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Macronutrients in context for cancer biology and risk of carcinogenesis

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ABSTRACT

The incidence of cancer cases is constantly rising despite the continuous development of medical science in this area of interest. Although neoplastic transformation and the mechanisms of tumor cell metabolism have already been widely studied, we still do not know enough how to prevent and treat cancer effectively. Every year, the picture of cancer cell physiology is dynamically changing due to ongoing research and discoveries. This review includes an analysis of publications in the scientific databases PubMed/Medline and Google Scholar, which were selectively reviewed for various compounds and metabolic processes involved in carcinogenesis. To systematize current knowledge, selected publications were divided into three groups representing each macronutrient. By understanding metabolic pathways and dietary influences of carbohydrates, lipids, and proteins, the review provides insights into potential preventive measures. The findings emphasize the need for continued research on cancer metabolism and nutrition-based interventions to prevent cancer and develop more effective therapies.

Keywords: Cancer biology; macronutrients; carbohydrates; lipids; proteins; diet

1. INTRODUCTION

In 2024, it is predicted that about 2 million patients will be diagnosed with cancer in the United States. About 600,000 Americans will die because of it. That means precisely 1,680 deaths per day. Even though cancer mortality has dropped by 33% in 2021 compared to 1991 due to a reduction in smoking, early diagnosis, and the development of modern therapies, the incidence of 6 out of 10 most common cancers is still rising. These include breast, prostate, uterine corpus, pancreas, oropharynx, liver (in women), kidney, melanoma, as well as colorectal cancer and cervical cancer (Siegel et al., 2024). The scientific world is trying to

explain the process of cancer development to reduce the number of new cases and create new, more effective therapies to increase survival rates.

Metabolic alterations occurring in cancer cells became a promising target for cancer therapies, especially when combined with other treatment methodes. In the face of the increasing cancer incidence, prevention plays an important role. It has been proven that one of the factors influencing carcinogenesis is diet (Key et al., 2020). It belongs to modifiable risk factors. It means that the severity of the risk factor effect can be reduced or increased by interventions such as lifestyle changes (Marino et al., 2024). Nutrients consist of two groups divided according to the amount a person requires for proper functioning.

Macronutrients include carbohydrates, fats, and proteins. Micronutrients consist of vitamins and minerals. Macronutrients supplied with food are digested in the gastrointestinal tract and then absorbed, after which they undergo many chemical transformations that ultimately allow them to perform their specific functions (Zohoori, 2020). Cancer cells metabolize carbohydrates, fats, and proteins, but due to their pathological nature, their metabolism differs from healthy cells (Pavlova et al., 2022). In this review, we will try to generally characterize the most crucial macronutrient metabolic changes occurring in cancer cells and determine the effects of dietary carbohydrates, fats, and proteins on the risk of cancer.

2. METHODS

Search Strategy

This article gathers information from publications available on PubMed and Google Scholar and focuses on metabolic changes occurring in cancer cells and the effect of diet on cancer development. The used keywords included “cancer biology”, “cancer metabolism”, “carcinogenesis”, “diet”, “carbohydrates”, “lipids”, and “proteins”. No time limits were applied to the searches.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: Quantitative and/or qualitative research studies; reviews (bibliographic, systematic, and/or meta-analyses); and materials and books related to cancer metabolism and/or diet. Publications in non-English language, journal articles published without a peer review publication system and preprint articles have been excluded.

Data Extraction

The preliminary search was divided into parts related to each of the three macronutrients separately. Filters were applied to include only English-language studies. An initial screening of titles from these three groups led to the exclusion of studies unrelated to macronutrient-specific cancer metabolism, describing the biology of cancer by focusing only on inorganic compounds, or not addressing the dietary aspects of macronutrient and cancer. The remaining publications were subjected to abstract review to evaluate their relevance and quality. Selected publications were subjected to a full-text review.

Data Synthesis

The collected materials were divided into three groups for each macronutrient. Finally, 51 studies were selected for the carbohydrates section, 35 for the lipids section, and 27 for the protein section. Additionally, publications needed for the discussion section on various eating patterns were searched separately.

3. RESULTS

The results of this study are presented in three parts, each focusing on a different group of macronutrients.

