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Short communications

Dietary creatine and cancer risk in the U.S. population: NHANES 2017–2020

Sergej M. Ostojic [a,b,c,*], Erik Grasaas [a], Jelena Cvejic [b]

[a] Department of Nutrition and Public Health, University of Agder, Kristiansand, Norway
[b] Applied Bioenergetics Lab, Faculty of Sport and PE, University of Novi Sad, Novi Sad, Serbia
[c] Faculty of Health Sciences, University of Pécs, Pécs, Hungary

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ABSTRACT

While creatine is generally considered a safe dietary compound, there have been concerns about excessive creatine intake and its possible link to cancer. The main of this study was to examine the relationship between dietary creatine intake and cancer risk in the general US population using data from the 2017–2020 National Health and Nutrition Examination Survey (NHANES). We extracted a dataset that included information on medical conditions and dietary intake from 7,344 NHANES respondents. We used individual data files containing detailed information about each food and beverage item consumed to calculate creatine intake from meat- and milk-based food sources. In a subset of NHANES respondents who reported their cancer status, the average daily creatine intake was 11.6 ± 11.5 mg per kg body mass (95 % CI, 11.3 to 11.8); all participants in the subset were 20 years or older. Cancer-free individuals consumed significantly more creatine per day than those with cancer (11.7 ± 11.6 mg/kg body mass vs. 10.6 ± 10.2 mg/kg body mass; $P = 0.01$). The odds ratio for having cancer in the subset of participants consuming < 10.5 mg of creatine per kg body mass daily (the 50th percentile of consumption) compared to those with higher intake ($\geq$10.5 mg) was 1.18 (95 % CI, from 1.01 to 1.37), indicating a significant association between lower dietary creatine intake and increased cancer risk ($P = 0.03$). Our findings suggest that consuming a diet that includes more creatine may be associated with a reduced risk of cancer or malignancy in U.S. adults aged 20 years and over, with the average difference in creatine intake between cancer-free individuals and cancer groups was relatively small (1.1 mg/kg body mass). Further studies are necessary to confirm the potential benefits of creatine-rich foods or dietary supplements in the management of cancer.

1. Introduction

Creatine is an amino acid derivative that plays a crucial role in providing energy to the human body, both spatially and temporally (Wallimann et al., 2011). Creatine has been considered as conditionally essential as it is mainly synthesized in the liver and pancreas, but can also be obtained from the omnivorous diet. On average, each source provides approximately one gram of creatine per day for the human body (Ostojic & Forbes, 2022). Creatine is generally recognized as a safe compound by the U.S. Food and Drug Administration (FDA) and has been labeled as non-toxic when used under the intended conditions (Food and Drug Administration, 2020). Despite this, there has been a long-standing concern regarding the potential association of excessive creatine intake with cancer. It has been suggested that creatine may facilitate the formation of carcinogenic chemicals or support cancer bioenergetics (Pereira et al., 2015). However, there have been no epidemiological studies that examine the possible link between creatine consumption and cancer risk in the general population. In this study, we aimed to evaluate the cancer risk associated with different levels of dietary creatine intake among the U.S. population aged one year and older, using data from the 2017–2020 National Health and Nutrition Examination Survey (NHANES) round.

2. Materials and methods

The NHANES population consists of non-institutionalized individuals residing in all fifty states of the United States, as well as Washington D.C. (for detailed information, please refer to CDC/National

* Corresponding author at: Department of Nutrition and Public Health, University of Agder, Universitetsveien 25, 4604 Kristiansand, Norway.
E-mail addresses: sergej.ostojic@chess.edu.rs, sergej.ostojic@uia.no (S.M. Ostojic).

