da epitelne stanice tankog crijeva koriste glutamin za metaboličke funkcije. Brojne studije promatrale su vezu između glutamina i gastrointestinalnog sustava kako bi pokazale opravdanost dodatka glutamina parenteralnim i enteralnim pripravcima. Glutaminom su bogati: govedina, piletina, riba, jaja, orašasti plodovi i mahunarke te se u bolesnika s CRC-om savjetuje obogaćivanje obroka navedenim namirnicama u svrhu smanjenja rizika od neželjenog gubitka na tjelesnoj masi. Za smanjenje gastrointestinalnih smetnji također je važno održavati ravnotežu crijevne mikrobiote probioticima i prebioticima. Dokazano je da probiotici uspješno čuvaju cjelovitost sluznice želuca i crijeva postizanjem ravnoteže između proupalnih i antiinflamatornih citokina. Utječu na motilitet i gibanje crijeva, čuvajući normalnu crijevnu peristaltiku (Martinis i Lasić, 2020). Prebiotici selektivno podržavaju rast i aktivnost određenih bakterija, posebno *Bifidobacterium i Lactobacillus*. Prebiotici, tijekom mliječne fermentacije postaju izvor energije za probiotke, omogućuju njihovo preživljavanje dok prolaze kroz gornji dio probavnog sustava te naseljavanje u debelom crijevu.

Spojevi koji pokazuju prebiotička svojstva uključuju: fruktooligosaharide, galaktooligosaharide, ksilooligosaharide, izomaltooligosaharide, sojine oligosaharide, laktulozu, rezistentni škrob i inulin (Markowiak i sur., 2017). Primjena prebiotika u

bolesnika s CRC-om nakon primjene kemoterapeutika i radioterapije utječe na intenzivniju ekspresiju tijesnih mukoznih konjugiranih proteina te smanjenje upale unutar gastrointestinalnog sustava (Everard i sur.,2014; Druart i sur., 2014).

Dijetoterapija bolesnika s CRC-om nakon kirurškog liječenja

U dosadašnjim pregledima literature nema randomiziranih kliničkih ispitivanja koja su pratila utjecaj određenih namirnica nakon operacije CRC-a. Dvije studije su pokazale da bolesnici s povećanim unosom procesuiranog mesa, crvenog mesa, slatkiša i rafiniranih žitarica imaju veću stopu recidiva karcinoma i manju stopu preživljavanja bez bolesti (*engl. disease-free survival-DFS*) (Thanikachalam i Khan, 2019; Lewandowska i sur., 2022).

Prehrana s visokim glikemijskim indeksom također je bila povezana s manjim DFS-om u bolesnika s CRC-om i prekomjernom tjelesnom masom kao i u pretilih (Meyerhardt i sur., 2012).

U bolesnika s CRC-om preporučuje se lako probavljiva hrana bez oštrih i nadražujućih začina (senf, hren, ajvar, alkoholni ocat, začinska paprika i pojačivač okusa mononatrijev glutamat).

Iz prehrane je potrebno izbaciti pržena i pohana mesa, dimljena mesa, salame i trajne kobasice, hrenovke, paštete, mesne konzerve, gazirana pića, alkohol te konzervirano povrće i voće. Osobito je važno izbjegavati navedene namirnice u slučaju zračenja u predjelu abdomena i zdjelice. Naime, mononatrijev glutamat (MSG) je prisutan u procesiranim proizvodima u svrhu poboljšanja okusa i organoleptičkih svojstava istih. MSG i masna hrana induciraju stvaranje reaktivnih kisikovih radikala (ROS) i time mijenjaju redoks-homeostazu izazivajući sistemski odgovor organizma. Konzumacija MSG-a u kombinaciji s masnom hranom dovodi do razvoja dislipidemije, nealkoholne masne jetre praćene metaboličkim i zloćudnim bolestima.

Na animalnim modelima unos MSG-a izazvao je pojačano lučenje proupalnih čimbenika: rezistina, TNF-α (čimbenik nekroze tumora-alfa), leptina i IL-6 (Banerjee i sur., 2021).

