CESPU
INSTITUTO UNIVERSITÁRIO
DE CIÊNCIAS DA SAÚDE

The Impact of Creatine Supplementation on Cancer

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Dissertação leading to the Degree of Bachelor of Master Science Pharmaceutical Sciences (Integrated Cycle)

Gandra, June of 2025

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Dissertation leading to the **Degree of Bachelor of Master** Science **Pharmaceutical Sciences (Integrated Cycle)**

The Impact of Creatine Supplementation on Cancer

Work carried out under the guidance of the Prof. Doutor José Carlos Marcia Andrade and the co-supervision of Prof.ª Ana Rita de Sousa Santos

INTEGRITY STATEMENT

I, SAYED Linda, declare that I have acted with absolute integrity in the preparation of this work, I confirm that in all the work leading to its preparation I have not resorted to any form of falsification of results or the practice of plagiarism (act by which an individual, even by omission, assumes authorship of the intellectual work belonging to another, in its entirety or in parts of it). I further declare that all the sentences I took from previous works belonging to other authors were referenced or written with new words, in which case I placed the citation of the bibliographic source

CONTRIBUTION OF THE WORK TO THE SUSTAINABLE DEVELOPMENT GOALS (SDGs):

The United Nations has defined seventeen SDGs, including SDG 3 – Good Health – which aims to ensure universal access to health services and promote well-being for all at all ages. This goal includes improving child, maternal, and reproductive health, reducing communicable and non-communicable diseases, and reducing premature mortality from diseases such as cancer, cardiovascular disease, diabetes, and chronic respiratory diseases. This work fits directly into this context, as it explores the role of creatine supplementation in cancer, one of the leading causes of mortality worldwide. Analyzing potential benefits, such as preserving muscle mass, strengthening anti-tumor immunity, and improving quality of life, as well as critically reflecting on the risks associated with creatine use in certain clinical settings, contributes to the prevention, treatment, and management of non-communicable diseases. Thus, this study is aligned with the SDG 3 targets, promoting safer, more personalized and evidence-based medical practice, and collaborating with the global effort to reduce the burden of cancer and ensure better health outcomes for the population [1]

Thanks

First and foremost, I would like to express my deepest gratitude to my family, especially my parents, who mean everything to me. Without their unconditional love, support, and guidance, I would not be where I am today. I also want to thank my sisters, who have always been by my side despite the distance. These five years away from them have been challenging, but their constant presence in my heart gave me strength.

I would like to thank Mohamed, whose presence and support have profoundly shaped my student life, which would never have been the same without him.

I also wish to dedicate a special word to my closest friends who have been part of this journey in Portugal. To Léa, Pauline, Chloé, Nine, and Eléonore, my friends since the very first year, I am forever grateful for your friendship. I love you, and I cherish the memories we created together. To Mathilde and Noa, with whom I had the privilege of living, thank you for turning everyday moments into unforgettable experiences.

My heartfelt thanks also go to my professors. I am especially grateful to Professor José Carlos Marcia Andrade, one of my first professors in this program and my dissertation supervisor, for his constant support, responsiveness, and guidance throughout my studies. I would also like to thank Professora Ana Rita Santos, my co-supervisor and professor of nutrition, whose valuable help and advice were essential in the development of this dissertation.

I also wish to acknowledge the pharmacy where I completed my final internship. This was my first true professional experience, and it marked an important step in my journey. I am particularly grateful to Nuno, who greatly supported me during my dissertation, and to the entire pharmacy team, who guided me with generosity and professionalism. They accompanied me through the final chapter of my studies in Portugal and allowed me to finish this journey on a positive and memorable note.

Finally, I want to extend my gratitude to Portugal itself, a country I knew very little about before arriving, but which has become a second home to me. What started as a challenge far from my family turned into a beautiful experience of growth and belonging. Today, I can sincerely say that I feel at home here, and if it were only up to me, I would choose to stay even longer.

ABSTRACT

Cancer, a complex and multifactorial disease, remains one of the leading causes of mortality worldwide and continues to drive the search for innovative therapeutic approaches. Creatine supplementation, primarily known for its ergogenic role in sports and its contribution to energy buffering, has recently attracted growing attention in oncology. Because cancer cells are highly dependent on energy metabolism for their growth, survival, and metastatic potential, understanding creatine's involvement in these processes may open new therapeutic perspectives.

This narrative review synthesizes evidence from twelve studies published between 2015 and 2025, including preclinical experiments, clinical trials, and epidemiological analyses, to evaluate the potential benefits and risks of creatine supplementation in cancer. Findings reveal a dual effect: creatine can enhance antitumor immunity by improving Adenosine Triphosphate (ATP) availability in immune cells, counteract cancer cachexia by preserving muscle mass, and improve rehabilitation outcomes in breast cancer survivors. Conversely, some cancers exploit creatine metabolism, particularly through the Monopolar Spindle Kinase 1 (MPS1)–Smad2/3 pathway, to promote tumor progression and metastasis. The non-metabolizable analogue cyclocreatine demonstrated inhibitory effects on prostate and breast cancer progression, suggesting therapeutic potential in disrupting tumor reliance on creatine pathways.

Epidemiological studies show no association between dietary creatine intake and cancer incidence, while safety data indicate that creatine does not contribute to the formation of carcinogenic heterocyclic amines in humans. Overall, creatine emerges as a context-dependent agent whose effects may be either beneficial or detrimental depending on tumor biology and patient characteristics. Future research should prioritize biomarker-driven clinical trials to identify subgroups most likely to benefit, paving the way for a personalized approach to creatine use in oncology.

Keywords : Creatine supplementation; Cancer; Metabolism; Immunity; Cachexia; Oncology

RESUMO

O cancro, uma doença complexa e multifatorial, continua a ser uma das principais causas de mortalidade em todo o mundo e mantém-se como um dos maiores impulsionadores da procura por abordagens terapêuticas inovadoras. A suplementação com creatina, amplamente conhecida pelo seu papel ergogénico no desporto e pela sua contribuição para o equilíbrio energético, tem despertado, recentemente, um interesse crescente no campo da oncologia. Dado que as células cancerígenas dependem fortemente do metabolismo energético para o seu crescimento, sobrevivência e potencial metastático, compreender o envolvimento da creatina nestes processos pode abrir novas perspetivas terapêuticas.