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Center for Health Statistics, 2023a). Due to the COVID-19 pandemic, the NHANES 2017–2020 round was compiled by combining data collected from 2019 to March 2020 with data from the NHANES 2017–2018 cycle to create a nationally representative sample of 15,560 male and female respondents. For this study, we extracted a dataset that included respondents aged one year and older who provided information on their medical conditions and dietary intake. The information about cancer was extracted from the NHANES 2017–2020 Questionnaire Data for Medical Conditions subset (MCQ). The MCQ section provides self- and proxy-reported personal interview data on a wide range of health conditions and medical history for both children and adults (CDC/National Center for Health Statistics, 2023b). In this study, cancer was determined for respondents who answered positively to the question, "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" Information on dietary intake was extracted from the NHANES 2017–2020 Dietary Data interview data files. Individual data files containing detailed information about each food and beverage item consumed were used to calculate creatine intake from meat- and milk-based food sources (U.S. Department of Agriculture food codes from 11100000 to 28522000), as previously described (Korovljev et al., 2021). Daily creatine intake was quantified in relative amount (mg per kg body mass), and did not include creatine from dietary supplements and/or pharmacological agents. The approval to conduct NHANES 2017–2020 was granted by the U.S. National Center for Health Statistics Ethics Review Board. The NHANES complex sampling design was employed for data management. Data series were first analyzed using the Kolmogorov-Smirnov test combined with visual inspection to determine normality of distribution. Independent Mann–Whitney U tests and chi-square tests were employed to compare mean values and proportions across creatine intake categories, respectively. The odds ratio was calculated to quantify the strength of the association between dietary creatine intake and cancer in two subpopulations (below or above the 50th percentile) of creatine intake. Data were analyzed using IBM SPSS Statistics for Mac (Version 24.0), with the significance level set at $P < 0.05$.

3. Results

A total of 14,300 NHANES respondents were interviewed to assess their dietary intake, and detailed information about the daily consumption of individual foods was provided by 12,634 individuals. Out of those, 11,944 individuals (94.6 %) reported consuming at least one food item that contained creatine and were included in further analyses. The general characteristics of the study sample are presented in Table 1. Among the respondents, 794 (10.8 %) reported having cancer or malignancy, while 6,550 reported no cancer (89.2 %). However, the response for 4,600 participants was missing or unknown.

Table 1
General characteristics of the NHANES 2017–2020 sample.

Variable		n
Age, years	34.7 ± 25.0	11,944
Women, %	50.3	11,944
Generation, %		11,944
Newborns and infants	3.4	
Children	23.5	
Adolescents	8.7	
Adults	49.1	
Older adults	15.3	
Race, %		11,944
Mexican American	12.7	
Other Hispanic	9.7	
Non-Hispanic White	35.3	
Non-Hispanic Black	26.4	
Other – including Multi-Racial	16.0	
Body mass index, kg/m^2	27.0 ± 8.4	11,063
Daily dietary intake		11,806
Energy, kcal	2021 ± 978	
Protein, g	73.7 ± 40.7	
Carbohydrate, g	240.7 ± 123.2	
Fat total, g	82.3 ± 47.2	
Alcohol, g	6.1 ± 21.9	
Cancer prevalence, %	10.8	7,344

The average daily creatine intake in the NHANES 2017–2020 sample was 15.0 ± 16.1 mg per kg of body mass, with a 95 % confidence interval (CI) of 14.7 to 15.3 (see Fig. 1 for creatine intake percentiles). The highest daily intake reported was in a boy aged one year at the time of screening, who consumed 255.4 mg of creatine per kg of body mass.

In a subset of NHANES respondents who reported their cancer status ($n = 7{,}344$), the average daily creatine intake was 11.6 ± 11.5 mg per kg body mass (95 % CI, 11.3 to 11.8); all participants in this subset of NHANES respondents were 20 years or older. Herein, cancer-free individuals consumed significantly more creatine per day than those with cancer (11.7 ± 11.6 mg/kg body mass vs. 10.6 ± 10.2 mg/kg body mass; $P = 0.01$). The mean difference in creatine consumption between the two groups was 1.1 mg per kg body mass per day (95 % CI, 0.3 to 2.0). The prevalence of cancer across the quartiles of creatine intake is depicted in Fig. 2, with the frequency significantly lower in the fourth quartile (daily creatine intake > 19.8 mg per kg body mass) as compared to other quartiles ($P < 0.05$), suggesting a threshold to reduce cancer risk. In addition, the odds ratio for having cancer in the subset of participants consuming < 10.5 mg of creatine per kg body mass daily (the 50th percentile of consumption) compared to those with higher intake (≥10.5 mg) was 1.18 (95 % CI, from 1.01 to 1.37), indicating a significant association between lower dietary creatine intake and increased cancer risk ($P = 0.03$).

