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Health Effects of a Vegan Diet and Pediatric Cancer Prevention

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Abstract

Veganism is a diet which excludes consumption of all animal products. With proper planning and vitamin supplementation to ensure adequate intake of protein, fat, calcium, zinc, iron, and vitamins D and B12, a vegan diet is widely accepted as suitable for growing and developing children. The decreased levels of dairy, red and processed meats, fat, and protein, and increased levels of fruits and vegetables characteristic of a vegan diet have been shown to reduce risk of mortality and a number of diseases including adult and childhood cancer. Childhood cancer is the second leading cause of childhood death in Western society. Understanding the effects of a vegan diet on childhood cancer prevention is thus an important and prevalent issue.

Health Effects of a Vegan Diet and Pediatric Cancer Prevention

Veganism is a strict subset of vegetarianism characterized by avoidance of all animal products, including, but not limited to, dairy, eggs, meat, and fish. In comparison, a lacto-ovo vegetarian (LOV) diet includes dairy and eggs, and a pesco-vegetarian (pescatarian) diet includes dairy, eggs, and fish (Tonstad, Nathan, Oda, & Fraser, 2013). The prevalence of Americans claiming to follow a vegan diet has increased 600% since 2014, with 6% of Americans claiming veganism in 2017 (Food Revolution Network, 2018). In 2018 veganism was estimated to be the top consumer trend of the year (Food Revolution Network, 2018). Moreover, a 2010 poll of over 1,200 children estimated that about 2% of American children follow a vegan diet (Pawlak, 2017). Due to its increasing prevalence in American culture, understanding the impacts of a vegan diet on childhood nutrition is vital.

A Vegan Diet and Nutrition

According to the American Dietetic Association (ADA), a well-organized vegan diet is nutritionally complete for all ages and can even provide considerable health benefits (as cited in Trapp, Barnard, & Katcher, 2010). A vegan diet is typically high in fruits, vegetables, cereals, nuts, and legumes (Key, Appleby, & Rosell, 2006). Consequently, vegans generally consume adequate levels of carbohydrates, fiber, folic acid, magnesium, vitamin C, and vitamin E. Compared to a typical omnivorous diet, vegans often consume lower levels of saturated fat, protein, calcium, vitamin D, and vitamin B12, all of which are typically found in animal products (Olabi et al., 2015).

Challenges concerning nutrition in vegan children are adequate intake of calories, protein, vitamins, and minerals. Total energy and protein intakes are equivalent between vegan and nonvegan children, but intakes are different in composition (Moilanen, 2004). Vegan children typically have sufficient nutrient intakes, and some studies claim that vegan children have nutrient levels that exceed those of their omnivorous counterparts (Messina & Mangels, 2001).

It should be noted that not all vegan diets are equivalent, and it is possible for an individual to consume an unbalanced, unhealthy vegan diet. However, the health benefits often associated with veganism refer to a well-rounded, low-fat, unrefined plant-based diet (Campbell & Campbell, 2006). It should also be noted that vegans are often more health conscious than non-vegetarians in regards to nutrition and lifestyle factors, which could introduce partial bias in human statistics (Key et al., 2006).

Macronutrient Intake of a Vegan Diet

Carbohydrate intake. A 2017 systematic review by Dinu et al. revealed vegetarians and vegans have significantly lower blood glucose levels in comparison to omnivores, with vegans showing the lowest concentrations (Dinu, Abbate, Gensini, Casini, & Sofi, 2017). Similarly, in a study of over 18,000 omnivores, 4,500 pescatarians, 6,500 LOVs, and 800 vegans, fiber intakes were highest in vegans, intermediate in LOVs and pescatarians, and lowest in omnivores (Sobiecki, Appleby, Bradbury, & Key, 2016). Good sources of fiber include beans, fruits, vegetables, and whole grains, all of which are typically high in a vegan diet (Trapp et al., 2010).