Esta revisão narrativa sintetiza evidência proveniente de doze estudos publicados entre 2015 e 2025, incluindo experiências pré-clínicas, ensaios clínicos e análises epidemiológicas, com o objetivo de avaliar os potenciais benefícios e riscos da suplementação com creatina no contexto oncológico. Os resultados revelam um duplo efeito: a creatina pode potenciar a imunidade antitumoral ao aumentar a disponibilidade de adenosina trifosfato (ATP) nas células imunitárias, contrariar a caquexia associada ao cancro através da preservação da massa muscular e melhorar os resultados de reabilitação em sobreviventes de cancro da mama. Por outro lado, alguns tipos de cancro exploram o metabolismo da creatina, particularmente através da via Monopolar Spindle Kinase 1 (MPS1)–Smad2/3, para promover a progressão tumoral e a metastização. O análogo não metabolizável, ciclocreatina, demonstrou efeitos inibitórios na progressão do cancro da próstata e da mama, sugerindo um potencial terapêutico na interrupção da dependência tumoral das vias metabólicas da creatina.

Os estudos epidemiológicos não mostram associação entre a ingestão alimentar de creatina e a incidência de cancro, enquanto os dados de segurança indicam que a creatina não contribui para a formação de aminas heterocíclicas carcinogénicas em humanos. De forma geral, a creatina emerge como um agente dependente do contexto, cujos efeitos podem ser benéficos ou prejudiciais, consoante a biologia tumoral e as características individuais do doente. Futuras investigações deverão dar prioridade a ensaios clínicos baseados em biomarcadores, com vista a identificar os subgrupos de doentes mais propensos a beneficiar da suplementação, abrindo caminho para uma abordagem personalizada ao uso da creatina em oncologia.

Palavras-chave : Suplementação com creatina; Cancro; Metabolismo; Imunidade; Caquexia; Oncologia;

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LIST OF ABBREVIATIONS

1-RM – One Repetition Maximum

ALS – Autophagy–Lysosome System

ATP – Adenosine Triphosphate

CKB – Creatine Kinase B

DEXA – Dual-Energy X-ray Absorptiometry

EMT – Epithelial–Mesenchymal Transition

GATM – Glycine AmidinoTransferase

GLUT-4 – Glucose Transporter Type 4

HCA – Heterocyclic Amines

HCAs – Heterocyclic Amines (pluriel)

IL-12 – Interleukin 12

MPS1 – Monopolar Spindle Kinase 1

mTORC1 – Mechanistic Target of Rapamycin Complex 1

NHANES – National Health and Nutrition Examination Survey

PI3K/Akt – Phosphatidylinositol 3-Kinase/Protein Kinase B

SDG - SUSTAINABLE DEVELOPMENT GOALS

PICO - Population, Intervention, Comparison, Outcome

T2DM – Type 2 Diabetes Mellitus

TGF-β – Transforming Growth Factor-beta

TNF-α – Tumor Necrosis Factor Alpha

UPS – Ubiquitin–Proteasome System

1) Introduction

Creatine is a nitrogenous molecule synthesized naturally in the liver, pancreas, and kidneys from the amino acids glycine, arginine, and methionine. It is stored mainly in skeletal muscle, where it plays a central role in energy metabolism, participating in the phosphocreatine/adenosine triphosphate (ATP) system. (Geng et al., 2024; Jiang et al., 2025) As a supplement, creatine is widely used in sports to improve physical performance, and is also useful in certain muscle and neurological pathologies, such as muscular dystrophy or amyotrophic lateral sclerosis. (D. I. Patel et al., 2022; Pereira et al., 2015)

In the last decade, growing interest has focused on the potential role of creatine in the field of oncology. (Geng et al., 2024; Zhang & Bu, 2022) In fact, several preclinical experimental studies have suggested that creatine can influence the progression of cancerous pathologies, either by favourably modulating anti-tumor immunity and muscle mass, or by negatively interfering with certain mechanisms of tumor proliferation and migration.(Peng & Saito, 2023; Wei et al., 2022) This complementarity raises a fundamental question as to its potential use in cancer patients.

From a pathophysiological point of view, cancer is characterized by profound changes in cellular metabolism, including increased dependence on glucose (Warburg effect) and dysregulation of the energy cycle. Creatine, as a phosphate donor for ATP, can affect this metabolic dynamic, namely by providing a quick source of energy for tumor or immune cells.(Lawrence Kazak et Paul Cohen, 2020) Some studies have shown an increase in immune functions through creatine supplementation, with an increase in the activation of CD8+ macrophages and lymphocytes, capable of slowing tumor progression in murine models. (Peng & Saito, 2023) Others have reported significant improvements in nutritional status and muscle mass in the context of cancer cachexia, a common syndrome in advanced cancers. (Jatoi et al., 2017; Wei et al., 2022) On the other hand, several studies have also highlighted the pro-tumor effects of creatine in certain models, particularly in prostate cancer, where it may promote progression through the activation of phosphatidylinosotol 3-kinase/protein kinase B (PI3K/Akt) pathways and modulation of the tumor microenvironment.(R. Patel et al., 2022) Furthermore, another study revealed that creatine could be diverted by cancer cells to fuel their energy metabolism, with possible consequences for tumor growth and metastatic spread.(Zhang et al., 2021; Zhang & Bu, 2022)

On a clinical level, the results from evidence are mixed. A multicentre randomised controlled trial did not demonstrate a significant effect of creatine on weight, quality of life or muscle strength in patients with advanced cancer and cachexia. (Jatoi et al., 2017) On the other hand, some studies with breast cancer survivors suggest that creatine, combined with physical exercise, may enhance the beneficial effects of post-chemotherapy rehabilitation.(D. I. Patel et al., 2022)

This review aims to gather and analyse the most relevant clinical and preclinical experimental data. It will explore the potential benefits, such as improvements in cachexia, immunity and metabolism, as well as the possible risks, such as tumor progression and deleterious metabolic effects, using a comparative and differentiated approach..