Carbohydrates

Carbohydrates (saccharides) are an essential element of the human diet. We can divide saccharides into groups - monosaccharides (glucose, fructose, galactose), disaccharides (maltose, sucrose, lactose), and complex carbohydrates (starch, glycogen, fiber), which are chain forms of linked simple sugars (Clemente-Suárez et al., 2022). In the human body, they perform many functions, the most important of which is to provide energy and store it. Moreover, they form cell membranes, regulate the functioning of the immune

system, mediate intercellular communication, and affect the antiinfection response (Tharanathan, 2002). Carbohydrates are present in many types of foods, mainly of plant origin.

Simple carbohydrates (monosaccharides) and disaccharides are naturally present in fruits (glucose, fructose, sucrose), milk (lactose), or honey (glucose and fructose). Complex sugars are found largely in whole-grain products, e.g. whole-grain bread, oats, pasta, and rice, as well as in vegetables - peas, and beans (Holesh et al., 2024). These products are rich in starch, a mixture of two glucose polymers amylose and amylopectin, which act as the storage material. Another complex sugar is cellulose. It is found in the plant cell walls and also belongs to the components of dietary fiber. The human organism can only hydrolyze the alpha-linked polysaccharide chains by digestion in the small intestine.

Therefore, sugars such as cellulose built of beta-linked glucose units are indigestible, and the alpha bonds of starch are hydrolyzed. However, the digestibility of starch depends on many other factors, such as the ratio of amylose to amylopectin, prior food processing, and the macrostructure of the food. Additionally, some polysaccharides not digested in the intestines can be fermented by the gut microbiota to short-chain fatty acids (Lovegrove et al., 2017). In 1920, biochemist Otto Warburg observed that cancer cells metabolize glucose through anaerobic lactate fermentation despite having access to oxygen. Paradoxically, aerobic phosphorylation is more efficient and provides more energy.

This process has been called the Warburg effect (Pascale et al., 2020). Even though extensive research on its function has been conducted, it has still not been fully clarified. Presumably, it is associated with the rapid generation of energy required by tumor cells for proliferation, enhanced cellular biosynthesis, modulation of cell signaling by ROS and chromatin modulation, immune escape, and acidification of the tumor microenvironment to disrupt healthy tissue architecture (Liberti and Locasale, 2016). Small-molecule inhibitors targeting glycolysis enzymes and blocking glucose usage as an energy source have become promising directions for cancer therapies (Barba et al., 2024). Increased glucose metabolism is characteristic of intensely growing tumor cells.

The discovery of this phenomenon allowed the development of positron emission tomography (PET). Isotope-labeled 18-fluorodeoxyglucose (FdG) accumulates in the localization of tumor foci, allowing detection of distant metastases in cancer patients (Gatenby and Gillies, 2004). Due to increased energy intake, cancer cells increase glucose uptake and upregulate the expression of the glucose transport protein GLUT1. It is correlated with a higher degree of malignancy and the potential for tumor metastasis (Calvo et al., 2010). Blocking such transporters with appropriate inhibitors has become an attractive target in the development of cancer therapy (Pliszka and Szablewski, 2021).

Glucose and its metabolism also play a role in maintaining proliferation, preventing apoptosis, and enabling angiogenesis and metastasis (Ediriweera and Jayasena, 2023). Saccharides in the human body are involved in glycosylation. This process involves linking saccharide molecules (glycans) to proteins and lipids (Reily et al., 2019). In cancer cells, glycosylation occurs incorrectly and differs from healthy cells. Alterations in the glycan pattern can contribute to changes in the intercellular interactions of cancer cells or incorrect binding to the extracellular matrix. This results in easier detachment of cells from others and an increased ability to metastasize (Thomas et al., 2021). Diabetes is associated with impaired sugar metabolism.

Type I diabetes is caused by a lack of insulin secretion due to the destruction of pancreatic beta cells as a result of an autoimmune reaction. Type II diabetes is based on increasing resistance to insulin, with consequent increased synthesis of insulin in the pancreas (hyperglycemia, hyperinsulinemia) and, in the next stage, dysfunction of its secretion (hyperglycemia, hyperinsulinemia) (Zaccardi et al., 2016). Diabetes and hyperglycemia are risk factors for cancers, including pancreas, liver, colorectal, breast, bladder, and endometrial cancer (Shahid et al., 2021). The mechanism explaining this phenomenon includes genetic predisposition, obesity, chronic inflammation, oxidative stress, hyperglycemia, hyperinsulinemia, or taking certain oral diabetic drugs (Zhu and Qu, 2022).