Američko društvo za borbu protiv raka (*engl. American Cancer Society, ACS*) i Američki institut za istraživanje raka/Svjetski fond za istraživanje raka (*engl. American Institute for Cancer Research /World Cancer Research Fund, AICR/WCRF*) preporučuju da osobe koje su preboljele karcinom ograniče unos crvenog i procesuiranog mesa. AICR/WCRF imaju različite preporučene količine unosa za neprocesuirano i procesuirano meso. Smjernice AICR/WCRF preporučuju ograničavanje konzumacije crvenog mesa na "ne više od oko 3 porcije tjedno" i na konzumaciju vrlo malo prerađenog mesa. Navedene preporuke temelje se na dokazima koji sugeriraju da bi procesuirano meso moglo biti više povezano s nepovoljnim zdravstvenim ishodima, u odnosu na neprocesuirano crveno meso (Van Blarigan i sur., 2022).

Kako bi se zadovoljio adekvatan unos proteina preporučuju se: svježi posni sir, fermentirani mliječni proizvodi, meso peradi, meso kunića, riba, jaja i tofu sir. Potrebno je povećati unos povrća, osobito tamnozelenog lisnatog u obliku u kojem će ga bolesnik tolerirati (kuhano ili pire) (Thanikachalam i Khan, 2019; Lewandowska i sur., 2022).

Bolesnici koji su povećali unos prehrambenih vlakana nakon što im je dijagnosticiran CRC imali su nižu stopu smrtnosti. Song i sur. (2018) navode kako je veći unos vlakana, posebice vlakana žitarica, povezan s poboljšanom osjetljivošću na inzulin, lipidni profil, funkciju endotela i smanjenje upale. Stoga, veći unos vlakana nakon dijagnoze CRC-a može povećati DFS ublažavanjem učinka hiperinzulinemije i upale na razvoj tumora (*engl. tumor-promoting effect*). Međutim, u prehrani je ponekad važno ograničiti unos vlakana i laktoze kako bi se smanjila pojava nadutosti, bolova u trbuhu i proljeva.

Prehrana bogata orašastim plodovima također je povezana s većim DFS-om. Nedavna studija Fadelu i sur. (2018) u bolesnika sa stadijem III CRC-a pokazala je kako su konzumacija orašastih plodova i zdrav način života povezani sa smanjenim recidivom CRC-a za 42 % i smanjenom smrtnosti za 57 %.

Konzumacija kave pokazala se korisnom kod pacijenata koji su imali rani stadij CRC-a. Dokazano je da konzumacija kave smanjuje rizik od smrtnosti (Guercio i sur., 2015).

Hu i sur. (2018) ističu kako je u bolesnika s CRC-om za 50 % smanjen rizik od smrtnosti ukoliko konzumiraju najmanje 4 šalice kave dnevno, u usporedbi s onima koji ne konzumiraju kavu.

Kvercetin je flavonoid prisutan u različitom povrću (rajčica, brokula) i voću (kruška, jabuka, bobičasto voće, nar). Hidrofilni glikozid, jedan od najčešćih sastojaka ekstrakata kvercetina, tijelo domaćina ne može izravno apsorbirati te se mora u interakciji s crijevnom florom i ključnim enzimima u probavnom sustavu transformirati u metabolite kvercetina (Zhao i sur., 2022). Višestruki farmakološki učinci, uključujući protuupalne, antioksidativne, antiaterosklerozne i antikancerogene učinke, otkriveni su u kvercetinu ili njegovim ekstraktima. Daljnje studije su pokazale da kvercetin može imati antikancerogene učinke kroz različite mehanizme, uključujući inhibiciju aktivnosti tirozin kinaze, reguliranje putova uključenih u tumorigenezu i interakciju sa specifičnim proteinima ili receptorima (Khan i sur., 2016). Utvrđeno je da kvercetin i njegovi derivati mogu učinkovito inhibirati progresiju tumora *in*

vivo i in vitro na animalnim modelima s CRC-om (Neamtu i sur., 2022).
(–)-epigalokatehin-3-galat glavni je polifenol zelenog čaja i smatra se važnim inhibitorom tumora. Pokazalo se da kombinacije EGCG-a i drugih katehina mogu imati relativno snažne učinke protiv karcinoma i *u in vitro i in vivo* eksperimentima. Neka su istraživanja pokazala da EGCG može smanjiti kemorezistenciju stanica karcinoma i recidiv istog (Zhao i sur., 2022).