2) Objectives

The aim of this dissertation is to critically and comprehensively evaluate the impact of creatine supplementation on cancer, considering the preclinical experimental, clinical and epidemiological data published between 2015 and 2025. It is intended to integrate the available evidence to clarify the potential benefits, risks and limitations of the use of creatine in an oncological context, and respond to the following objectives:

- To analyze the molecular and metabolic mechanisms associated with creatine supplementation, evaluate how it can be used both by tumor cells to sustain their progression and metastasis, and by immune cells to strengthen their antitumor activity.
- To explore the immunomodulatory role of creatine in the activation of macrophages and $CD8^+$ T lymphocytes and discuss its potential as an adjuvant in immunotherapy strategies.
- To evaluate the influence of creatine supplementation on cancer cachexia, considering the preservation of muscle mass, the improvement of mitochondrial function and the impact on the quality of life of patients.
- To examine the existing clinical evidence regarding the use of creatine in cancer patients and cancer survivors, identifying contexts in which it can favor functional recovery, but also recognizing the limitations observed in situations of advanced disease.
- To consider the risks associated with supplementation, namely the pro-tumor potential in certain models, and to assess the relevance of analogues such as cyclocreatine in the selective inhibition of tumor metabolism.
- To identify gaps in knowledge and propose lines of future research, with emphasis on the need for clinical trials stratified according to metabolic biomarkers, to promote a personalized approach to the use of creatine in oncology.

3) Materials and methods

The present study was developed in the form of a narrative review of the literature that comprised several stages: (1) definition of the research question, (2) conduct a structured bibliographic research, (3) careful selection of studies according to previously established inclusion and exclusion criteria, and (4) systematic extraction of relevant information. For this purpose, a data extraction form was developed to standardize the collection of the most relevant variables of each study. Finally, the results were organized and discussed according to the main topics identified in the literature search, allowing for a critical, integrated and coherent analysis of the existing information.

3.1. Population, Intervention, Comparison, Outcome (PICO)

According to the PICO strategy, the research question is:

"What is the impact of creatine supplementation on the evolution of cancer of any etiology and its associated parameters?"

- P (Population): Cancer patients or experimental models of cancer;
- I (Intervention): Creatine supplementation ;
- C (Comparator): Placebo, no supplement, or control group;
- O (Outcome): Effects on tumor growth, metastasis, cachexia, immunity, and energy metabolism.

3.2. Research Strategy

The literature search was conducted using the electronic databases PubMed, ScienceDirect, and Google Scholar. To guarantee methodological rigor and thematic relevance, predefined inclusion and exclusion criteria were established and systematically applied during the selection process. The inclusion criteria encompassed original articles presenting either clinical or experimental research, as well as scientific reviews published in indexed journals, since both primary data and comprehensive analyses contribute to a more complete understanding of the topic. Only studies with a direct focus on creatine supplementation in the context of cancer were retained, ensuring that the final selection remained aligned with the central research question. Both human studies and those involving relevant animal models were considered eligible, as preclinical findings are essential to explore mechanistic pathways and may provide a rationale for clinical investigation. To ensure the accessibility and quality of the data, only articles available in full text were included, and to guarantee accurate comprehension and critical analysis, the language was restricted to English, French, or Portuguese.

The exclusion criteria were equally important to refine the corpus of studies. Articles without full text access were excluded, as the lack of methodological and results details would prevent proper evaluation. Similarly, works that dealt exclusively with creatine in a sports or performance-enhancement context, without establishing a link to cancer biology or clinical oncology, were not considered relevant and were excluded from the review.

After applying these criteria, the selected studies were subjected to a process of systematic data extraction carried out manually and independently, ensuring consistency and uniformity. The extracted information was then organized and synthesized in order to highlight the main objectives, evaluated parameters, results, and conclusions of each study. This comparative analysis is presented in detail in section 4.3, where the studies are summarized in tabular form to facilitate clarity and comprehension.

3.3. Search Terms

The search terms were defined based on the core concepts of the research question and entered into the English databases, using appropriate combinations with Boolean operators (AND, OR) to maximize the comprehensiveness and specificity of the results.

The following main terms were used, alone or in combination:

- “creatine”
- “creatine supplementation”
- "cancer"
- "tumor"
- “cancer progression”

- ”cachexia”

Some examples of combinations used include:

- PubMed: ("creatine" OR "creatine supplementation") AND ("cancer" OR "tumor" OR "cancer progression" OR "cachexia" OR "immune system")

These terms were adapted according to the characteristics of each database, in order to ensure the retrieval of the largest possible number of relevant articles, without compromising the specificity of the theme.

The selection of studies was carried out in two main stages:

1. Initial screening: the titles and abstracts of the identified articles were analyzed to exclude those that did not meet the inclusion criteria, such as publications not directly related to creatine in the oncological context. The remaining articles were then read in full.
2. Full-text evaluation: at this stage, the eligibility criteria were confirmed, and key information was extracted for further analysis. Randomized clinical trials, observational studies, in vitro and in vivo preclinical experimental study and narrative reviews with detailed methodology that provided relevant data on the effects of creatine in oncological situations were included in the present review.

4) Results

4.1 Research results

The bibliographic search initially retrieved 32 scientific articles from PubMed, ScienceDirect, and Google Scholar, using the search terms described in section 3.4. After screening the abstracts, 15 articles were excluded as they were not relevant to the central theme, leaving 17 studies for detailed evaluation. From these, 3 articles were excluded according to the pre-established exclusion criteria (1 written in a language other than English or Portuguese, and 2 focusing exclusively on creatine in a sports context). A total of 14 articles were therefore assessed in full text for eligibility. Following this step, 2 additional studies were excluded because they did not directly address the research question.

Consequently, 12 articles published between 2015 and 2025 fully met the methodological criteria and were included in the final analysis. The selection process is presented in the PRISMA flow diagram (Figure 1), which provides an overview of the identification, screening, eligibility, and inclusion phases.

