Perspective

Obesity and Cancer: Potential Mediation by Dysregulated Dietary Phosphate

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Abstract: Next to smoking, obesity is the second leading preventable risk factor for cancer, but increasing rates of obesity and overweight are estimated to overtake smoking as the leading preventable cancer risk factor. Few research studies have investigated the dysregulated endocrine metabolism of dietary phosphate as a potential mediating factor in the association of obesity with cancer. Phosphate toxicity, the accumulation of excess phosphate in the body from dysregulated phosphate metabolism, is associated with tumorigenesis. High levels of hormones that regulate phosphate metabolism, such as parathyroid hormone and fibroblast growth factor 23, are also associated with obesity, providing a potential link between obesity and phosphate toxicity. Increased dietary intake of inorganic phosphate is linked to excessive consumption of foods processed with phosphate additives, and consumption of ultra-processed foods is associated with an increase in the incidence of obesity. Sugar-sweetened beverages provide the single largest source of sugar and energy intake in the U.S. population, and colas containing phosphoric acid are associated with tumorigenesis, suggesting another potential connection between obesity and cancer. Furthermore, dietary phosphate is positively correlated with increases in obesity, central obesity, and metabolic syndrome. The present perspective article proposes that dysregulated dietary phosphate potentially mediates the association of obesity with cancer.

Keywords: obesity; cancer; tumorigenesis; dysregulated phosphate; phosphate toxicity; FGF23; parathyroid hormone; vitamin D; phosphoric acid; ultra-processed food

1. Introduction

The World Health Organization (WHO) defined obesity as "abnormal or excessive fat accumulation that may impair health," caused by "an energy imbalance between calories consumed and calories expended" [1]. Noting that "overweight and obesity, as well as their related noncommunicable diseases, are largely preventable," WHO recommended reducing obesity and overweight through supportive environments and communities that provide easier access to regular physical activity, with more affordable and greater availability of healthy food choices.

Next to smoking, obesity is the second leading preventable risk factor for cancer, but increasing rates of obesity and overweight are estimated to overtake smoking as the leading preventable cancer risk factor within the next two decades [2]. Yet, much of the population remains unaware of the association of obesity with cancer [3]. Evidence is sufficiently strong to link obesity with at least 13 sites of cancer: esophagus, stomach, colorectum, liver, gallbladder, pancreas, breast, uterus, ovary, kidney, meninges, thyroid, and white blood cells [4]. Paradoxically, a higher bodyweight has also been associated with reduced cancer risk—an obesity paradox that some researchers suggest may be related to selection bias from reliance on body mass index (BMI), which does not measure fat mass and fat-free mass [5].

Hypotheses of the pathophysiological mechanisms linking obesity and cancer commonly investigate hormonal and enzyme dysregulation of glucose and lipid metabolism [6]. For example, obesity in humans is associated with higher levels of the hepatic protein kinase

Cβ (PKCβ), which negatively regulates glycogenesis [7]. Dysregulated PKCβ is common in many cancers and may be implicated in cancer development. Additionally, dysregulated inositol synthesis in *Drosophila melanogaster* fed a high-sucrose diet is a potential model for similar inositol abnormalities in human cancer and obesity [8]. However, few research studies have investigated dysregulated endocrine metabolism of dietary phosphate as a potential mediating factor in the association of obesity with cancer.

The present perspective article reviews epidemiologic and pathophysiologic relationships between obesity, unhealthy food choices associated with dysregulated dietary phosphate, and tumorigenesis in obesity-related cancers. Articles from the research literature were selected and analyzed in this perspective paper using a grounded theory method [9]. Keyword searches were conducted in Google, Google Scholar, PubMed, Scopus, and other online sources. Comparative analyses of the literature findings were synthesized into themes and formed into causative and associative relationships linking obesity, dysregulated phosphate metabolism, and cancer. All the findings and proposals in the present perspective article are grounded in evidence, and offer the present author's insights and point of view.