Zaključak

Nutritivnu procjenu i plan nutritivne njege je važno provesti odmah nakon postavljanja dijagnoze u bolesnika s CRC-om bez obzira je li riječ o pothranjenosti, gubitku potporne mišićne mase, normalnoj ili prekomjernoj tjelesnoj masi. Time se smanjuju rizici od nastanka nutritivnih deficita i komplikacija koje rastu s promjenama nutritivnog statusa. Multidisciplinarni pristup liječenju bolesnika i dijetoterapija ima važnu ulogu u svakoj fazi liječenja CRC-a. Problemi s prehranom trebaju se uzeti u obzir i rješavati od vremena postavljanja dijagnoze, terapijskog puta, te paralelno s antineoplastičnim liječenjem (kemoterapija, imunoterapija i endokrina terapija) i radioterapijom. Studije daju ohrabrujuće rezultate u primjeni fitonutrijenata poput zelenog čaja, ekstrakta kvercetina, omega-3 masnih kiselina, probiotika, prebiotika, prehrambenih vlakana i orašastih plodova zahvaljujući njihovim protuupalnim i antioksidativnim svojstvima. Osnovni princip periopeartivne dijetoterapije je adekvatnim namirnicama smanjiti ili spriječiti pojavu simptoma i mogućih komplikacija, dok u poslijeoperacijskoj i terapijskoj fazi liječenja ubrzati bolesnikov oporavak te povratak svakodnevnim aktivnostima.

Literatura

American Cancer Society (2017): *Colorectal Cancer Facts & Figures 2017–2019*, Atlanta, American Cancer Society.

Ballinger, A.B., Anggiansah, C. (2007): Colorectal cancer. *BMJ*. 335(7622), 715-8.

Banerjee, A., Mukherjee, S., Maji, B.K. (2021): Worldwide flavor enhancer monosodium glutamate combined with high lipid diet provokes metabolic alterations and systemic anomalies: An overview, *Toxicol Rep*. 8, 938-961.

Burden, S.T., Gibson, D.J., Lal, S., Hill, J., Pilling, M., Soop, M. i sur. (2017): Pre-operative oral nutritional supplementation with dietary advice versus dietary advice alone in weight-losing patients with colorectal cancer: single-blind randomized controlled trial. *J Cachexia Sarcopenia Muscle*. 8, 437-46.

Daniele, A., Divella, R., Abbate, I., Casamassima, A., Garrisi, V.M., Savino, E., Casamassima, P., Ruggieri, E., D.E. Luca, R. (2017): Assessment of Nutritional and Inflammatory Status to Determine the Prevalence of Malnutrition in Patients Undergoing Surgery for Colorectal Carcinoma. *Anticancer Res*. 37(3), 1281-1287.

Deftereos, I., Kiss, N., Brown, T., Carey, S., Carter, V.M., Usatoff, V., Ananda, S., Yeung, J.M. (2021): Awareness and perceptions of nutrition support in upper gastrointestinal cancer surgery: A national survey of multidisciplinary clinicians. *Clin Nutr ESPEN*. 46, 343-349.

De van der Schueren, MAE., Laviano, A., Blanchard, H., Jourdan, M., Arends, J., Baracos, V.E. (2018): Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials. *Ann Oncol*. 29(5), 1141-1153.

Druart, C., Alligier, M., Salazar, N., Neyrinck, A.M., Delzenne, N.M. (2014): Modulation of the gut microbiota by nutrients with prebiotic and probiotic properties. *Adv. Nutr*. 5, 624S–633S.

Everard, A., Cani, P.D. (2014): Gut microbiota and GLP-1. *Rev. Endocr. Metab. Disord*. 15, 189–196.

Fadelu, T., Zhang, S., Niedzwiecki, D., Ye, X., Saltz, L.B., Mayer, R.J., Mowat, R.B., Whittom, R., Hantel, A., Benson, A.B., et al. (2018): Nut Consumption and Survival in Patients with Stage III Colon Cancer: Results from CALGB 89803 (Alliance). J. *Clin. Oncol.* 36, 1112–1120.

Fan, S., Sayed, R.H., Davenport, A. (2012): Extracellular volume expansion in peritoneal dialysis patients. *Int J Artif Organs*. 35, 338-45.

Gomes, T.L.N., Soares, J.D.P., Borges, T.C., Pichard, C., Pimentel, G.D. (2020): Phase angle is not associated with fatigue in cancer patients: the hydration impact. *Eur J Clin Nutr*. 74, 136973.