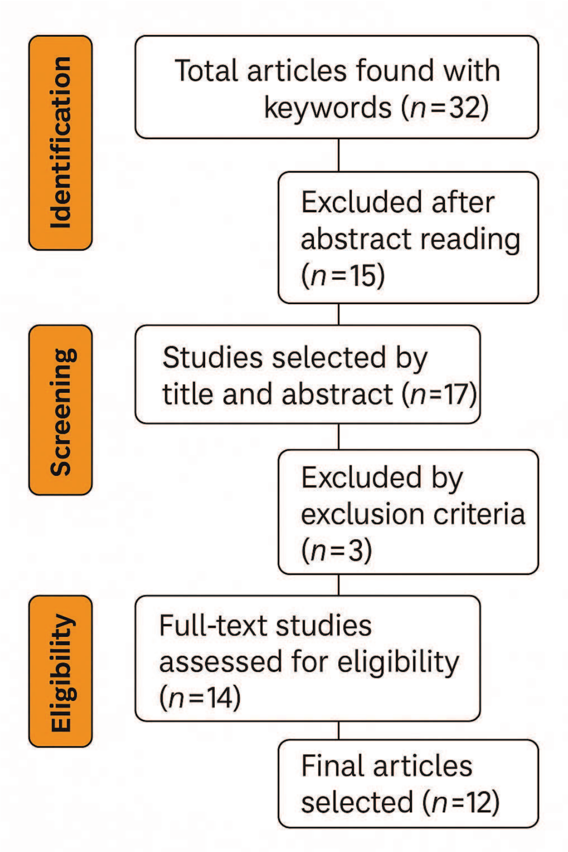

Figure 1: PRISMA flow diagram of study selection process

4.2. Study characteristics

This review includes twelve scientific articles that directly examine creatine supplementation within an oncological context. Three human clinical trials assessed the effects of creatine in different stages of cancer care: a randomized, double-blind, placebo-controlled trial investigating creatine in patients with cancer-related anorexia and cachexia (Jatoi et al., 2017); a pilot clinical study in breast cancer survivors after chemotherapy (D. I. Patel et al., 2022); and a controlled safety trial evaluating the potential formation of carcinogenic heterocyclic amines following creatine supplementation (Pereira et al., 2015). Additionally, safety concerns regarding the formation of carcinogenic heterocyclic amines were addressed and refuted in the controlled trial (Pereira et al., 2015), confirming that creatine supplementation does not increase HCA levels in human urine. Four preclinical experimental study studies (in vivo and/or in vitro) explored the role of creatine in tumor progression, energy metabolism, immune function, and metastatic processes (R. Patel et al., 2022; Peng & Saito, 2023; Wei et al., 2022; Zhang et al., 2021).One cross-sectional epidemiological study, based on National Health and Nutrition Examination Survey (NHANES) data (2007–2018), investigated the association between dietary creatine intake and self-reported cancer prevalence among U.S. adults (Jiang et al., 2025). Four narrative reviews provided insights into the molecular, immunological, and energetic aspects of creatine's role in cancer, discussing both its therapeutic potential and associated risks (Geng et al., 2024; Lawrence Kazak et Paul Cohen, 2020; Solis et al., 2021; Zhang et al., 2021) . The narrative reviews offered broad perspectives on creatine's impact on cellular energetics, tumor immunity, glucose metabolism, and cancer cachexia (Jiang et al., 2025; Lawrence Kazak et Paul Cohen, 2020; Wei et al., 2022; Zhang et al., 2021) Some highlighted its positive contributions to muscle preservation and immune cell function (Geng et al., 2024), while others warned of dual effects depending on tumor type and stage (Zhang & Bu, 2022), particularly in relation to metastasis (Zhang et al., 2021) or energy system hijacking by cancer cells 12.

In the clinical trials (Jatoi et al., 2017; D. I. Patel et al., 2022; Pereira et al., 2015), sample sizes ranged from 10 to 263 participants, including advanced cancer patients, post-treatment survivors, and healthy volunteers. All studies used oral creatine supplementation, with or without placebo, and evaluated outcomes such as body composition, muscle strength, fatigue, metabolic safety, appetite, and quality of life. The preclinical experimental study (R. Patel et al., 2022; Peng & Saito, 2023; Wei et al., 2022; Zhang et al., 2021) employed mouse models with induced tumors (e.g., colon carcinoma C26, melanoma B16-F10) and human tumor cell lines (e.g., prostate, colon, breast, pancreas). Outcomes included tumor growth and metastasis, ATP production, mitochondrial function, immune cell activation (macrophages, CD8+ T cells), and the modulation of signaling pathways such as smad 2/3. The cross-sectional study involved 22,692 American adults and found no statistically significant association between dietary creatine intake and cancer prevalence. Even in high-intake subgroups, no elevated cancer risk was observed, reinforcing creatine's safety profile in general populations.(Jiang et al., 2025)