2. Phosphate Metabolism

2.1. Phosphate Functions

The dietary mineral phosphorus, often found in chemical combination with oxygen as phosphate (PO_4), is an essential micronutrient with a dietary reference intake (DRI) of 700 mg/day for adults [10]. Phosphate performs a wide variety of functions in the human body [11], as shown in Figure 1. Bones and teeth contain 85% of total body phosphate. Inorganic phosphate (Pi) forms hydroxyapatite with calcium, which mineralizes the extracellular matrix of bone. The lipid bilayers of cell membranes contain phosphate, and phosphate is a component in nucleic acids, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA). Energy is derived from the metabolism of adenosine triphosphate (ATP) and adenosine diphosphate (ADP). Phosphate also acts as a urinary buffer, and many enzymatic reactions involve inorganic phosphate.
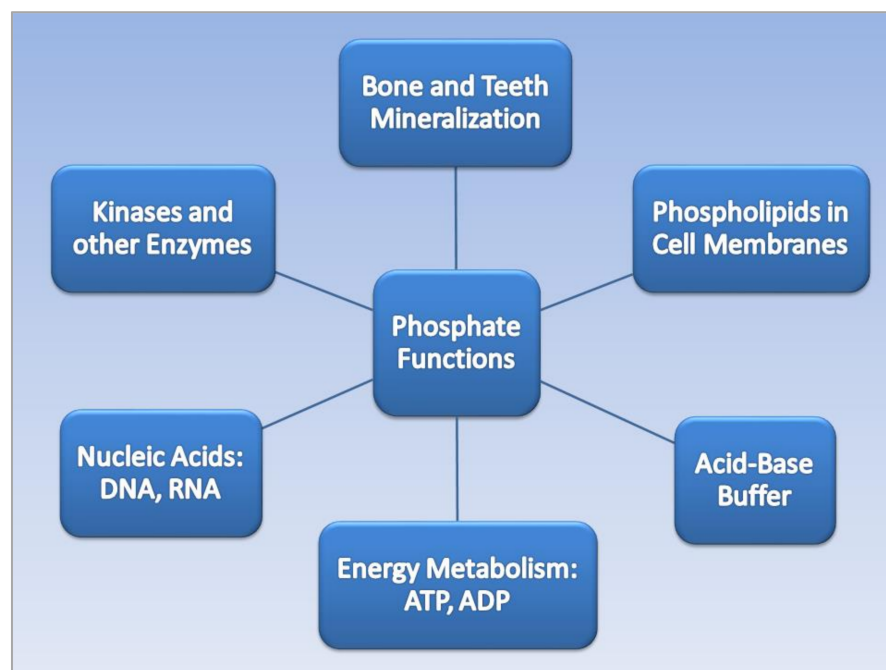

Figure 1. Phosphate functions in the human body.

2.2. Phosphate Regulation and Dysregulation

Serum Pi is regulated by a sensitive network of endocrine hormones that form a bone–kidney–parathyroid–intestine axis, as shown in Table 1. Ref. [12]. Pi absorption in the intestines occurs mainly through type II sodium-dependent phosphate cotransporters, and intestinal absorption is regulated by bioactive vitamin D3 released by the kidneys, $1,25(OH)_2D_3$, or calcitriol. The kidneys regulate serum Pi through reabsorption largely in the renal proximal tubule. Fibroblast growth factor 23 (FGF23) released from osteocytes in the bones, together with parathyroid hormone (PTH) from the parathyroid glands, reduce high serum Pi levels by inhibiting kidney reabsorption of Pi and increasing Pi urinary excretion [13]. PTH also increases the resorption of calcium from bone to maintain serum calcium levels. Excess calcium phosphate formed in the blood serum from dysregulated phosphate metabolism can lead to ectopic calcification deposited throughout the soft tissue [14].

Table 1. Endocrine Regulation of Serum Pi through the Bone–Kidney–Parathyroid–Intestine Axis.