Guercio, B.J., Sato, K., Niedzwiecki, D., Ye, X., Saltz, L.B., Mayer, R.J., Mowat, R.B., Whittom, R., Hantel, A., Benson, A., et al. (2015): Coffee Intake, Recurrence, and Mortality in Stage III Colon Cancer: Results from CALGB 89803 (Alliance). *J. Clin. Oncol.* 33, 3598–3607.

Gupta, D., Lis, C.G., Dahlk, S.L., King, J., Vashi, P.G., Grutsch, J.F. (2008): The relationship between bioelectrical impedance phase angle and subjective global assessment in advanced colorectal cancer. *Nutr J*. **7,** 19.

Gustafsson, U.O., Scott, M.J., Hubner, M. *et al.* (2019): Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations: 2018. *World J Surg.* 43, 659–695.

Hu, Y., Ding, M., Yuan, C., Wu, K., Smith-Warner, S.A., Hu, F.B., Chan, A.T., Meyerhardt, J.A., Ogino, S., Fuchs, C.S., et al. (2018): Association Between Coffee Intake After Diagnosis of Colorectal Cancer and Reduced Mortality. *Gastroenterology 2018.* 154, 916–926.

Khan, F., Niaz, K., Maqbool, F., Ismail Hassan, F., Abdollahi, M., Nagulapalli Venkata, K.C., et al. (2016): Molecular targets underlying the anticancer effects of quercetin: an update. *Nutrients*. 8, 529.

Kondrup, J., Allison, S.P., Elia, M., Vellas, B., Plauth, M.; Educational and Clinical Practice Committee, European Society of Parenteral and Enteral Nutrition (ESPEN) (2003): ESPEN guidelines for nutrition screening 2002. *Clin Nutr*. 22(4), 415-21.

Krznarić, Z., Juretić, A., Samija, M., Dintinjana, R.D., Vrdoljak, E., Samarzija, M., Kolacek, S., Vrbanec, D., Prgomet, D., Ivkić, M., Zelić, M. (2007): Croatian Society of Parenteral and Enteral Nutrition, Croation Society of Oncology, Croation society of Medical Oncology, Croation Medical Association. Hrvatske smjernice za primjenu eikozapentaenske kiseline I megestrol-acetata u sindromu tumorske kaheksije [Croatian guidelines for use of eicosapentaenoic acid and megestrol acetate in cancer cachexia syndrome]. *Lijec Vjesn*. 129(12), 381-6.

Lee, Y., Kwon, O., Soo Shin, C., Lee, S.M. (2015): Use of bioelectrical impedance analysis for the assessment of nutritional status in critically ill patients. *Clin Nutr Res*. 4, 32-40.

Lewandowska, A., Religioni, U., Czerw, A., Deptała, A., Karakiewicz, B., Partyka, O., Pajewska, M., Sygit, K., Cipora, E., Kmieć, K., Augustynowicz, A., Mękal, D., Waszkiewicz, M., Barańska, A., Mináriková, D., Minárik, P., Merks, P. (2022): Nutritional Treatment of Patients with Colorectal Cancer. *Int J Environ Res Public Health*. 19 (11), 6881.

Liu, L., Liu, L., Liang, L.C., Zhu, Z.Q., Wan, X., Dai, H.B., Huang, Q. (2018): Impact of Preoperative Anemia on Perioperative Outcomes in Patients Undergoing Elective Colorectal Surgery. *Gastroenterol Res Pract*. 2018, 2417028.

Malmstrom, T. K., Miller, D. K., Simonsick, E. M., Ferrucci, L., Morley, J. E. (2016): SARCF: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. J. Cachexia Sarcopenia Muscle 7, 28-36.

Markowiak, P., ´Sli˙zewska, K.(2017): Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients 2017.* 9, 1021.

Martinis, I., Lasić, M. (2020): Nutritivni status kirurških bolesnika. U: Zdravstvena njega kirurških bolesnika, Kalauz i sur., Zdravstveno veleučilište Zagreb, str. 102-146.

Matsui, M., Nishikawa, H., Goto, M., Asai, A., Ushiro, K., Ogura, T., Takeuchi, T., Nakamura, S., Kakimoto, K., Miyazaki, T., et al. (2022): Prognostic Impact of the SARC-F Score in Gastrointestinal Advanced Cancers. *Cancers 2022*. 14, 10.