The diet of a vegan child, on average, relies more heavily on carbohydrates than the diet of a nonvegan child (Moilanen, 2004). Specifically, vegan children typically have significantly higher fiber intakes than both LOV and omnivorous children. It is not uncommon for vegan children to have fiber intakes exceeding daily recommended values (Messina & Mangels, 2001). A high fiber diet can provide considerable health benefits including decreased risk of diabetes, gastrointestinal disorders, obesity, cancer, and heart disease. Fiber intake can also lower blood pressure, aid in digestion, promote weight loss, and boost the body's immune system (Anderson et al., 2009). Disadvantages from high fiber intake, other than increased satiety, have not been revealed (Messina & Mangels, 2001). However, if children are not meeting their energy and nutrient intake requirements due to early satiety, a lower-fiber, nutrient dense diet may be beneficial (Messina & Mangels, 2001; Moilanen, 2004).

Fat intake. Vegetarians and vegans have significantly lower serum total cholesterol and LDL-cholesterol in comparison to omnivores, with vegans showing the greatest decrease (Dinu et al., 2017). Comparing omnivores, LOVs, pescatarians, and vegans, total fat intake was comparable at 30-31% of diet for each group according to a 2016 cohort. However, mean consumption of saturated fatty acids (SFAs) was 33% lower in vegans than omnivores, and mean consumption of polyunsaturated fatty acids (PUFAs) was 45% higher in vegans than in omnivores. Mean consumption of SFAs and PUFAs in LOVs and pescatarians fell in-between those of vegans and omnivores (Sobiecki et al., 2016).

Vegan children typically consume less fat than omnivorous and LOV children (Messina & Mangels, 2001). Higher-fat foods in a vegan child's diet can include avocado, soy, nuts, seeds, and vegetable oils. Fat intake in a vegan child's diet is important in helping meet their needed levels of energy intake and essential fatty acids (Messina & Mangels, 2001).

Protein intake. Vegan diets typically contain lower amounts of protein than omnivorous diets (Sobiecki et al., 2016). In comparison to animal-based proteins, plant-based proteins are typically lower in total protein, harder to digest, and lacking in one or more essential amino acid (Di Genova & Guyda, 2007). However, recommended daily protein levels can be obtained through consumption of a variety of legumes, vegetables, and grains. A plant-based diet provides quality protein and often in amounts exceeding recommendations (Trapp et al., 2010).

Adequate dietary protein is of great significance, especially for a growing child. The amino acids present in dietary protein are important building blocks for the synthesis of bodily proteins and other nitrogenous compounds (Schürmann, Kersting, & Alexy, 2017). Dietary protein deficiency can disturb normal neural and physical development (Schürmann et al., 2017). When comparing vegan and nonvegan diets in children, Moilanen (2004) discovered equivalent protein intakes between both groups. Even though plant-proteins are typically lower in essential amino acids, a vegan diet can provide the protein that a child's body needs (Moilanen, 2004; Schürmann et al., 2017).

Micronutrient Intake of a Vegan Diet

Calcium and vitamin D intake. Most plants have minimal amounts of bioavailable calcium, often leading to inadequate calcium intake in vegans (O'Neill, 2010). Components of plant-based foods such as phytates, oxalates, and fiber may decrease calcium absorption (Di Genova & Guyda, 2007). In research by Sobiecki et al. (2016), vegans had the lowest levels of calcium in all of the groups, 25% lower than omnivores and approximately 28% lower than LOVs and pescatarians.

Although animal products contain considerably higher amounts of calcium than plant-based foods, the high acidity of animal products in a typical omnivorous diet has been shown to impede calcium absorption and promote bone fracture. Plants have low acidity and are not known to cause calcium loss (Trapp et al., 2010). However, the amount of calcium in animal products is usually enough to compensate for the loss (O'Neill, 2010). While omnivores typically have higher calcium intake, calcium absorption from many plants is excellent. Cow's milk has an average of 32% calcium absorption. Low-oxalate vegetables such as kale, collard greens, and broccoli range from 52-59% calcium absorption (Messina & Mangels, 2001). Green vegetables, figs, beans, and fortified dairy substitutes are also good sources of calcium (Trapp et al., 2010). Calcium-fortified soy and rice milks provide just as much calcium as traditional dairy milk (Moilanen, 2004).