Bone	Kidney	Parathyroid	Intestine
FGF23 inhibits serum Pi reabsorption in kidneys.	Regulates serum Pi reabsorption and Pi urinary excretion.	PTH increases serum calcium through bone resorption.	Pi absorption from dietary sources.
Increases Pi urinary excretion.	Biosynthesis of calcitriol from vitamin D_3 increases Pi intestinal absorption.	Increases Pi urinary excretion with FGF23.	Type II sodium-dependent phosphate cotransporters.

3. Phosphate Toxicity and Tumorigenesis

Phosphate toxicity, the accumulation of excess phosphate in the body from dysregulated phosphate metabolism, is associated with tumorigenesis [15]. Excessive cell growth during tumor promotion and progression is stimulated by the uptake of excess phosphate into cellular ribosomal RNA, and suppressed uptake of phosphorus within nuclear RNA was shown to delay carcinogenesis in precancerous tissue [16]. High levels of phosphate within the tumor microenvironment have been found to stimulate cell signaling in tumorigenesis [17] and tumor neovascularization [18]. Moreover, high phosphate levels in patients with hyperphosphatemia are associated with chromosome instability and increased parathyroid cell proliferation—further investigations of a direct effect of phosphate on DNA damage are needed [19]. Additionally, high extracellular levels of Pi have been linked to cancer progression through metastasis [20].

Cancer cells absorb and sequester large amounts of inorganic phosphate from the tumor extracellular microenvironment through sodium-phosphate cotransporters, which were overexpressed in cancer cells of the breast, lung, ovaries, and thyroid gland [21,22]. Levels of inorganic phosphate were up to twice as high in lung and colon tumor cells compared to normal cells [23], and high dietary phosphate levels were found to increase skin cancer growth in an animal model [24]. As well, lung tumorigenesis was stimulated in mice fed high levels of dietary inorganic phosphate [17]. Cancer in humans was also associated with higher serum phosphate levels in adults, with the exception of reproductive cancers in females, which may be due to phosphate shifting into the reproductive tissue for rapid growth [25,26].

More recently, H^+-dependent Pi transporters in breast cancer cells were found to transport high concentrations of Pi at five-times the rate of sodium-phosphate cotransporters [27]. Patients with high levels of FGF23, which regulates Pi metabolism, had reduced overall survival compared to patients with low levels [28], and FGF23 levels were significantly higher in patients with urothelial carcinoma of the bladder and upper urinary tract compared to normal controls [29]. Additionally, compared to men with benign prostate hyperplasia, men with prostate cancer had higher levels of PTH, which also regulates Pi metabolism [30].

High serum PTH levels are associated with all-cause mortality in U.S. adults [31], and patients with primary hyperparathyroidism had significantly higher risks of diagnosis with cancers of the breast, skin, and kidney [32].

4. Phosphate Toxicity and Obesity

The same hormones that regulate phosphate metabolism are also associated with obesity, providing a transitive link between obesity and phosphate toxicity. For example, high serum FGF23 was associated with increased fat mass in a cohort of elderly white people with normal renal function [33]. Participants in the study who had the highest levels of FGF23 also had a significantly higher risk for overweight compared to individuals with the lowest FGF23 levels. A 10% increase in FGF23 in the cohort was associated with a 3% increase in body weight and BMI and a 2% increase in waist circumference (WC) and waist–hip ratio (WHR). Additionally, a 10% increase in FGF23 in males was associated with a 4% increase in total body fat mass and trunk fat mass.

Hyperparathyroidism is commonly found in high-grade obesity, and higher serum levels of PTH were found in 72% of bariatric patients with severe obesity who underwent laparoscopic sleeve gastrectomy (LSG) [34]. Patients' PTH levels dropped along with BMI following surgery, likely related to a lower caloric density and volume of food intake following LSG [35]. These findings imply that diet is an etiological factor in hyperparathyroidism related to obesity, which provides an additional transitive link between obesity and phosphate toxicity from excessive dietary phosphate intake. Higher concentrations of serum PTH were also positively associated with obesity in females with metabolic abnormalities, while levels of 25(OH)D3, which are converted to calcitriol to increase phosphate absorption in the intestines, were inversely associated with obesity in males with metabolic abnormalities [36].