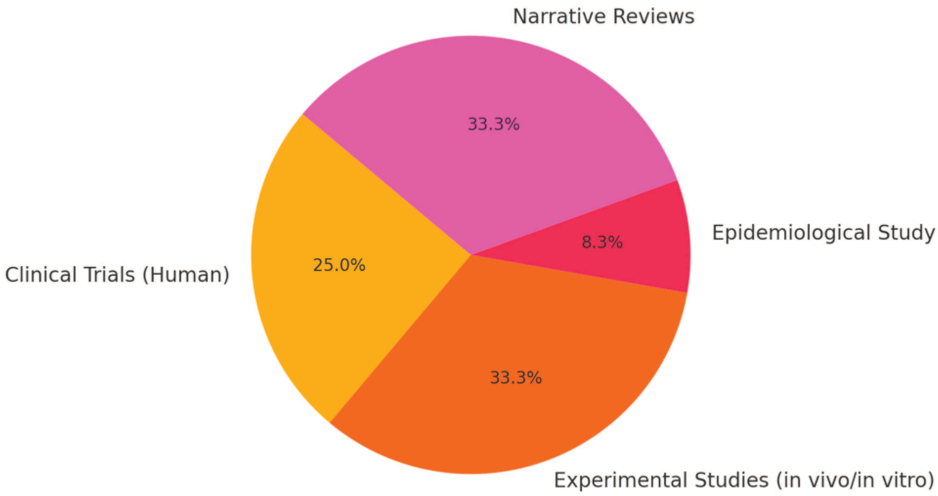

Figura 2: Distribution of study types in the 12 articles

4.3. Synthesis of the included studies

Table 2 : Synthesis of results

	Type of study	Objective	Evaluated parameters:	Results	Conclusion
(Jiang et al., 2025)	Epidemiological study traversal (cross-sectional analysis of NHANES data)	To assess the correlation between dietary creatine intake and cancer prevalence in U.S. adults.	Estimated daily creatine intake from food (based on 24h recalls), self-reported cancer diagnosis, sociodemographic variables (age, sex, race/ethnicity), lifestyle factors (smoking, alcohol, physical activity), and BMI categories.	Higher dietary creatine intake was associated with a modest but statistically significant reduction in cancer prevalence. Protective associations were stronger among men, overweight individuals, and adults ≥52 years. However, no consistent pattern was observed across all subgroups.	A potential protective association exists between dietary creatine intake and cancer prevalence, but due to the cross-sectional design, causality cannot be inferred. Since dietary creatine is mainly derived from meat, which is itself a risk factor for certain cancers such as colorectal cancer, the findings should be interpreted with caution and confirmed in prospective studies.
(R. Patel et al., 2022)	Preclinical study	To investigate whether cyclocreatine, a creatine analog, could inhibit creatine metabolism and	Tumor volume, metastasis, intracellular creatine and ATP levels, expression of creatine	Cyclocreatine reduced creatine uptake and intracellular ATP production, significantly slowing tumor growth and	Inhibiting creatine metabolism with analogs like cyclocreatine offers a promising therapeutic avenue, particularly for cancers like prostate

		thereby suppress prostate cancer progression.	transporters and kinases.	metastasis in prostate cancer models. Unlike creatine, which can support tumor energy metabolism, cyclocreatine disrupted these pathways.	cancer where creatine metabolism is upregulated. This supports a nuanced view where blocking—rather than supplementing—creatine may be beneficial in certain tumor types.
(Zhang et al., 2021)	Preclinical in vivo experimental study (orthotopic mouse models)	To determine how dietary creatine supplementation or increased endogenous synthesis affects metastasis in colorectal and breast cancer.	Liver metastases, mouse survival, Glycine AmidinoTransferase (GATM) expression, MPS1 and SMAD2/3 pathway activation, Snail/Slug expression.	•Creatine supplementation or GATM overexpression significantly increased liver and lung metastases. •The MPS1 → SMAD2/3 → Snail/Slug axis was activated, promoting epithelial–mesenchymal transition (EMT) and tumor dissemination. •Inhibition of GATM or MPS1 reduced metastasis and prolonged survival in mice.	Creatine supplementation can promote metastasis through the MPS1–SMAD2/3 pathway. Its use in patients with colorectal or breast cancer should be approached with caution.
(D. I. Patel et al., 2022)	Clinical trial	To assess whether creatine supplementation	Muscle strength (via 1-RM (one Repetition	Participants who received creatine showed significantly	Creatine supplementation is safe and may enhance

		combined with resistance training enhances muscle function and body composition in breast cancer survivors.	Maximum) tests), lean body mass (via Dual-Energy X-ray Absorptiometry (DEXA)), physical performance measures, and body weight.	greater improvements in muscle strength and lean mass compared to those in the placebo group. No adverse effects related to creatine were observed.	physical rehabilitation in cancer survivors. Although not directly affecting tumor biology, these findings suggest a supportive role for creatine in post-treatment recovery and functional health.
(Solis et al., 2021)	Narrative review	To explore the therapeutic potential of creatine supplementation in improving glucose metabolism, insulin sensitivity, and managing type 2 diabetes (T2DM).	Creatine's effects on insulin secretion, Glucose Transporter Type 4 (GLUT-4) translocation, muscle glucose uptake, and glycemic control with/without exercise.	•Animal studies: Creatine improves glucose uptake, glycogen storage, and insulin response. •Human studies: Creatine + exercise enhances glycemic control in sedentary and diabetic individuals. •Mechanism: Involves GLUT-4 translocation, AMPK activation, and cell osmolarity changes.	Creatine has promising anti-diabetic effects and may indirectly affect cancer risk via metabolic modulation. However, large-scale human trials are still needed for conclusive evidence.
(Wei et al., 2022)	Preclinical experimental study (mouse model of cancer cachexia +	To evaluate whether creatine supplementation could prevent or reverse muscle wasting in	Skeletal muscle mass, grip strength, mitochondrial function, activity of proteolytic systems (Ubiquitin–	Cachectic mice showed significantly reduced creatine levels and muscle atrophy. Creatine supplementation	Creatine has a protective role in the context of cancer cachexia. By improving energy metabolism and stabilizing muscle

	human tissue samples)	cancer cachexia, a syndrome marked by severe body weight and muscle loss.	Proteasome System (UPS) and Autophagy–Lysosome System (ALS)), and histological markers of muscle integrity.	restored mitochondrial function, inhibited overactivation of protein degradation pathways (UPS and ALS), and improved grip strength and muscle fiber integrity.	tissue, creatine may support quality of life and physical function in patients undergoing cancer treatment. It highlights the non-oncogenic, yet clinically valuable, application of creatine in oncology care.
(Pereira et al., 2015)	Human clinical intervention study	To determine if creatine supplementation increases the formation of carcinogenic heterocyclic amines (HCAs) in the human body.	Levels of HCAs in urine before and after creatine supplementation.	•No increase in urinary HCAs was detected after 5 days of creatine supplementation (21 g/day). •Creatine alone did not result in endogenous formation of carcinogenic HCAs.	Creatine supplementation does not induce the formation of carcinogenic heterocyclic amines in vivo. Therefore, the concerns about creatine forming HCAs under normal dietary conditions are unsubstantiated.
(Jatoi et al., 2017)	Randomized, double-blind, placebo-controlled clinical trial	To determine whether creatine could improve weight, muscle mass, and quality of life in patients suffering from cancer-related	Body weight, grip strength, lean mass, appetite scores, and overall quality of life (via questionnaires).	There were no statistically significant differences between the creatine and placebo groups in weight gain, muscle strength, or quality of life metrics over the treatment period.	In this clinical context, creatine supplementation did not produce measurable benefits for cancer patients suffering from anorexia-cachexia syndrome. This suggests that creatine