As an example, many types of cancer are characterized by overexpression of the insulin receptor (IR). Hyperinsulinemia associated with type II diabetes, but also obesity, leads to activation of the IR receptor, which, through metabolic pathways including phosphoinositide 3-kinase (PI3K), protein kinase B (Akt) or mammalian target of rapamycin kinase (mTOR), enables cells uncontrolled proliferation and puts them on the path to carcinogenesis (Talib et al., 2021). Specific carbohydrates are essential in the metabolic pathways of cancer cells, but their effect on cancer development as a diet component is equally interesting. Dietary fibers are a wide range of plant-origin substances that cannot be digested by the human gastrointestinal tract.

Food fibers can be divided based on their structure into non-starch polysaccharides (including cellulose, hemicellulose, and pectin), resistant to digestion starches, and resistant to digestion oligosaccharides (Guan et al., 2021). It is found in vegetables, fruits, pulses, whole grain products, and rice and groats. Various properties of dietary fibers explain their beneficial health. Insoluble dietary fibers

such as cellulose, hemicellulose, and lignin increase stool volume and accelerate intestinal passage, which shortens the contact of carcinogens contained in digested food with the intestinal surface (Guan et al., 2021; Weisburger et al., 1993). On the other hand, the viscous and gel-forming fraction of the soluble fibers (inulin, resistant starches, oligosaccharides) undergoes bacterial fermentation in the colon.

The short-chain fatty acids synthesized during fermentation exhibit immune system-modulating properties, reduce the inflammatory response, and positively affect lipid and glucose metabolism (McRorie and McKeown, 2017; Ney et al., 2023). Additionally, whole grains and fruits contain phenolic acids, which also possess anti-inflammatory properties (Khan et al., 2024). Viscous, gel-forming properties of the soluble fibers hinder and delay carbohydrate absorption, decreasing postprandial glucose excursion (Xie et al., 2021). Interestingly, prospective cohort studies have shown that a diet high in insoluble cereal dietary fibers significantly reduced the risk of diabetes. No such evidence was obtainable for a diet rich in soluble fibers (Weickert and Pfeiffer, 2018).

Moreover, a systemic review with a meta-analysis of dietary fiber showed that dietary fiber intake reduces the risk of pancreatic cancer with no prevalence of soluble or insoluble fiber (Nucci et al., 2021). In murine models, dietary supplementation of soluble and insoluble fibers inhibits bacterial beta-glycosidase and was shown to exhibit a protective effect against mammary adenocarcinoma tumorigenesis, presumably due to changes in estrogen metabolism (Cohen et al., 1996). After studying 11 meta-analyses, the group of Hu et al., (2023) concluded that dietary fiber provides beneficial protective properties against a variety of cancers, including those affecting the gastrointestinal tract (such as colorectal, gastric, and esophageal cancers), as well as gynecologic cancers (including breast, endometrial, and ovarian cancers) and cancers of the pancreas, prostate, and kidney.

The term sugars is often assigned to monosaccharides such as glucose, galactose, and fructose and disaccharides such as sucrose, lactose, and maltose. Their increased consumption is associated with the development of diseases such as obesity, diabetes, and cardiovascular disease (Walton et al., 2023). A large cohort study proved that a diet high in sugar was associated with an increased overall risk of cancer, especially breast cancer, which was independent of weight gain (Huang et al., 2023). Lack of sweet taste does not necessarily mean that a product does not contain sugar. Added sugars are sugars added during the production of highly processed foods to enhance their flavor. Their increased intake is associated with adverse health effects (Gillespie et al., 2023).

In their study, Epner et al., (2022) link consumption of increased amounts of added sugars with a higher risk of cancer and death, especially breast cancer. In addition, the study shows a correlation between the added sugar intake and the incidence of colorectal cancer. This association is explained by the fact that increased consumption of sugar results in obesity, which is a risk factor for many cancers. Moreover, the study indicates their pro-inflammatory potential, their harmful effect on glucose/fructose metabolic pathways, and their influence on the immune system (Epner et al., 2022). The most relevant aspects related to the involvement of carbohydrates in cancer processes are presented in (Table 1).