Vegan children frequently have calcium intake below the recommended daily value (Moilanen, 2004). If children need sources of calcium other than fortified milks, alternative foods and calcium supplements should be considered (Moilanen, 2004). While

calcium supplements come in many forms, the National Institute of Health Osteoporosis and Related Bone Diseases National Resource Center claims that all major forms are equivalent in regard to calcium absorption (NIH, 2018). Care should be taken to ensure children are not ingesting calcium in excess of recommended amounts, as doses above 1000 mg/day in adults have resulted in adverse health effects on the gastrointestinal tract, kidneys, and cardiovascular system (Bolland et al., 2015). There is little data on the health effects of high calcium intake in children (Institute of Medicine, 2011). However, a randomized control trial of 67 children found no serious complications in those ingesting 1,800 mg/day of calcium (Markowitz, Sinnett, & Rosen, 2004)

Vitamin D is an integral component in the body's absorption and metabolism of calcium and therefore plays a role in bone health (Schürmann et al., 2017). Vitamin D is primarily obtained through sun exposure. Children and adults living in northern regions are at greater risk for vitamin D deficiency (Sanders, 1988). Proper intake of vitamin D through both sun exposure and diet is important in a growing child's bone health (Schürmann et al., 2017). Dietary sources of vitamin D for vegan children include fortified soy milks and cereals. Supplements can be taken as well (Moilanen, 2004).

Iron intake. Green vegetables and legumes can provide adequate iron to a plant-based diet (Trapp et al., 2010). Research is conflicting on whether vegans and vegetarians have higher or lower iron levels than omnivores (Messina & Mangels, 2001; Sobiecki et al., 2016). The amount of bioavailable nonheme iron in plants is much lower than that in animal products. However, the high vitamin C levels in a typical vegan diet aid in iron

absorption and are likely to counterbalance this decreased bioavailability (Di Genova & Guyda, 2007; Messina & Mangels, 2001).

Several studies have indicated that iron intake in vegan children is greater than the recommended daily value (Messina & Mangels, 2001). Iron levels should still be monitored with care in children, as iron is essential to a child's neuronal development (Di Genova & Guyda, 2007; Schürmann et al., 2017). Although a vegan diet can provide the needed bioavailable iron for a growing child, iron-fortified foods should be considered and may be necessary for some children (Messina & Mangels, 2001).

Zinc intake. Vegans are known to be at risk for zinc deficiency (Tonstad et al., 2013). According to Sobiecki et al. (2016), vegans have considerably lower intakes of zinc compared to omnivores, and many in their study were below the recommended value. Symptoms of zinc deficiency include diarrhea, immune depression, and central nervous system defects (Hambidge, 2000). Special attention should be given to providing children with zinc-rich foods and foods which promote zinc absorption. Good sources of zinc in a vegan diet include whole grains, nuts, legumes, fortified cereals, tofu, and wheat germ. Zinc supplementation may be required for some children (Messina & Mangels, 2001).

Vitamin B12 intake. Vitamin B12 is important in neural development, and deficiencies can lead to psychological, hematological, and neural defects (Schürmann et al., 2017). B12 is not present in plants, so it is critical that vegan children receive vitamin B12 fortified foods or B12 oral supplements. In a 1991 study on childhood vitamin B12 deficiency, 55% of vegan children and 67% of LOV children tested positive for vitamin

B12 deficiency (Pawlak, 2017). Additionally, in a European prospective study of 803 vegans, over 50% of vegan participants had inadequate B12 status (Sobiecki et al., 2016).