		anorexia and cachexia.			alone may not be effective in reversing late-stage cancer-related muscle and weight loss, highlighting the need for multimodal interventions.
(Zhang & Bu, 2022)	Scientific review	To explore and reconcile both anti-tumor and pro-tumor roles of creatine and its metabolism in various cancer types.	Tumor growth, metastasis, expression of enzymes (Glycine AmidinoTransferase (GATM), Creatine Kinase B (CKB)), creatine transport (SLC6A8), CD8+ T cell function, and creatine-related metabolic pathways.	•Anti-tumor effects: Creatine and its analog cyclocreatine suppress subcutaneous tumor growth; enhance ATP buffering in CD8+ T cells, improving antitumor immunity. •Pro-tumor effects: In orthotopic models, creatine promotes invasion and metastasis (e.g., colorectal, pancreatic, breast cancer) through metabolic crosstalk and energy shuttling •Upregulation of creatine kinase and transporter SLC6A8 is linked to aggressive cancer	Creatine plays a complex, stage- and context-dependent role in cancer. While it boosts immunity and suppresses growth in some models, it enhances metastasis in others. Supplementation should be approached with caution, especially in advanced cancers.

				phenotypes and poor prognosis.	
(Peng & Saito, 2023)	Preclinical study (in vitro on macrophages and in vivo in tumor-bearing mice)	To explore how creatine supplementation influences macrophage energy metabolism and its downstream effects on anti-tumor immunity.	ATP production in macrophages, cytokine secretion (Tumor Necrosis Factor Alpha (TNF-α), Interleukin 12 (IL-12)), tumor growth rate, immune cell infiltration in the tumor microenvironment.	Creatine significantly increased ATP production in macrophages, which led to enhanced pro-inflammatory cytokine release. Tumor-bearing mice receiving creatine had smaller tumor volumes and a higher presence of cytotoxic immune cells in the tumor tissue.	Creatine supplementation strengthens macrophage-mediated anti-tumor immune responses through improved energy metabolism. These findings support a potential adjuvant role for creatine in immunotherapy-based cancer treatment strategies.
(Geng et al., 2024)	Narrative review	To explore the diverse and sometimes contradictory roles of creatine in tumor biology and immunology, highlighting both its cancer-promoting and cancer-inhibiting effects.	Effects of creatine on tumor growth, apoptosis, CD8+ T-cell function, macrophages, anti-tumor immunity, and metabolic pathways such as Mechanistic Target of Rapamycin Complex 1 (mTORC1).	•Anti-cancer effects: Enhancement of CD8+ T-cell activity and modest tumor growth inhibition in animal models; improved response to anti-PD1 therapy. •Pro-cancer effects: High creatine kinase (CKB) expression observed in several cancer types; activation of pro-metastatic signaling	Creatine plays a dual role in oncology. It can enhance anti-tumor immunity while also supporting cancer progression depending on the cellular and tumor context. Its therapeutic use must be approached with caution.

				pathways such as MPS1–SMAD2/3. • The role of macrophages is ambiguous: creatine may support either M1 (anti-tumoral) or M2 (pro-tumoral) phenotypes.	
(Lawrence Kazak et Paul Cohen, 2020)	Scientific review	To present new insights into creatine metabolism, with a focus on its role in energy homeostasis, immunity, and cancer.	Creatine's function in various tissues, CK enzyme activity, cancer-related signaling pathways.	•Creatine goes beyond energy buffering, playing key roles in immune regulation and epigenetics. •It supports cancer cell survival by optimizing mitochondrial metabolism and influencing macrophage polarization. •Cyclocreatine, an analog of creatine, may inhibit tumor growth without promoting cell proliferation.	Creatine has complex roles in cancer. It can support tumor cell survival and modulate immune responses. The use of analogs like cyclocreatine may be a promising alternative for cancer therapy.

5) Discussion

The impact of creatine supplementation on cancer presents a complex and bidirectional relationship that requires a comprehensive analysis. Creatine is no longer viewed solely as an ergogenic aid for athletes but is now being explored for its implications in cancer metabolism, immunity, muscle preservation, and clinical outcomes. This discussion synthesizes findings from twelve articles, highlighting both the therapeutic promise and potential risks of creatine in oncology. These studies collectively reveal that the effects of creatine are highly context-dependent, modulated by tumor type, host physiology, treatment phase, and metabolic reprogramming.

A crucial starting point for this discussion is the review by Kazak and Cohen (2020), which provides an in-depth synthesis of the role of creatine metabolism in tumor biology and immunology. The authors emphasize that creatine extends beyond its classical function as an intracellular energy buffer: it also participates in the regulation of key metabolic and immune pathways that shape tumor progression. In normal cells, creatine metabolism is tightly controlled, ensuring balance between energy demands and cellular stability. In contrast, many cancer cells display dysregulation of this pathway, including upregulation of creatine-related enzymes and transporters such as creatine kinase B (CKB) and the creatine transporter SLC6A8. This dysregulation contributes to tumor survival and metabolic adaptation, but at the same time reveals therapeutic vulnerabilities that could be exploited. The review also highlights the ambivalent role of creatine in antitumor immunity. On the one hand, creatine can enhance the activity of CD8+ T lymphocytes and support macrophage function in the context of immune defense, suggesting a potentially beneficial role in immunotherapy. On the other hand, creatine metabolism may promote tumor growth and metastatic dissemination under certain conditions, reflecting its dual and context-dependent nature in oncology. Finally, Kazak and Cohen stress the importance of integrating creatine metabolism into precision oncology. According to their framework, metabolic profiling of patients could help identify when creatine supplementation may be advantageous—for example, to boost immune responses or counteract cachexia—and when, conversely, inhibition of creatine pathways might be more appropriate to reduce the metabolic advantage of tumor cells. This personalized approach underscores the need to evaluate creatine not as universally beneficial or harmful, but as a context-dependent factor whose role must be defined within specific tumor and patient profiles. (Lawrence Kazak et Paul Cohen, 2020)