Melnyk, M., Casey, R.G., Black, P., Koupparis, A.J. (2011): Enhanced recovery after surgery (ERAS) protocols: Time to change practice? *Can Urol Assoc J*. 5(5), 342-8.

Meyerhardt, J.A., Sato, K., Niedzwiecki, D., Ye, C., Saltz, L.B., Mayer, R.J., Mowat, R.B., Whittom, R., Hantel, A., Benson, A., et al. (2012): Dietary glycemic load and cancer recurrence and survival in patients with stage III colon cancer: Findings from CALGB 89803. *J. Natl. Cancer Inst*. 104, 1702–1711.

Miyano, K., Ueno, T., Yatsuoka, W., Uezono, Y. (2016): Treatment for cancer patients with oral mucositis: Assessment based on the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer in International Society of Oral Oncology (MASCC/ISOO) in 2013 and Proposal of Possible Novel Treatment with a Japanese Herbal Medicine. *Curr. Pharm*. 22, 2270–2278.

Moghadamyeghaneh, Z., Hanna, M.H., Hwang, G., Carmichael, J.C., Mills, S.D., Pigazzi, A., i sur. (2015): Outcome of preoperative weight loss in colorectal surgery. *Am J Surg*. 210, 291–7.

Muscaritoli, M., Arends, J., Bachmann, P., Baracos, V., Barthelemy, N., Bertz, H., Bozzetti, F., Hütterer, E., Isenring, E., Kaasa, S., et al. (2021): ESPEN practical guideline: Clinical Nutrition in cancer. *Clin. Nutr*. 40, 2898–2913.

Neamtu, A.A., Maghiar, T.A., Alaya, A., Olah, N.K., Turcus, V., Pelea, D., et al. (2022): A comprehensive view on the quercetin impact on colorectal cancer. *Molecules*. 27, 1873.

Ng, K., Wolpin, B.M., Meyerhardt, J.A., Wu, K., Chan, A.T.,Hollis, B.W., Giovannucci, E.L., Stampfer, M.J., Willett, W.C., Fuchs, C.S. (2009): Prospective study of predictors of vitamin D status and survival in patients with colorectal cancer. *Br. J. Cancer 2009.* 101, 916–923.

Ryan, A.M., Power, D.G., Daly, L., et al. (2016): Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. *Proc Nutr Soc*.75(2), 199–211.

Song, M., Wu, K., Meyerhardt, J.A., Ogino, S., Wang, M., Fuchs, C.S., Giovannucci, E.L., Chan, A.T. (2018): Fiber Intake and Survival After Colorectal Cancer Diagnosis. *JAMA Oncol*. 4, 71–79.

Sun, Z., Kong, X.J., Jing, X., Deng, R.J., Tian, Z.B. (2015): Nutritional Risk Screening 2002 as a Predictor of Postoperative Outcomes in Patients Undergoing Abdominal Surgery: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *PLoS One*.10, e0132857.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., Bray, F. (2021): Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 71(3), 209-249.

Thanikachalam, K., Khan, G. (*20*19): Colorectal Cancer and Nutrition. *Nutrients*. 11(1), 164.

Tsaousi, G., Kokkota, S., Papakostas, P., Stavrou, G., Doumaki, E., Kotzampassi, K. (2017): Body composition analysis for discrimination of prolonged hospital stay in colorectal cancer surgery patients. *Eur J Cancer Care*. 26, 12491.

Van Blarigan, E.L., Ou, F.S., Bainter, T.M., Fuchs, C.S., Niedzwiecki, D., Zhang, S., Saltz, L.B., Mayer, R.J., Hantel, A., Benson, A.B. 3rd, Atienza, D., Messino, M., Kindler, H.L., Venook, A.P., Ogino, S., Sanoff, H.K., Giovannucci, E.L., Ng, K., Meyerhardt, J.A. (2022): Associations Between Unprocessed Red Meat and Processed Meat With Risk of Recurrence and Mortality in

Patients With Stage III Colon Cancer. *JAMA Netw Open*. 5(2), e220145.

Van Cutsem, E., Arends, J. (2005): The causes and consequences of cancerassociated malnutrition. *Eur J Oncol Nurs*. 9, S51–S63.