Obesity is often associated with inadequate intake of micronutrients such as calcium, magnesium, copper, iron, and zinc, but a recent analysis of the US National and Health Nutrition Examination Survey (NHANES) 2007–2014 found that phosphorus dietary intake in adults, along with sodium, was positively associated with BMI [37]. Of relevance, type II sodium-phosphate cotransporters (Na/Pi-2b) and type III inorganic phosphate transporters (Pit-1 and Pit2) are found in the salivary glands, and obese and overweight children were found to have significantly higher saliva levels of phosphate than normal-weight children, despite having normal serum phosphate levels [38]. A plausible mechanism accounting for higher saliva phosphate in obese and overweight children could be related to increased salivary gland cotransport of phosphate from higher levels of ingested dietary phosphate—more investigations are needed in this area.

Hypophosphatemia has also been linked to high BMI, but rather than resulting from low dietary phosphate intake or phosphate losses in urine, low serum phosphate is most frequently caused by a transcellular shift of internal phosphate [39]. Because dietary carbohydrates require phosphorylation of glucose compounds during glycolysis, excessive intake of carbohydrates releases increased levels of insulin which may cause phosphate to shift from extracellular blood serum to liver and skeletal muscle cells during metabolism of a heavy load of sugars [40]. Moreover, abdominal obesity is a part of metabolic syndrome [41], and high serum levels of catecholamines in metabolic syndrome also increase metabolic glycolysis of sugars, which further contributes to a phosphate transcellular shift that lowers serum phosphate levels.

A paradoxical relationship also exists in the association of obesity with a lower risk of breast cancer in premenopausal women compared to postmenopausal women [42]. The mid-luteal phase of the menstrual cycle is when the uterus undergoes growth [43], and women self-reported consuming more animal-based foods during this phase [44]. Animal-based foods contain high levels of protein and phosphorus, which are needed to support the monthly growth of the uterus. The need for more phosphorus during the menstrual cycle could mitigate the risk of phosphate toxicity associated with heavy dietary

phosphate intake in obese premenopausal women, which would lower the risk of breast cancer compared to obese postmenopausal women.

Before closing this section on phosphate toxicity and obesity, it should be mentioned that low levels of vitamin D are consistently linked with obesity and with cancer, but researchers found that "the mediating role of vitamin D in the biological pathways linking obesity and cancer is low" [45]. On the other hand, high serum Pi can signal endocrine-controlled reductions in the renal biosynthesis of calcitriol (bioactive vitamin D), thus lowering dietary phosphate intestinal absorption. In other words, low vitamin D appears to be a consequence rather than a cause of dysregulated Pi metabolism in obesity and cancer.

5. Pi, Ultra-Processed Food, and Obesity

Increased dietary intake of inorganic phosphates is linked to excessive consumption of processed foods, but the actual amount of phosphate intake from processed foods is often unknown because food labels do not list the amount of inorganic phosphates in food additives [46]. Inorganic phosphate is effectively absorbed in the body, and people with a lower socioeconomic status (SES) consume the highest amount of processed and convenience foods with added phosphate [47]. Of relevance, obesity in high-income countries is more prevalent among people with a lower SES [48], inferring that a lower SES mediates the association of greater Pi intake with high consumption of processed foods by obese people.

Additionally, a recent prospective cohort study showed that consumption of ultra-processed foods was associated with a 79% increase in the incidence of obesity measured by BMI and a 30% increase in the incidence of abdominal obesity measured by WC [49]. Ultra-processed foods in the study included breads, snacks, desserts, frozen and ready-to-eat meals, beverages, breakfast cereals, spreads, and sauces. Over a median of 5.6 years, ultra-processed food consumption was associated with a 5% or higher risk of increasing BMI, WC, and body fat percentage in the cohort. Another study found that a 10% increase in ultra-processed food consumption was associated with a 10% and higher risk of breast cancer and overall cancer [50]. Animal products with greater phosphorus absorption also "contribute to the poor dietary habits linked with the rising rate of obesity in the USA", with every 0.5 mg/dL increase in serum Pi levels associated with a 2% increase in odds of obesity [51].