One of the central themes emerging from this review is the role of creatine in modulating cancer immunology. Findings suggest that creatine enhances the function of innate and adaptive immune cells by increasing their intracellular ATP reserves, thereby supporting their energy-demanding antitumor activities. In article of (Peng & Saito, 2023), researchers demonstrated that macrophages exposed to creatine had enhanced ATP production, which led to a phenotypic shift toward pro-inflammatory M1 macrophages. These immune cells produced more IL-12 and TNF-Α, and their tumoricidal capacity improved in mouse models of melanoma and colon cancer. Furthermore, creatine administration resulted in enhanced $CD8^+$ T cell infiltration into tumors and reduced tumor burden. In addition, study [11] revealed that creatine supports T cell expansion and survival via mTORC1 activation. By boosting energy stores, creatine allowed T cells to maintain effector function and memory phenotype in immunosuppressive tumor environments. (Lawrence Kazak et Paul Cohen, 2020) contextualized these findings within a broader metabolic framework, explaining how creatine metabolism intersects with immunometabolism and contributes to the balance between immune activation and tolerance. Together, these studies suggest that creatine could serve as a metabolic co-adjuvant to immunotherapy by revitalizing exhausted immune cells. However, the same metabolic pathways that benefit immune cells can be exploited by tumor cells.

Certain cancers exhibit high expression of creatine kinase and creatine transporter genes, enabling them to use creatine as an alternative energy source. (Zhang et al., 2021) showed that dietary creatine supplementation enhanced metastasis in breast and colorectal cancer models through the activation of the MPS1–Smad2/3 signaling cascade. Smad2 and Smad3 are intracellular proteins that act as key mediators of the transforming growth factor-beta (TGF-Β) signaling pathway. Upon activation by upstream signals such as MPS1, Smad2 and Smad3 become phosphorylated, form complexes with Smad4, and translocate into the nucleus, where they regulate the transcription of target genes involved in cell proliferation, differentiation, and migration. In the context of cancer, activation of Smad2/3 promotes epithelial-mesenchymal transition (EMT), a process by which epithelial tumor cells acquire mesenchymal features, enhancing their motility and invasiveness. This activation led to increased expression of EMT markers such as Snail and Slug, facilitating tumor cell migration and invasion. Mice treated with creatine displayed significantly higher metastatic loads in lung and liver tissues. (Zhang & Bu, 2022) expanded on this by explaining how aggressive tumors increase creatine uptake and phosphocreatine buffering to support proliferation under hypoxic and nutrient-deprived conditions. This metabolic plasticity underscores the risk of creatine supplementation in tumor types with elevated creatine transport or utilization. It Is noteworthy that these findings came from research with mice and cellular lines, whose results may not be directly applied to the clinical setting.

In contrast, Patel et al. (2022) investigated cyclocreatine, a synthetic analog of creatine that cannot be converted into phosphocreatine. In prostate cancer models, cyclocreatine inhibited tumor growth and metastasis by disrupting intracellular energy homeostasis. Specifically, the compound impaired SLC6A8-mediated creatine uptake, resulting in reduced intracellular ATP levels, diminished cell viability, and suppression of metastatic dissemination. Notably, normal tissues were less affected, indicating that tumor cells are more dependent on creatine metabolism than non-malignant counterparts. These findings suggest that targeting creatine metabolism, through analogs such as cyclocreatine, could represent a promising therapeutic strategy in tumors characterized by creatine addiction.

Beyond immunology and tumor metabolism, creatine's role in cancer-related muscle wasting has also been investigated. Cachexia, characterized by the progressive loss of skeletal muscle mass, is a major determinant of morbidity and mortality in cancer patients. In the preclinical study by Wei et al. (2022), creatine supplementation in tumor-bearing mice preserved muscle fiber size, restored mitochondrial function, and attenuated catabolic activity through the ubiquitin-proteasome and autophagy-lysosome systems. Treated animals also demonstrated improved grip strength and locomotor activity, parameters directly linked to functional status and survival. Importantly, the same study reported that muscle tissue from cachectic patients exhibited significantly lower creatine levels compared to healthy controls, indicating a physiological deficit that could potentially be corrected with supplementation. Complementary evidence was provided by Peng and Saito (2023), who demonstrated in vitro that creatine increased ATP production and cytokine release in macrophages, and confirmed in vivo in tumor-bearing mice that supplementation enhanced immune cell infiltration and slowed tumor growth. By improving systemic immune control, creatine may indirectly mitigate cancer-induced inflammation and subsequent muscle breakdown.

The potential for creatine to support patient rehabilitation after cancer treatment is demonstrated by clinical evidence. Patel et al. (2022) conducted a pilot clinical trial in breast cancer survivors who had completed chemotherapy. Participants received creatine or placebo alongside a resistance training program for 12 weeks. Those in the creatine group experienced greater improvements in muscle strength, lean body mass, and functional capacity compared to the placebo group. These benefits were achieved without adverse effects, suggesting that creatine is safe and effective, supporting post-treatment physical recovery. This finding is particularly important given the increasing emphasis on survivorship care and long-term quality of life in oncology.

However, creatine's effectiveness in advanced cancer settings remains questionable. Jatoi et al. (2017) reported the results of a randomized, double-blind, placebo-controlled trial assessing creatine supplementation in patients with cancer cachexia. Despite adequate dosing, the study found no significant improvements in body weight, appetite, grip strength, or quality of life. These findings may reflect the severity of systemic inflammation and metabolic disruption in late-stage cancer, where creatine's anabolic effects are insufficient to counteract the ongoing catabolic state. This highlights the need to tailor supplementation strategies to the clinical context rather than adopting a uniform approach across all stages of the disease.

By analyzing more than a decade of NHANES data, Jiang et al. (2025) identified a modest but statistically significant inverse association between dietary creatine intake and cancer prevalence in the U.S. adult population. The protective association appeared stronger in men, in overweight individuals, and in adults over 52 years, although no consistent trend was observed across all subgroups. Despite these findings, interpretation must remain cautious due to the cross-sectional design, in which dietary exposure and disease status were evaluated simultaneously, preventing any causal inference. An additional complexity lies in the fact that dietary creatine is mainly derived from meat, particularly red meat, which is a well-established risk factor for several cancers, most notably colorectal cancer. This paradox illustrates the difficulty of isolating the specific contribution of creatine from its food sources in nutritional epidemiology. Moreover, survival bias may have influenced the results, as patients with advanced cancers are underrepresented in population-based surveys, and although multiple statistical adjustments were performed, residual confounding cannot be excluded. Overall, while the study suggests a potential protective role for dietary creatine, prospective longitudinal studies are needed to determine whether this association reflects a genuine causal relationship.