Vaughan, V.C., Harrison, M., Dowd, A., Eastman, P., Martin, P. (2021): Evaluation of a Multidisciplinary Cachexia and Nutrition Support Service— The Patient and Carers Perspective. *Journal of Patient Experience*. 8.

Weimann, A., Braga, M., Carli, F., Higashiguchi, T., Hübner, M., Klek, S., Laviano, A., Ljungqvist, O., Lobo, D.N., Martindale, R., Waitzberg, D.L., Bischoff, S.C., Singer, P. (2017): ESPEN guideline: Clinical nutrition in surgery. *Clin Nutr*. 36(3), 623-650.

Xie, B., Sun, Y., Sun, J., et al. (2022): Applicability of five nutritional screening tools in Chinese patients undergoing colorectal cancer surgery: a cross-sectional study. *BMJ Open*. 12, e057765.

Yasui-Yamada, S., Oiwa, Y., Saito, Y., Aotani, N., Matsubara, A., Matsuura, S. i sur. (2020): Impact of phase angle on postoperative prognosis in patients with gastrointestinal and hepatobiliarypancreatic cancer. *Nutrition*. 79, 110891.

Zelić, M., Bender, D.V., Kelecic, D.L., Zupan, Z., Cicvaric, T., Maldini, B. i sur. (2014): Hrvatske smjernice za perioperativnu enteralnu prehranu kirurskih bolesnika. *Liječ vjesn*. 136, 179-85.

Zgaga, L., Theodoratou, E., Farrington, S.M., Din, F.V., Ooi, L.Y., Glodzik, D., Johnston, S., Tenesa, A., Campbell, H., Dunlop, M.G. (2014): Plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer. *J. Clin. Oncol*. 32, 2430–2439.

Zhao, L., Zhao, H., Zhao, Y., Sui, M., Liu, J., Li, P., Liu, N., Zhang, K. (2022): Role of Ginseng, Quercetin, and Tea in Enhancing Chemotherapeutic Efficacy of Colorectal Cancer. *Front Med (Lausanne)*. 9, 939424.

Zhuang, C.L., Zhang, F.M., Li, W., Wang, K.H., Xu, H.X., Song, C.H., Guo, Z.Q., Shi, H.P. (2020): Associations of low handgrip strength with cancer mortality: a multicentre observational study. *J Cachexia Sarcopenia Muscle*. 11(6), 1476-1486.

Ziętarska, M., Krawczyk-Lipiec, J., Kraj, L., Zaucha, R., Małgorzewicz, S. (2017): Nutritional status assessment in colorectal cancer patients qualified to systemic treatment. *Contemp Oncol (Pozn)*. 21(2), 157-161.

THE IMPORTANCE OF NUTRITIONAL STATUS ASSESSMENT IN PATIENTS WITH COLORECTAL CANCER

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professional paper

Summary

Colorectal cancer (CRC) is the third most common malignant tumor in the world. It is estimated that 10-20 % of cancer patients die as a result of malnutrition rather than the cancer itself. The nutritional status of patient with CRC significantly affects the outcome of the treatment, whether it is malnutrition, skeletal muscle loss, normal body weight or overweight. Nutritional problems should be addressed from the time of cancer diagnosis, within surgical treatment and in parallel to antineoplastic treatment (chemotherapy, immunotherapy and endocrine therapy) and radiotherapy. It is important to have a multidisciplinary team because the procedures include assessments of the nutrition status and counselling, using: validated screening questionnaires for malnutrition NRS 2002 (*Nutritional Risk Screening 2002*) and sarcopenia SARC-F (*Strength, assistance with walking, rising from a chair, climbing stairs and falls*), measurement of handgrip strength, body composition by bioelectrical impedance analysis, assessment of eating habits and food intake. Studies show encouraging results with the intake of green tea phytonutrients, quercetin extract, omega-3 fatty acids, probiotics, prebiotics, dietary fiber and nuts due to their anti-inflammatory and antioxidant properties. The principle of perioperative diet therapy is to reduce or prevent nutritional deficits and complications which increase when the nutritional status changes, while in the postoperative and therapeutic phase positively influence the patient's recovery and return to daily activities.

Keywords: colorectal cancer, nutritional status, nutritional support, perioperative diet therapy

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