Table 1 Summary of carbohydrate-related mechanisms in cancer metabolism and their impact on cancer risk as a dietary component

Role of carbohydrates in cancer biology	
Key cancer metabolic mechanisms	**Nutritional aspects**
Preferential anaerobic glucose metabolism - the Warburg effect (Liberti and Locasale, 2016; Pascale et al., 2020)	Protective effect of adequate dietary fiber intake against cancer (Hu et al., 2023)
Increased glucose metabolism and up-regulation of glucose transporter GLUT1 (Calvo et al., 2010)	High sugar diet as a risk factor for cancer (Huang et al., 2023)
Modulations of glycosylation of proteins and lipids (Thomas et al., 2021)	Increased consumption of added sugars as a risk factor for cancer (Epner et al., 2022)
Hyperinsulinemia, hyperglycemia, and overexpression of the insulin receptor (IR) (Shahid et al., 2021; Talib et al., 2021)	

Lipids

Lipids are a diverse group of water-insoluble organic compounds (Cockcroft, 2021). They are substrates for energy production but also have a separating function by forming cell membranes and dividing the water spaces inside the cell. As signaling molecules, they regulate cellular processes and provide substrates for synthesizing steroid hormones (Petrenko et al., 2023). The group of lipids includes cholesterol, fatty acids, triacylglycerols, glycerophospholipids, glycosphingolipids, and sphingomyelins (Cockcroft, 2021). Fats are also divided by the presence of unsaturated bonds in the molecule. Saturated fats have only single bonds in their carbon chain (Roche, 1999). Most saturated fat intake comes from cheese, beef, milk, cookies and cakes, margarine, and butter (Huth et al., 2013).

On the other hand, many plants (like avocados) and plant oils (olive oil, sesame oil, sunflower oil) are rich in monounsaturated fats. Polyunsaturated fats can be classified as omega-3 or omega-6 based on the location of the first double bond from the methyl end in their carbon chain. Sources of polyunsaturated fatty acids include fish, seed, and plant oils (Saini and Keum, 2018). One of the most significant cancer-related metabolic changes is an increased demand for fatty acids and cholesterols. These substrates are required for the cell membranes of proliferating cells but also the synthesis of signaling molecules or the production of energy storage material (Broadfield et al., 2021). As healthy cells mainly obtain lipids from the bloodstream, cancer cells preferentially synthesize lipids de novo (Mashima et al., 2009).

It has been shown in some cancer cell lines that fatty acids synthesized de novo account for 93% of the total cellular lipid levels (Ookhtens et al., 1984). Increased levels of the enzyme responsible for this process - fatty acid synthase (FASN) are typical for invasive and aggressive prostate cancers compared to benign lesions (Pflug et al., 2003; Swinnen et al., 2002). High levels of FASN expression were also associated with poorer prognosis in pancreatic ductal adenocarcinoma patients (Bian et al., 2015). Cancer cells modify the synthesis of various enzymes responsible for lipid metabolism, which modulate their lipid composition through the activation, desaturation, and elongation of fatty acids (Butler et al., 2020).

This reprogramming of lipid metabolic pathways has been linked to processes involving various factors, such as transcription factors, signaling pathways, and noncoding RNA (Fu et al., 2020). Eicosanoids represent a diverse family of lipid signaling molecules. The main substrate for synthesizing eicosanoids is arachidic acid, which belongs to the polyunsaturated fatty acids (Khanapure et al., 2007). A number of the compounds in this group affect the proliferation, migration, and invasion of cancer cells (Wang and DuBois, 2010). For example, prostaglandin E2, a member of the prostaglandin subfamily, increases tumor growth and tumor invasiveness, promotes angiogenesis, and modulates the tumor microenvironment (Finetti et al., 2020). Leukotriene B4, from the leukotrienes subfamily, appears to influence tumor progression mainly through immune modulation (Jala et al., 2017).

On the other hand, prostaglandin D2 in studies on mouse models with transplanted lung cancer had tumor suppressor effects, and deficiency of its receptor enhanced angiogenesis and tumor growth (Murata et al., 2011). Fats are the most energy-rich source of calories, providing 37kJ/g (9kcal/g) (Karam et al., 2020). As a component of the diet, lipids are also responsible for the absorption and transport of carotenoids and fat-soluble vitamins (Ofoedu et al., 2021). They play a role in the proper functioning of the cardiovascular and nervous systems (Custers et al., 2022). Moreover, lipids in dietary intake also influence the processes of cancer formation. Polyunsaturated omega-3 and omega-6 acids must be delivered to the organism with food because the body cannot adequately synthesize them.