To address persistent concerns about the potential carcinogenicity of creatine, Pereira et al. (2015) conducted a human intervention study designed to test whether creatine supplementation could induce the endogenous formation of heterocyclic amines (HCAs). These compounds are recognized carcinogens that are typically generated during the high-temperature cooking of meat, which is also the primary dietary source of creatine. Some critics of creatine supplementation had hypothesized that high doses of creatine could undergo similar chemical transformations within the human body, thereby leading to HCA formation and increasing cancer risk. In order to test this hypothesis, the investigators recruited healthy adult volunteers who received high-dose creatine monohydrate supplementation (21 g per day for five consecutive days). Urine samples were collected both before and after the supplementation period to assess the excretion of HCAs. The analyses showed no significant increase in urinary HCA levels after supplementation, indicating that creatine, under normal physiological conditions, does not undergo endogenous conversion into carcinogenic compounds. These findings provide strong evidence against a frequently cited safety concern surrounding creatine supplementation. While the formation of HCAs is a genuine risk in the context of meat consumption — particularly red meat — due to cooking-related chemical reactions, this process is unrelated to creatine itself. The study by Pereira et al. therefore demonstrates that creatine as an isolated supplement does not share the same carcinogenic potential as cooked meat, and it helps to dispel the misconception that creatine supplementation is inherently carcinogenic. (Pereira et al., 2015)

Another noteworthy aspect is the link between creatine and glucose metabolism. (Solis et al., 2021) demonstrated that creatine supplementation improves glucose tolerance and insulin sensitivity by enhancing glucose transporter translocation in skeletal muscle. While this study focused on diabetes, it may have indirect implications for cancer, especially in tumors sensitive to insulin or glycolytic flux. Improved glucose handling could benefit patients undergoing chemotherapy, which often disrupts metabolic homeostasis. However, further research is needed to establish how creatine's effects on glucose metabolism interact with tumor biology.

In summary, the impact of creatine supplementation on cancer is highly multifaceted and context dependent. On one hand, creatine supports immune function, mitigates muscle wasting, and improves physical recovery after treatment. (Geng et al., 2024; Peng & Saito, 2023; Wei et al., 2022) provide strong preclinical evidence for these benefits, while (Wei et al., 2022) confirm them in a clinical setting. On the other hand, creatine can be hijacked by tumors with high metabolic flexibility (R. Patel et al., 2022; Zhang et al., 2021; Zhang & Bu, 2022). These tumors use creatine to buffer ATP and sustain proliferation, migration, and invasion. In such cases, inhibition of creatine transport or metabolism, as exemplified by cyclocreatine in article written by (R. Patel et al., 2022), may be therapeutically advantageous.

Safety data from both epidemiological and clinical studies provide important reassurance that creatine is not associated with an increased cancer risk. Jiang et al. (2025) reported a modest but statistically significant inverse association between dietary creatine intake and cancer prevalence in U.S. adults, suggesting no evidence of harm at the population level. Complementary findings were provided by Pereira et al. (2015), who demonstrated in a controlled human trial that high-dose creatine supplementation did not lead to the endogenous formation of heterocyclic amines, carcinogenic compounds typically generated during meat cooking. Together, these results help to dispel concerns that creatine itself could be carcinogenic, whether in the general population or in survivorship settings. However, the clinical utility of creatine in advanced disease appears more limited. In a randomized controlled trial, Jatoi et al. (2017) found that creatine supplementation did not produce significant improvements in weight, muscle strength, or quality of life in patients with cancer cachexia, likely reflecting the irreversible metabolic disruption characteristic of late-stage disease. These results suggest that the benefits of creatine may be restricted to earlier disease phases or to rehabilitation after treatment rather than to advanced cancer contexts. Expanding the discussion beyond direct cancer outcomes, Solis et al. (2021) highlighted the potential of creatine to improve glucose metabolism, enhance insulin sensitivity, and modulate pathways implicated in diabetes. Since metabolic dysregulation is a hallmark of cancer, these findings open new avenues for investigating creatine not only as a supportive supplement but also as a metabolic modulator that may indirectly influence cancer progression.

Moving forward, it is imperative to adopt a personalized approach to creatine supplementation in oncology. Biomarkers such as SLC6A8 expression, creatine kinase activity, and tumor metabolic phenotype should inform clinical decisions. Creatine should not be universally recommended or avoided but rather considered in light of individual patient and tumor characteristics. Clinical trials that stratify patients by metabolic markers and assess both efficacy and safety are urgently needed. Nevertheless, several limitations must be acknowledged. Most of the current evidence derives from preclinical studies using in vitro or animal models, which may not fully replicate the complexity of human cancer. The few available clinical trials have been small, heterogeneous in design, and often underpowered to detect long-term effects. Moreover, epidemiological data remain limited to cross-sectional analyses, precluding causal inference. Another important challenge is the difficulty of isolating creatine's effects from those of its dietary sources, particularly meat, which carries its own established cancer risks. Finally, there is insufficient evidence regarding the long-term safety of high-dose supplementation in oncology populations. In this context, creatine holds promise as an adjunct therapy in supportive oncology, but its application must be carefully targeted and rigorously tested to avoid unintended promotion of tumor progression.

CONCLUSION :

This review demonstrates that creatine supplementation plays a dual and context-dependent role in oncology. While it may enhance immunity, preserve muscle mass, and support rehabilitation, it can also be exploited by certain tumors to promote growth and metastasis. Current evidence indicates no direct carcinogenic risk, but clinical results remain inconsistent, particularly in advanced disease. Creatine should therefore be considered neither universally beneficial nor harmful, but as a context-specific agent whose use must be guided by tumor type, disease stage, and metabolic profile. Its future in oncology lies in carefully targeted, biomarker-driven clinical applications.

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