In addition, a crude binomial logistic regression analysis indicated that there was a significant association between higher creatine intake and lower cancer rates ($P = 0.013$), with each additional milligram of creatine per kg body mass consumed daily resulting in a 0.92 % reduction in cancer rates. The association remained significant ($P = 0.028$) after adjusting for dietary factors (such as total sugars, dietary fiber, total saturated fatty acids, and alcohol). Furthermore, after correcting for main demographic and lifestyle variables, including age, gender, race, education level, family income, body mass index, and moderate physical activity, the association remained statistically significant ($P = 0.039$); these findings suggest that individuals who consume more creatine on a daily basis are less likely to report any type of cancer or malignancy.

4. Discussion

This cross-sectional study reveals no evidence of a link between higher dietary creatine intake and increased cancer risk in U.S. adults aged 20 years and over. In contrast, individuals who consumed more creatine in the NHANES 2017–2020 round had a significantly lower risk of cancer or malignancy compared to those who consumed less creatine. The risk of cancer was found to be 18 % higher among individuals who consumed <10.5 mg of creatine per kg body mass daily compared to their peers who consumed more than this amount. This association remained statistically significant even after controlling for demographic and nutritional variables, highlighting the potential significance of promoting creatine-containing foods in reducing cancer risk. Still, the mean difference in creatine intake between cancer-free individuals and individuals with cancer was rather small (1.1 mg/kg body mass).

Creatine is one of the most extensively studied dietary compounds in human nutrition. Over the past three decades, >1,500 studies have evaluated its safety and efficacy in various health domains, including high-performance sports, clinical medicine, and the general population (Kreider & Stout, 2021; Ostojic, 2021a). The vast majority of pharmacovigilance studies have demonstrated its favorable safety, with dietary creatine considered risk-free at daily dosages ranging from 1 to 20 g across all human ages, from infants to elders (for a detailed review, see Balestrino & Adriano, 2019). After conducting a comprehensive review