Foods fortified with vitamin B12 include cereals, tofu, soymilk, and soy meat. It is thought that fortified foods can provide suitable amounts of vitamin B12 for children but not for infants, who have higher B12 needs and whose foods contain considerably lower B12 levels. Nonetheless it is suggested that children following a vegan diet be given multivitamins or B12 supplementation to ensure proper vitamin B12 intake (Pawlak, 2017; Trapp et al., 2010). To maintain B12 levels, 50 µg/day of B12 supplementation is recommended for pregnant and breastfeeding mothers, 5 µg/day for children 6 months to 3 years, 25 µg/day for children 4 to 10 years, and 50 µg/day for children 11 and up (Baroni et al., 2018). There is no set protocol for B12 supplementation in B12 deficient children, but Baroni et al. (2018) proposed B12 supplementation of 250-1000 µg/day until sufficient levels are attained. B12 can also be injected intramuscularly. This method is valuable if supplementation in breastfeeding mothers is not adequate to maintain B12 levels in infants (Smelt et al., 2016).

A Vegan Diet and Growth and Life-Cycle Nutrition

There is currently no consensus among international dietary associations on whether vegetarian and vegan diets are suitable for children. The German Nutrition Association claims a vegan diet increases risk of nutrient deficiencies and does not recommend a vegan diet for the young (as cited in Schürmann et al., 2017). The body's energy needs are higher during times of growth, thus increasing the risk of nutrient deficiencies in infants, children, and adolescents (Schürmann et al., 2017). Conversely,

the Academy of Nutrition and Dietetics, the American Academy of Pediatrics, and the Canadian Dietary Association all affirm properly managed vegan and vegetarian diets to be nutritionally appropriate for children and adolescents (as cited in Piccoli et al., 2015; as cited in Schürmann et al., 2017).

Pregnancy and Breastfeeding and a Vegan Diet

A recent systemic review of 262 articles on vegetarian and vegan diets in pregnant women found no significant association between a vegan-vegetarian diet and risk of adverse pregnancy events or severe birth defects (except one report of increased rate of hypospadias) (Piccoli et al., 2015). These results were associated with adequate vitamin B12 and iron status throughout the duration of pregnancy (Piccoli et al., 2015).

Vitamin B12 is one of the most common micronutrient deficiencies in pregnant women (Piccoli et al., 2015). In fact, vitamin intake and absorption during pregnancy and breastfeeding has a greater impact on an infant's vitamin stores than it does on the mother's. Even relatively short-term restrictions in a pregnant mother's diet can lead to vitamin B12 deficiency in her infant (Dror & Allen, 2008). Vitamin B12 deficits during pregnancy may cause adverse pregnancy-related events such as miscarriage, preeclampsia, preterm delivery, low birth weight, and infant neural tube defects. B12 deficient infants are then at risk of developing a number of neural, hematological, and developmental defects (Pawlak, 2017).

The concentration of vitamin B12 in the fetal compartment is about twice that of the concentration in the umbilical cord, revealing the high vitamin B12 demand of the growing and developing fetus (Pawlak, 2017). Koebnick et al. (2004) reported that

vegetarian mothers had a significantly higher risk of vitamin B12 deficiency than meat-eating mothers. The vitamin B12 status of the vegetarian mothers in Koebnick et al.'s study was vastly lower than that needed to meet the demands of the fetus. Without supplementation, vegan pregnant women may have even lower vitamin B12 levels than LOV mothers (Pawlak, 2017). Vitamin B12 oral supplements are therefore recommended for pregnant vegan women to maintain sufficient vitamin B12 levels (Pawlak, 2017).

Breastfeeding mothers need to maintain relatively high B12 levels to nourish their breastfeeding baby, as infant B12 deficiency is not uncommon in vegan families. One study of mothers following a vegan diet without vitamin supplementation concluded that the longer a woman adhered to a vegan diet, the lower her B12 milk concentration (Specker, Black, Allen, & Morrow, 1990). Multiple cases of infant and childhood deaths from B12 deficiency have been reported. Because it is very unlikely for breastfeeding vegan mothers to meet the required B12 levels through dietary means, B12 oral supplementation is advised (Pawlak, 2017).