Short-chain alpha-linolenic acid (ALA) is notably present in chia, perilla, and flax seeds. Humans can enzymatically elongate it to longer-chain omega-3 acids - eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA). However, this process occurs inefficiently and these acids must be supplied with food like wild (marine) fish (salmon, sardine, cod) (Huth et al., 2013). Omega-3 fatty acids have been assumed to pose protective effects against cancer development. They are credited with anti-inflammatory properties, stabilizing impact on the insulin receptor, promoting analgesia through beta-endorphins, and controlling hemostasis (Freitas and Campos, 2019). The group of Lee et al., (2020) analyzed 57 meta-analyses comparing the intake of fish or omega-3 fatty acids with cancer risk. Of those, only 15 presented statistically significant results.

Admittedly, only weak evidence was obtained for an association of omega-3 fatty acid intake with breast cancer, hepatocellular carcinoma, prostate cancer, or brain tumor (Lee et al., 2020). Wei et al., (2022) despite the lack of a proven anticancer impact of omega-3 fatty acids, after analyzing the results of 49 clinical trials, indicate a positive effect of these compounds on disease-related symptoms such as cachexia, inflammation, neuropathy, postoperative complications, and quality of life. The high-fat diet is based on consuming high amounts of saturated fatty acids and low amounts of dietary fiber, vitamins, and minerals. Such a diet has been proven to affect

the intestinal microbiota and subsequently promote the onset of gastrointestinal cancers, including esophageal, gastric, liver, pancreatic, and colorectal cancer (Tong et al., 2021).

On the other hand, a ketogenic diet, which is consuming only foods containing fat and protein but keeping carbohydrate intake to a minimum, in preclinical studies appears to have a positive effect in combination with cancer therapy (Batch et al., 2020). A ketogenic diet has a positive influence on radiotherapy effectiveness in treating tumors and has a protective effect against radiation on healthy tissues (Klement, 2018). In mouse models of neuroblastoma, it also affected chemotherapy. The combination of metronomic cyclophosphamide with a ketogenic diet resulted in tumor regression (Morscher et al., 2016). Finally, it sensitized mouse pancreatic tumors to the cytotoxicity of triple chemotherapy (gemcitabine, nab-paclitaxel, cisplatin).

Combinations of the ketogenic diet with chemotherapy slowed tumor growth and prolonged survival compared to the treatment with chemotherapy alone (Yang et al., 2022). These positive effects of the ketogenic diet are explained by the reduction of glucose levels in the blood, conversion of the metabolism to obtaining energy from keto acids, modulation of amino acid metabolism, signaling molecules, and expression of specific genes (Weber et al., 2020). Although data from preclinical studies indicate an anticancer effect of the ketogenic diet, clinical observations are inconclusive. Urzì and colleagues summarized seven clinical trials exploring the impact of the ketogenic diet on patients diagnosed with breast cancer.

As of the time of writing this review, none of these trials has provided precise results indicating an advantage of the ketogenic diet (Urzì et al., 2023). Lane et al., (2021) despite the alignment of more than 40 clinical trials that reported promising results, indicate methodological limitations such as the small size of the heterogeneous study group, lack of randomization, poor dietary protocols, problems with assessing dietary adherence, short study duration, and insufficiently defined and measured outcomes. The ketogenic diet is associated with effects that are particularly undesirable for cancer patients, including weight loss, reduction of skeletal muscle protein, decreased dietary fiber intake, or undernutrition of a nervous system that cannot use fatty acids as an energy source (Tamraz et al., 2023).

Most importantly, a systematic review and a prospective evaluation in EPIC-Heidelberg Cohort using an iso-caloric substitution model found that increasing the proportion of animal protein at the expense of carbohydrates and fats in dietary energy intake increased cardiovascular mortality risks (Bajracharya et al., 2023). Considering the presented data, it should be emphasized that the ketogenic diet as an additional intervention during cancer therapy does not have well-established recommendations and requires further research. Not only the composition of the eaten food is important but also how it is prepared.

Repeated heating of vegetable oils used for frying at high temperatures leads to the formation of various compounds, including polycyclic aromatic hydrocarbons (PAHs). These substances are known to be carcinogenic compounds. They can bind to DNA, leading to mutations that can be the first step in cancer transformation. They are associated with the pathogenesis of lung, breast, colorectal, and prostate cancer (Ganesan et al., 2019). The most relevant aspects related to the involvement of lipids in cancer processes are presented in (Table 2).