Participants in a randomized controlled trial ate as much food as they wanted after being assigned to either an unprocessed diet or an ultra-processed diet, served in meals with equivalent amounts of nutrients and calories [52]. Over two weeks, the unprocessed diet caused participants to eat less food, fewer calories, and lose a mean weight of 0.9 kg compared to the ultra-processed diet which caused participants to eat more food, additional calories, and gain a mean weight of 0.9 kg. Additional calories consumed in ultra-processed foods were from carbohydrates and fats. Results reversed when the participants switched diets. More studies are needed to measure the dietary intake of phosphorus from ultra-processed diets compared to unprocessed diets.

6. Soft Drinks, Phosphoric Acid, and Obesity

Sugar-sweetened beverages provide the single largest source of sugar and energy intake in the U.S. population [53] and also provide the largest source of sugar intake in the Mexican population [54]. Obesity and weight gain associated with greater consumption of sugar-sweetened beverages was found in systematic reviews of epidemiological and experimental evidence in 2006 [55], in a majority of reviewed studies of children and adolescents in 2015 [56], and in studies of adults and children in 2017 [57]. Another systematic review and meta-analysis found that obesity was associated with artificially sweetened as well as sugar-sweetened beverages [58].

In addition to an increased risk of obesity, a recent meta-analysis of prospective cohort studies found that increased consumption of sugar-sweetened and artificially sweetened beverages was associated with increased all-cause mortality [59]. A cohort study involving

participants from the European Prospective Investigation into Cancer and Nutrition (EPIC) found an association between a high risk of death from all causes and a high consumption of total, artificially sweetened, and sugar-sweetened beverages [60].

Phosphoric Acid

Reports in clinical and experimental literature from 1970 to 1997 linked mineral metabolism disorders and neoplasms with soft drinks such as colas that contain phosphoric acid [61]. Consumption of cola soft drinks negatively affected biomarkers of bone, liver, and kidney function in adult male rats [62]. A more recent study found that adult male rats who consumed Pepsi Cola for three months had lower serum levels of vitamin D and calcium but higher levels of phosphorus along with histopathological changes in the liver and kidney tissue compared to a control group [63].

Consumption of phosphoric-acid-containing soft drinks was associated with hypocalcemia in children [64,65] and with elevated serum PTH, hypocalcemia, and hyperphosphaturia in postmenopausal women [66]. Hypocalcemia occurs when phosphate ions from phosphoric acid consumed in cola react with serum calcium ions and precipitate into calcium hydrogen phosphate—followed by a release of PTH that resorbs calcium from bone to restore serum calcium levels [67]. Low bone mineral density in older women was also associated with cola consumption but not with other carbonated beverages, which the researchers attributed to mineral imbalances from the phosphoric acid in cola [68]. High intake of sugar-sweetened beverages containing phosphoric acid was inversely associated with bone health in a recent systematic review and meta-analysis [69], and cola intake was inversely associated with bone mineral density in male adolescents and young adults from the Korea National Health and Nutrition Examination Survey, 2008–2011 [70].

7. Soft Drinks and Cancer

Lab results of long-term carcinogenicity bioassays of Coca-Cola consumed by 1999 rats showed an increase in bodyweight and increased incidence of malignant mammary tumors and pancreatic adenomas, with insignificant increases in pancreatic islet cell carcinomas [71]. Consumption of sugary drinks, including 100% fruit juices, was associated with overall cancer and breast cancer risk in a large prospective cohort study [72]. Researchers suggested that the association of cancer with sugary drinks might be partially explained by the relationship of consumption with overweight and obesity, which the researchers attempted to adjust based on BMI. Sugar-sweetened beverage consumption among postmenopausal women was also associated with an increased risk of type I endometrial cancer [73].