Height and Weight and a Vegan Diet

The Farm Study investigated over 400 children fed healthy, appropriate, and vitamin-rich vegan diets and compared their development to reference values from the National Center for Health Statistics (O'Connell et al., 1989). Results from the Farm Study indicated that height for age and weight for age in these vegan children were below the median value in most age groups. On average, weights of the vegan children were 1.11 kg lower than the reference values. However, values were only significantly lower in height for age in those younger than five and in weight for age in those ages nine to ten.

All children were between the 25th and 75th percentiles of growth rate in the United States. Development was within the reference values for all children, with the exception of children under the age of three being below the reference height by an average of 2 cm. Statistical tendencies revealed that as age increased, height and weight in vegan children tended to approach the median reference range (O'Connell et al., 1989).

A 1988 study of 39 British vegan children ages one to seven revealed average height and weight to be below the median reference value but within the appropriate reference value for age (Sanders, 1988). A separate British study on children up to age 18 also showed vegan children to be within the appropriate reference range for height and weight as well as chest and head circumference, and no instances of growth failure were seen (Moilanen, 2004).

With proper supplementation and attention to nutrition, a vegan diet can promote adequate growth in children. Somewhat smaller stature may be seen in vegan children; however, smaller size is not associated with - and may even be protective against - long-term health deficiencies (Di Genova & Guyda, 2007; Moilanen, 2004).

Neural Development and a Vegan Diet

Proper iron levels are necessary for adequate neural development. Iron aids in myelin production, neurotransmitter function, and dendrite synthesis. (Di Genova & Guyda, 2007; Schürmann et al., 2017). However, adequate vitamin B12 intake is the main nutritional concern when it comes to neural development in vegan children. B12 is not a natural component of plant foods, and vegan children typically have adequate iron levels (Dror & Allen, 2008; Messina & Mangels, 2001; Pawlak, 2017).

Long-term B12 deficiency can impair synthesis and promote degradation of myelin in the central nervous system, leading to neural defects (Dror & Allen, 2008). The rate of myelination is greatest within the first six months of human life, and infants have very low reserves of vitamin B12 compared to adults (Dror & Allen, 2008). Therefore, proper B12 intake is vital to the neural development of infants and toddlers. Children and infants with neurological defects from vitamin B12 deficiency can be treated with intramuscular B12, and major recovery is typically seen within days of treatment. However, long-term developmental and cognitive delays are typical (Dror & Allen, 2008).

Both a 1988 study in Great Britain and a 1989 study in the United States were conducted to study development in vegan children (O'Connell et al., 1989; Sanders, 1988). Almost all of the children studied were given adequate vitamins and nutrients, and cognitive development was valued age-appropriate in all 444 children. Results revealed that as long as vegan children receive adequate vitamin B12 intake, there is no concern of delayed neural development (O'Connell et al., 1989; Sanders, 1988).

Bone Health and a Vegan Diet

It is widely accepted that calcium and vitamin D are crucial for bone health, and that low intakes can cause rickets, low bone mineral density, increased fractures, and osteoporosis (Di Genova & Guyda, 2007). Both meat and dairy intake are associated with worsened bone health, whereas vegetable intake is associated with increased bone health (Frassetto, Todd, Morris, & Sebastian, 2000). Western society has the largest intake of dairy products, but interestingly also has the highest rates of hip fractures, which is the

largest indicator of poor bone health (Green, 2010). Countries with the highest dairy intake, and consequently the highest calcium intake, exhibit the highest rates of hip fracture (Campbell & Campbell, 2006; Hegsted, 1986). High dietary calcium decreases circulating levels of calcitriol, a form of vitamin D, decreasing regulation and absorption of calcium and decreasing bone health (Campbell & Campbell, 2006; Hegsted, 1986).