Table 2 Summary of lipids-related mechanisms in cancer metabolism and their impact on cancer risk as a dietary component

Role of lipids in cancer biology	
Key cancer metabolic mechanisms	**Nutritional aspects**
Preferential lipids de novo synthesis and fatty acid synthase upregulation (Bian et al., 2015; Swinnen et al., 2002)	Cancer protective effect of omega-3 acids and their positive impact on disease-related symptoms (Lee et al., 2020; Wei et al., 2022)
Modulation of cellular lipidic composition through activation, desaturation, and elongation of fatty acids (Butler et al., 2020)	High-fat diet as a risk factor for cancer (Tong et al., 2021)
Eicosanoids as signaling molecules and their impact on tumor growth (Wang and DuBois, 2010)	Inconclusive effect of ketogenic diet on patients undergoing cancer therapies (Weber et al., 2020)
	High-temperature oil heating and the formation of carcinogenic compounds (Ganesan et al., 2019)

Proteins

Proteins are built from chains of linked amino acids. The sequence of amino acids in the chain is strictly defined and determines the final structure of the protein and its specific abilities (Alberts et al., 2002). Proteins are a diverse group in terms of their role in cell physiology. They function as building materials, biochemical catalysts, hormones, enzymes, or cell death initiators (LaPelusa and Kaushik, 2024). In the human body, protein synthesis occurs in an exact and specific manner and is divided into stages. The particular sequence of ribonucleic bases written in DNA defines` the final sequence of amino acids in the protein. The specified fragment of the DNA chain, with the help of appropriate enzymes, is transcribed into an mRNA chain, a process we call transcription.

Subsequently, the transcribed genetic material is decoded with the involvement of ribosomes. On its basis, the corresponding polypeptide chain is synthesized, consisting of amino acids arranged in the order according to the DNA transcript. This process is called translation (Alberts et al., 2002). The resulting chain then undergoes post-translational modifications, involving the necessary folding of the protein and the attachment of various additional compounds to its primary structure. All these stages of protein synthesis are essential for the protein to reach its final form and perform its specific function (Rattan et al., 1992). Moreover, cells can regulate protein synthesis at each stage of its formation (Merrick, 1992).

A tumor cell must reprogram its metabolism, which includes alternation of protein synthesis to undergo continuous divisions, adapt to the surrounding environment, and avoid the immune system response. Increased translation processes can even be seen by observing the cells of some tumors under a microscope. The presence of an enlarged nucleus, where the ribosomes necessary for the translation are produced, can signify an increase in protein biosynthesis and cell metabolism and even be associated with an increase in tumor malignancy (Busch et al., 1963). During oncogenesis, specific oncogenic pathways are activated, including c-Myc, RAS, and PI3K-mTOR. This affects translation and modulates tumor cell metabolism (Biffo et al., 2018).

Enzymatic post-translational modifications of proteins involve the covalent attachment of various molecules to the protein, such as phosphorylation, acetylation, glycosylation, and ubiquitination. They have also been proven to affect oncogenesis, metastasis, and the effectiveness of various anticancer therapies (Pan and Chen, 2022). All the transformations occurring at the level of protein metabolism are enormously complicated and not fully understood. They are well beyond the subject of this review, so they will not be discussed in detail. Foods containing high amounts of protein include beef, black beans, egg, milk, peanuts, and soy products (Hoffman and Falvo, 2004). After consuming protein products, humans digest them in the gastrointestinal tract into single amino acids, and only in this form are they absorbed (Loveday, 2023).

Typically, twenty basic amino acids are listed from which human proteins are composed. The organism can synthesize some of them from others circulating in the body. However, nine amino acids must be supplied to the body with diet, as humans cannot synthesize them independently (Lopez and Mohiuddin, 2024). Cancer cells primarily use amino acids as a building material or an energy source in the Krebs cycle. Additionally, they regulate reactive oxygen species (ROS) homeostasis and modulate epigenetic regulation through DNA methylation and histone acetylation (Lieu et al., 2020). Therefore, there have been efforts to find correlations between the levels of various amino acids and their effects on tumorigenesis.

Analysis of the serum concentrations of 13-21 amino acids in the blood of patients detected a relationship between high concentrations of histidine and probably glutamine inversely correlated with the risk of colorectal cancer. This suggests that low concentrations of these amino acids may have a protective effect against the development of this cancer (Rothwell et al., 2023). Another study indicates that high concentrations of alanine in the blood are inversely correlated with the risk of developing colorectal cancer. Moreover, high levels of alanine in patients with this type of cancer were associated with longer survival rates. The authors point to a possible protective effect of alanine and its role as a predictive marker of a more favorable diagnosis (Wang et al., 2023).