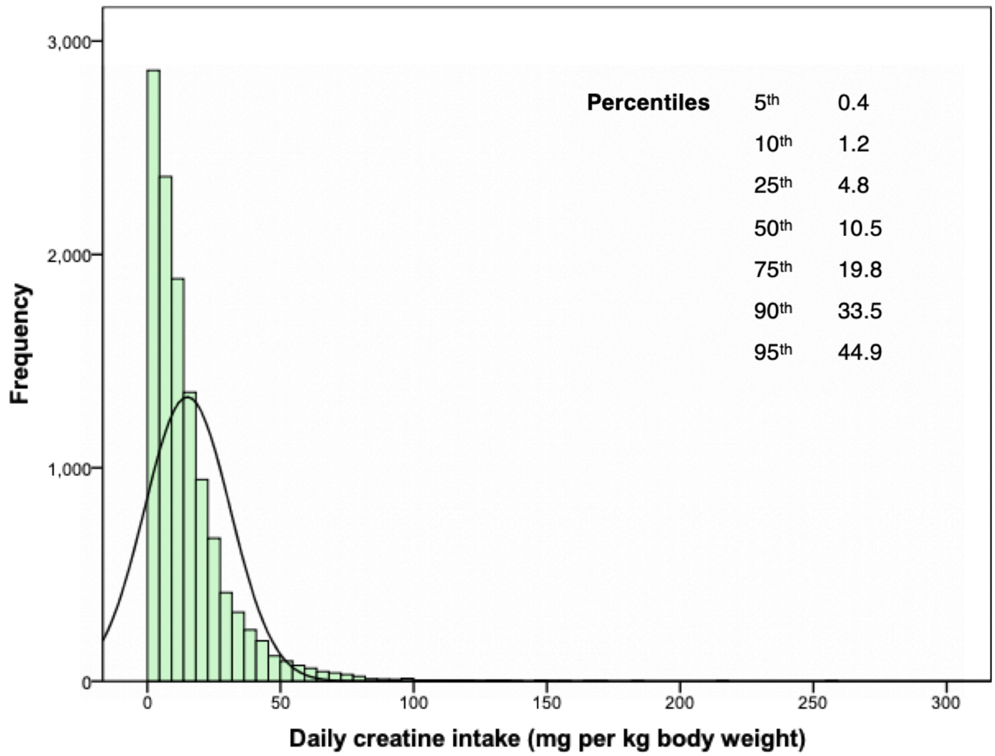

Fig. 1. The distribution and percentiles of daily creatine intake in the NHANES 2017–2020 cohort.

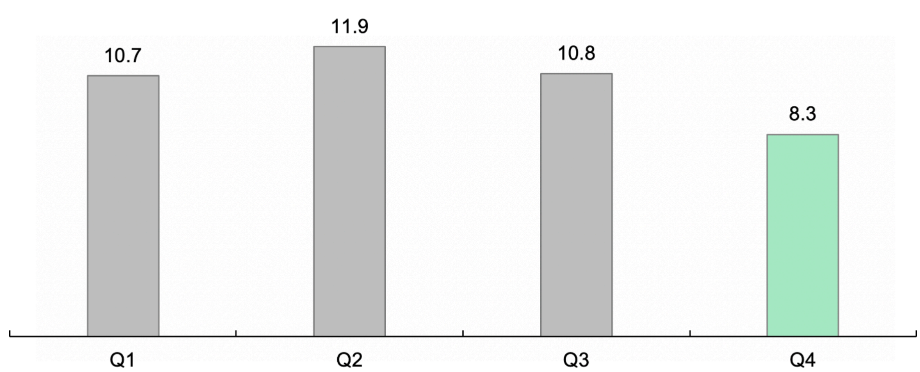

Fig. 2. The prevalence of cancer (%) across the creatine intake quartiles in the subset of NHANES 2017–2020 respondents who reported their cancer status. If a pair of values significantly differ at $P < 0.05$, a different color is displaced in each column.

of the literature, the Center for Food Safety and Applied Nutrition at the U.S. FDA issued a GRAS Notice (# GRN 931) on creatine in March 2020, recognizing creatine (monohydrate) as a safe, non-toxic food substance (Food and Drug Administration, 2020). Although both the research community and regulatory authorities generally consider creatine to be a safe dietary compound, a few recent studies have raised concern about its possible carcinogenic potential. For example, a case-control study including 356 testicular germ cell cancer cases and 513 controls showed that muscle-building products (including those containing creatine) are associated with increased risks of testicular cancer in American men (Li et al., 2015). An orthotopic mouse model study showed that a creatine diet (5 % w/w creatine monohydrate supplement) can promote colorectal and breast cancer metastasis and shorten mouse survival (Zhang et al., 2021). Although both studies have several limitations, including a small sample size, poor control of confounding factors, and/or unclear mechanisms of creatine action, the findings from those studies call for exploring the potential connection between dietary creatine and cancer more extensively.

The present NHANES study adds to published literature by employing a population-wide approach and controlling for critical confounding variables, demonstrating no connection between higher intake of food creatine and higher cancer risk in the non-institutionalized U.S. civilian population aged 20 years and over. In contrast, we found that the participants who consumed the highest amount of creatine daily (the fourth quartile of creatine intake, taking >19.8 mg of creatine per kg body mass) had the lowest prevalence of cancer (8.3 %) compared to other quartiles of creatine intake. Our findings suggest a cancer-protective effect of consuming more creatine in the context of the regular diet, which corroborates preclinical studies indicating that creatine can suppress cancer growth (Miller et al., 1993; Kristensen et al., 1999; Di Biase et al., 2019) although there are specie specific differences in creatine metabolism. Our trial also supports a series of recent epidemiological studies demonstrating a significant association between consuming more creatine from food sources and lower risk of depression (Bakian et al., 2020), kidney damage (Ostojic, 2021b), cardiovascular disease (Ostojic et al., 2021), and liver dysfunction (Todorovic et al., 2022). Considering that cancer is a major public health and economic issue, with over 29 million cases expected by 2040 (American Cancer Society, 2023), adopting a creatine-rich diet could be promoted as a simple and inexpensive public health initiative to tackle the burden of cancer.