Evidence that calcium increases bone health is weak and inconsistent. In a recent meta-analysis of 58 cohorts, 43 studies exposed neutral associations between dietary consumption of calcium and risk of fracture (Bolland et al., 2015). Of the 15 studies that reported an association, 13 revealed a negative relationship between calcium and fracture risk, one revealed a positive association, and one revealed a U-shaped association. Of these 15 studies, 11 showed weak association. This meta-analysis did not take into account any confounding lifestyle factors or the calcium intake levels within these cohort studies (Bolland et al., 2015).

Of the 26 random control trials in this meta-analysis, calcium supplements lowered the risk of total fracture incidence by 11% and spinal fracture incidence by 14% but did not affect risk of arm or hip fracture. However, results were inconsistent, and the largest trials with the least chance of bias did not show any association between calcium supplements and fracture risk (Bolland et al., 2015). A separate review found similar results. Of 15 studies on dietary calcium intake and 51 studies on calcium supplement intake, calcium consumption only slightly and non-progressively increased bone mineral density and was not believed to result in significant decreased fracture risk (Tai, Leung, Grey, Reid, & Bolland, 2015).

Reproductive Health and a Vegan Diet

Average onset of puberty occurs at an earlier age in the Western world compared to Third World and primarily vegan societies (McCarty, 1999). A vegetarian diet has been revealed to delay menarche onset by 6 months compared to omnivorous girls, which may be associated with decreased risk of breast cancer (Kissinger & Sanchez, 1987; De Waard & Trichopoulos, 1988). A study comparing pubertal growth spurts in over 2,000 children found that growth spurts in public school girls occurred one year earlier than in children from a vegetarian society, indicating a chronological delay in the pubertal onset in vegetarians. However, this delayed pubertal onset had no effect on growth rates or final heights (Sabate, Lindsted, Harris, & Johnston, 1990).

A Vegan Diet and Disease

Chronic Disease and a Vegan Diet

Inflammatory disease and a vegan diet. Normal intake of dairy products and red meat have been observed to have unfavorable effects on gut health and lead to increased inflammation (do Rosario, Fernandes, & Trindade, 2016; Lanou, 2009; Tonstad et al., 2013). A vegan diet decreases inflammatory markers and reduces inflammation (Eichelmann, Schwingshackl, Fedirko, & Aleksandrova, 2016; Glick-Bauer & Yeh, 2014). Specifically, a vegan diet can help manage rheumatoid arthritis and slow down the progression of multiple sclerosis (McCarty, 1999).

It is thought that the high fiber content and low intake of sugar, SFAs, trans fats, and refined starches normally associated with a vegan diet help mediate its anti-inflammatory properties (Eichelmann et al., 2016; Glick-Bauer & Yeh, 2014).

Additionally, the vegan microbiome contains significantly greater concentrations of bacteria strains protective of inflammation, compared to omnivorous and LOV diets (Glick-Bauer & Yeh, 2014; Luongo et al., 2017).

Obesity and a vegan diet. Cross-sectional studies have revealed that vegans and other vegetarians typically have relatively low body mass indexes (BMIs) (Key et al., 2006). Vegetarians on average can have anywhere from 1 to 5 points lower BMI than non-vegetarians (Le & Sabaté, 2014; Sabaté & Wien, 2010). A 2002 cohort study of 97,000 subjects revealed vegans to have the lowest BMI among LOVs, pescatarians, and omnivores, with BMI increasing as animal product consumption increased (Tonstad, Butler, Yan, & Fraser, 2009). These results are consistent with data from the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition study (Spencer, Appleby, Davey, & Key, 2003). In a separate study, Appleby, Thorogood, Mann, and Key (1998) reported a protective role of a meatless diet in obesity prevention, even after adjusting for lifestyle factors and other dietary factors.