More recently, a higher risk of early-onset colorectal cancer among women was associated with higher sugar-sweetened beverage consumption in adolescence and adulthood [74]. A recent meta-analysis of observational studies also found that overall cancer risk and mortality was associated with sugary drink consumption, especially for risk of hepatocellular carcinoma, colorectal cancer, prostate cancer, and risk and mortality for breast cancer [75]. Furthermore, another meta-analysis of observational studies found that artificially sweetened soft drink consumption was associated with an increased risk of liver cancer [76]. Consumption of a combination of sugar-sweetened and artificially sweetened drinks and fruit juices was also associated with an increased risk of liver cancer in a European cohort [77].

In response to the global obesity crisis, artificially sweetened beverages have been proposed as an important part of a healthy diet—yet, evidence of their effectiveness to prevent weight gain and long-term studies of their health effects are lacking for artificially sweetened beverages, which also provide a low nutritional value and contain additive ingredients [78]. Of relevance, artificially sweetened colas contain as much added phosphoric acid as sugar-sweetened colas, and the promotion of artificially sweetened colas could potentially pose a risk of tumorigenesis and other adverse health effects associated with dysregulated phosphate metabolism and phosphate toxicity. Investigations of phosphoric acid and dysregulated dietary phosphate in obesity and cancer should be given

equal consideration to other dietary factors such as glucose and lipids contained in highly processed foods.

8. Phosphate Additives and Obesity

In addition to soft drinks with added phosphoric acid, processed cheese contributes the highest amount of phosphate additives in the American diet, according to an analysis of NHANES 2015–2016 [79]. Other processed foods contributing high amounts of phosphate include bakery products that utilize phosphate for leavening—pies and cakes, rolls and buns, cookies and brownies, doughnuts, sweet rolls, pastries, and tortillas. The foods that contribute the most total phosphate from a combination of natural and additive ingredients are cheese, pizza, whole chicken pieces, reduced-fat milk, eggs and omelets, yeast breads, and cold cuts and cured meats.

An analysis of a biracial cohort, Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS), found that cheese and yogurt consumption were associated with an increased risk of central obesity [80]. Increased consumption of cheese and phosphorus intake were also positively correlated with increases in obesity (BMI), central obesity (WC), and metabolic syndrome in a cross-sectional study of participants from NHANES 1999–2004 [81]. Furthermore, a dietary pattern with a low calcium: phosphorus ratio (low calcium and high phosphorus) was also associated with increased obesity measured by Waist to Height Ratio (WHtR) in a Brazilian population [82]. A Japanese study found that patients with schizophrenia, "known to be prone to be overweight," consumed more phosphorus than the general public, and phosphorus consumption was highest in patients with higher BMIs [83]. The researchers suggested high phosphorus intake could be attributed to patients who "often used fast food products."

A study using a mouse model demonstrated that high amounts of dietary inorganic phosphate altered cell signaling and increased tumorigenesis of the lungs [17]. Lead investigator Myung-Haing Chou commented on the study:

> "In the 1990s, phosphorus-containing food additives contributed an estimated 470 mg per day to the average daily adult diet," Chou said. "However, phosphates are currently being added much more frequently to a large number of processed foods, including meats, cheeses, beverages, and bakery products. As a result, depending on individual food choices, phosphorus intake could be increased by as much as 1000 mg per day" [84].

If excessive consumption of ultra-processed food is an epidemiological determinant of obesity and cancer, then modification of ultra-processed food intake and a return to dietary patterns emphasizing whole, natural, unprocessed foods, is a viable strategy to prevent these diseases. Nutritional epidemiologist Marian L. Neuhouser recently wrote:

> "A shift towards healthy dietary patterns has the potential to curtail the current unsustainable high level of obesity, cardiovascular disease, diabetes mellitus and cancer in the United States and around the globe" [85].