On the other hand, high aspartate concentrations correlated positively with the risk of prostate and breast cancer (Lin et al., 2022). Methionine is an essential sulfur-containing amino acid involved in numerous metabolic reactions called the methionine cycle. Cancer cells alter methionine metabolism similarly to the Warburg effect described earlier. As a result of methionine substitution with homocysteine, the vast majority of cancer cell lines are unable to proliferate, unlike non-cancer cells. This dependence of cancer cells on exogenous methionine is called the methionine stress sensitivity or the Hoffman effect (Kaiser, 2020). In animal models, a correlation has been suggested between the amount of methionine taken in with food and cancer risk.

In studies on rats with Walker-256 carcinosarcoma-fed methionine-deficient foods, reductions in tumor growth were observed (Sugimura et al., 1959). In Yoshida sarcoma mice fed such a diet, cell cycle blockade and regression of tumor growth were reported (Guo et al., 1993). Moreover, a methionine-free diet in mice with xenografted human solid tumors like colon cancer, small cell lung

cancer, and glioma sensitized cancer cells to the appropriate chemotherapy, resulting in prolonged survival and inhibition of tumor growth (Poirson-Bichat et al., 2000). In a clinical trial, patients with gastric cancer received methionine-depleting total parental nutrition in combination with 5-fluorouracil for seven days before resection surgery.

In histopathological evaluation of the resected specimens, marked degeneration of tumor cells was observed compared to the control group (Goseki et al., 1995). On the other hand, methionine together with folate, choline, betaine, and other B vitamins participate in one-carb metabolism, affecting the synthesis of substrates required for DNA methylation, and subsequently regulating gene expression (Anderson et al., 2012). In addition, it has been demonstrated that a diet low in folate and methionine, especially when combined with alcohol consumption, has been associated with an increased risk of colorectal cancer (Giovannucci et al., 1995). The data presented here indicate the danger posed by a methionine-free diet, despite its anticancer properties, but with weak evidence.

Not only is the individual amino acid intake relevant in the context of cancers, but also the source of consumed protein. A systematic review by the Alzahrani et al., (2022) group analyzed papers examining correlations between the amount of protein in dairy products and prostate cancer risk. Among men consuming more than 30g of dairy protein per day, a 20g per day increase in dairy protein intake was associated with a 10% increase in the incidence of prostate cancer. Interestingly, such a relationship was not observed in the case of animal or vegetable protein intake (Alzahrani et al., 2022). A meta-analysis of thirty-three cohort studies suggested that consumption of total dairy products, milk, cheese, and butter, was associated with an increased risk of the same type of cancer (Zhao et al., 2023).

However, a possible explanation for these findings is not the amount of protein but the amount of calcium intake. The high calcium content of dairy products in many epidemiological studies has shown a positive association with prostate cancer risk (Pernar et al., 2018). In the case of colorectal cancer, it was demonstrated that substituting the source of protein intake from red meat to plant-based protein was associated with a reduced incidence risk (Liao et al., 2019). On the other hand, an analysis of eight systematic reviews showed that higher total protein intake was not associated with an increased risk of colorectal and breast cancer. A similar correlation was demonstrated for prostate, ovarian, and pancreatic cancers, but the quality of evidence was insufficient (Kühn et al., 2024).

These data suggest that while the origin of protein may be relevant to the risk of various cancers, its amount in the diet is not associated with such a dependency. It should be emphasized that patients with cancer often suffer from excessive weight loss and cachexia, which significantly affects their quality of life, the effectiveness of treatment, and chances of survival. Therefore, especially among these patients, it is crucial to maintain an adequate caloric supply and proper protein levels in the diet (Muscaritoli et al., 2021). The most relevant aspects related to the involvement of proteins in cancer processes are presented in (Table 3).