Despite the promising findings of this study, there are several limitations that should be considered. These include the use of self-reported data to collect information on cancer occurrence and dietary intake, which may introduce bias and affect the accuracy of the results. Another limitation is that the cross-sectional design used in this study may not fully capture a typical diet, as dietary habits can vary over time. Additionally, the lack of additional biomarkers of dietary creatine exposure may limit the ability to accurately assess creatine intake. The study also controlled for a relatively short list of confounding nutritional variables, which may not fully account for other factors that could affect cancer risk. We failed to analyze the possible role of other nutrients in creatine-containing foods that may play a role in cancer risk. For example, how much of the creatine came from fish or seafood which contains vitamin D and omega 3-fatty acids, both shown to have a role in cancer prevention (Zheng et al., 2013). Furthermore, what proportion of creatine originated from red meat which has been linked to higher rates of cancer (Diallo et al., 2018). In addition, there is a possibility that those who consumed more creatine-containing foods, which are typically more expensive, had a healthier lifestyle in general. Further, we have no information of the 4600 respondents who were missing or unknown, which might have overestimated the prevalence of cancer and reduced the statistical strength of the data. Interestingly, a subset of NHANES respondents who reported their cancer status included no children and adolescents; whether dietary creatine affects creatine risk in those generations remain unaddressed at this moment. Moreover, the study did not account for endogenous creatine production, which may also impact the results. Finally, it is important to note that this study did not take into consideration the potential contribution of other carcinogens such as those found in occupational or environmental exposures, medications, or other lifestyle factors (*e.g.*, tobacco use). As a result, the findings should not be interpreted as indicating a cause-effect relationship between creatine intake and cancer risk. A longitudinal study design is also strongly recommended to reduce the chances of reverse causation bias.

5. Conclusion

Consuming a diet that includes more creatine has been found to be associated with a reduced risk of cancer or malignancy in U.S. adults aged 20 years and over. In fact, for every additional milligram of food creatine per kilogram of body mass consumed daily, the cancer rate is reduced by approximately one percent. While the initial findings are encouraging, the mean difference in creatine intake between cancer-free individuals and individuals with cancer was relatively small, and extracted from the self-reported data. Further epidemiological and interventional studies are thus required to validate the potential benefits of creatine-rich foods in the management of cancer.

Statement of ethics

Study approval statement: The ethical approval was granted by the U.S. National Center for Health Statistics Ethics Review Board (Continuation of Protocol #2011-17 [Effective through October 26, 2017] and Protocol #2018-01 [Effective beginning October 26, 2017]). Consent to participate statement: Written informed consent was obtained from all respondents to participate in the study. The research was conducted ethically following the World Medical Association Declaration of Helsinki.

CRediT authorship contribution statement

Sergej M. Ostojic: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Erik Grasaas:** Writing – review & editing, Methodology, Investigation. **Jelena Cvejic:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SMO serves as a member of the Scientific Advisory Board on Creatine in Health and Medicine (AlzChem LLC). SMO co-owns patent "Supplements Based on Liquid Creatine" at European Patent Office (WO2019150323 A1). SMO has received research support related to creatine during the past 36 months from the Serbian Ministry of Education, Science, and Technological Development; Provincial Secretariat for Higher Education and Scientific Research; Alzchem GmbH; ThermoLife International; and Hueston Hennigan LLP. SMO does not own stocks and shares in any organization. EG and JC declare no known competing financial interests or personal relationships that could have appeared to influence the authorship of this paper.

Data availability

Data will be made available on request.

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