9. Summary and Future Directions

The biological pathways linking obesity and cancer proposed in the present paper are summarized in Figure 2—a directed acyclic graph (DAG) [86]. The dashed line in the figure represents an associative relationship between obesity and tumorigenesis in cancer involving suspected factors other than phosphate. This associative relationship is potentially mediated by solid lines representing a pathway of causative links between obesity and dysregulated dietary phosphate and between dysregulated dietary phosphate and tumorigenesis. Mediation by these proposed causative relationships provides the basis to generate testable hypotheses for further investigations of obesity and cancer.
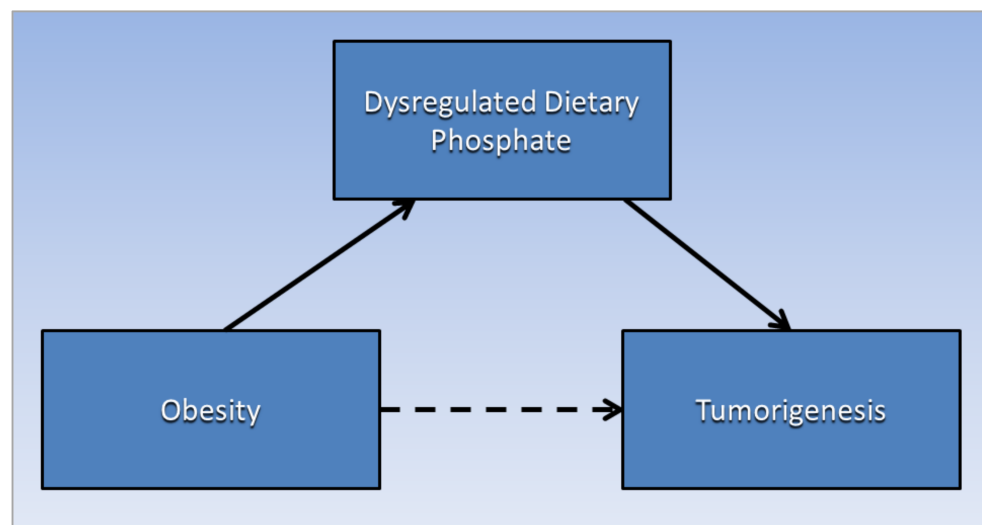
Figure 2. Obesity increases levels of dysregulated dietary phosphate, which mediates the association between obesity and tumorigenesis.

Additionally, conditions comorbid with obesity could contribute to renal damage, thereby increasing the risk of dysregulated phosphate, phosphate toxicity, and associated tumorigenesis discussed in the present paper. Comorbid conditions such as atherogenic dyslipidemia, hypertension, insulin resistance, and type 2 diabetes cause renal damage in obesity through oxidative stress, inflammation, upregulation of the renin–angiotensin–aldosterone system, increased activity of the sympathetic nervous system, and endothelial dysfunction [87]. Future research should investigate the biological pathways between obesity-related cancers and comorbid conditions involving impaired kidney function and dysregulation of phosphate metabolism.

Finally, writing in the *Lancet* in 1996, Schipper et al. [88] proposed a new regulatory model for cancer research. The researchers suggested that dysregulated metabolic pathways linked to the clinical course of cancer are reversible. Supporting evidence provided by the researchers at the time included cancer cell genetic differentiation in treatment for leukemia and recovery from gastric lymphoma related to the eradication of *Helicobacter pylori* infection. More recently, supporting evidence linking dysregulated phosphate metabolism and cancer appears highly concordant and coherent with the regulatory model. The model can be used to guide future cancer research to test whether modification or reversal of dysregulated phosphate metabolism through dietary interventions can alter the clinical course of cancer. Restricted-phosphate diets are currently used to modify the progression of chronic kidney disease [89], and similar diets should be tested for use in patients with obesity-related cancers.

10. Conclusions

In conclusion, the evidence presented in this paper supports an endocrine pathway in which dysregulated dietary phosphate potentially mediates the association of obesity with cancer. Excessive consumption of ultra-processed foods and other foods high in phosphate in obesity increase the intake of inorganic phosphate, phosphoric acid, and other phosphate additives, leading to dysregulated dietary phosphate. In turn, dysregulated dietary phosphate and phosphate toxicity are associated with tumorigenesis. Further studies should investigate the involvement of dysregulated dietary phosphate and impaired kidney function in obesity-related cancers.

Conflicts of Interest: The author declares no conflict of interest.

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