Table 3 Summary of protein-related mechanisms in cancer metabolism and their impact on cancer risk as a dietary component

Role of proteins in cancer biology	
Key cancer metabolic mechanisms	**Nutritional aspects**
Alterations in the expression of enzyme proteins and activation of oncogenic pathways (Biffo et al., 2018)	Protective effect of alanine, histidine, and glutamine against colorectal cancer (Rothwell et al., 2023; Wang et al., 2023)
Alternated post-translational modifications of proteins during oncogenesis (Pan and Chen, 2022)	High aspartate serum concentrations as a risk factor for prostate and breast cancer (Lin et al., 2022)
	Positive effects of methionine-free diet on tumor growth inhibition and sensitivity to chemotherapy in animal models (Guo et al., 1993; Poirson-Bichat et al., 2000)
	Impact of changing the source of protein intake from red meat to plant-based protein on reduced cancer risks (Liao et al., 2019)

4. DISCUSSION

Metabolic changes in cancer have become an intensive area of scientific research because of their possible potential as a target for cancer therapy. Each cancer cell adjusts its metabolism to adapt to uncontrollable divisions, survival in the tumor microenvironment, and the host immune response evasion. Cancer cells adapt to the increased energy demand by intensifying glucose uptake and converting their metabolism to anaerobic glycolysis. Modified posttranslational modifications of surface proteins on the cell membrane, including alternative forms of glycosylation, presumably contribute to the acquisition of the ability of cells to dissociate from the intercellular matrix, resulting in the ability to metastasize. Undergoing continuous division requires lipids needed for cell membranes.

Cells upregulate the enzymes that synthesize fatty acids, thus becoming independent of their external supply. Finally, an essential step in carcinogenesis is mutations of oncogenes, the expression of which results in malfunctioning proteins. These abnormal proteins promote cell growth and division. It should be highlighted that each cancer is different and has its characteristic metabolic adaptations. Moreover, during cancer cell divisions, some of them mutate. This process may lead to their progression and give them new features like resistance to cancer therapy. The metabolic pathways of glucose, glutamine, and fatty acids have become targets for research. Studies use substrate analogs of enzymes that block them and prevent a particular reaction from taking place.

For example, 2-deoxyglucose binds to the enzyme hexokinase, blocks its action, and impairs the process of glycolysis in the cell, which leads to apoptosis of cancer cells mediated by reactive oxygen species (ROS). Cancer metabolism is characterized by different responses to metabolic stress compared to normal cells. As a result, therapies targeting cancer-specific metabolic changes can inhibit the progression of tumor growth while causing less harm to healthy cells. This offers the possibility of developing more effective therapies by combining the effects of several drugs that block tumor metabolic pathways at various levels (Park et al., 2020). Dietary components may influence the process of cancer development.

In our review, we have given examples of nutrients and compounds that have divergent impacts on oncogenesis. However, instead of focusing on individual nutrients, it is essential to look at eating habits as a whole. A dietary pattern that has proven health benefits is the Mediterranean diet. It involves an increased intake of plant-based foods, especially whole grains, vegetables, fruits, nuts and pulses. Fish and seafood are also consumed regularly, and eggs, red meat, and high-fat dairy products are limited. Fat intake is mainly in the form of olive oil. A meta-analysis by the group of Schwingshackl et al., (2017) noted an inverse relationship between adherence to the Mediterranean diet and cancer mortality and the risk of developing colon, breast, stomach, liver, head and neck, gallbladder, and biliary tract cancers.

Most findings on cancer mechanisms are derived from in vitro studies or studies on animal models and involve only selected cancer lines. Confirmation of these relationships in the human body requires appropriate clinical studies. Some presented clinical trials may present low-quality evidence and have insufficient statistical power. The conclusions obtained require confirmation in further studies on larger randomized experimental groups. The authors would like to emphasize that the purpose of this review is to discuss cancer mechanisms regarding different groups of organic compounds and describe their presumed role in carcinogenesis. The review should not be interpreted as any recommendations for dietary interventions.

5. CONCLUSIONS

In summary, macronutrients influence cancer processes at every stage of oncogenesis. Ongoing researches seek to better prevent cancer but also find new mechanisms and therapeutic targets and increase the survival of patients with cancer. However, cancer metabolism requires further study and a broader exploration to be entirely understandable.

Ethical approval

Not applicable.

Authors' Contribution

Gustaw Laskowski: Conceptualization, writing- rough preparation, methodology, investigation, project administration
Piotr Węgrzyn: Formal analysis, supervision
Konstancja Węgrzyn: Visualization, data curation
Agnieszka Góra: Conceptualization, investigation

Marcin Wasilewski: Methodology, writing- rough preparation
Maciek Nowicki: Conceptualization, methodology, data curation
Julia Skwara: Methodology, writing- rough preparation
Dawid Barański: Resources, writing- rough preparation
Natalia Dąbrowska: Conceptualization, investigation
Anna Salińska: Writing - Review and editing, supervision
All authors have read and agreed to the published version of the manuscript.

Informed consent
Not applicable.

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Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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