A vegan diet is typically low in fat, protein, and energy density and high in fiber, water, complex carbohydrates, and nutrient density (Sabaté & Wien, 2010). A high-carbohydrate diet as well as a high ratio of PUFA to SFA can increase resting metabolic metabolism (Sabaté & Wien, 2010). Findings from one study revealed increased basal metabolic rate by 3.6% in response to a plant-based diet (van Marken Lichtenbelt, Mensink, & Westerterp, 1997). Another study showed that vegetarians have a basal metabolic rate 11% higher than non-vegetarians (Toth & Poehlman, 1994). Additionally, the high fiber content in a vegan diet may promote satiety and decreased energy intake

(Sabaté & Wien, 2010). It has been revealed in obesity-prone rats that replacing meat and casein-based diets with plant-based diets can reduce weight gain (Iritani, Hosomi, Fukuda, Tada, & Ikeda, 1996).

In the United States, over 16% of children are obese and over 33% are overweight, and approximately 10% of children in the world are obese (Sabaté & Wien, 2010). Childhood obesity can lead to numerous adverse health conditions in childhood as well as in adolescence and adulthood (Sabaté & Wien, 2010). According to the Harvard Growth Study, being overweight in adolescence is positively correlated with adult risk of chronic disease and all-cause mortality (Must, Jacques, Dallal, Bajema, & Dietz, 1992).

A two-year longitudinal study of over 2,200 vegetarian and omnivorous children showed both vegetarian boys and vegetarian girls to have leaner physiques and lower BMIs than nonvegetarian children (Sabate, Llorca, & Sanchez, 1992). A separate study of 215 Australian children reported similar results. In this study vegetarian children exhibited lower values for BMI and waist circumference than nonvegetarian children (Grant et al., 2008). In a 2010 review, Sabaté and Wien evaluated the odds ratios of overweight childhood risk for six different food groups (meat; dairy and eggs; junk food; fruits and vegetables; plant-based protein product; and cereals, legumes, and nuts). Results revealed a positive correlation between meats and dairy and eggs with risk of being overweight in childhood. Cereals, legumes, and nuts displayed a protective correlation, and fruits and vegetables and plant-based protein products displayed no correlation (Sabaté & Wien, 2010).

Diabetes and a vegan diet. Diabetes incidence is relatively low in those who follow a vegetarian diet (Trapp et al., 2010). Two separate studies of Seventh-Day Adventists both showed a significant association between a meatless diet and decreased risk of diabetes (Snowdon & Phillips, 1985; Tonstad et al., 2009). One study on over 60,000 vegetarians revealed vegan and LOV diets to decrease type 2 diabetes (T2D) prevalence by 50% compared to omnivorous diets (Tonstad et al., 2009). A vegan diet can extend even further protection from T2D than a LOV diet (Fields, Millstine, Agrwal, & Marks, 2016). In their review, Le and Sabaté (2014) confirmed that a LOV diet decreased T2D risk by 35-61% while a vegan diet decreased T2D risk by 47-78%

In a control trial comparing the effects of a low-fat vegan diet and the low-fat American Diabetic Association (ADA) diet, a vegan diet proved the most effective for diabetes management. After 22 weeks on their respective diets, diabetic medications were reduced in 26% of subjects following the ADA diet and in 43% of subjects following a vegan diet (Barnard et al., 2006). In a separate study by Crane and Sample (1994), diabetic nerve pain was decreased in all 21 subjects following a two-week vegan diet. Of those 21 patients, 17 experienced total improvement of pain (Crane & Sample, 1994).

Cardiovascular health and a vegan diet. Vegetarian diets are associated with significantly decreasing incidence of and mortality from CVD and ischemic heart disease (IHD) as well as significantly decreasing risk of hypertension (Dinu et al., 2017; Fields et al., 2016; Le & Sabaté, 2014). A 2014 meta-analysis of 13 studies and over 1.5 million subjects revealed a positive correlation between red processed meats and CVD mortality. However, total meat intake (red meat, processed meat, and white meat) and white meat

intake were not significantly associated with CVD or IHD mortality (Abete, Romaguera, Vieira, Lopez de Munain, & Norat, 2014). A recent review revealed that vegetarians have a 25% lower risk of IHD incidence than omnivores (Dinu et al., 2017). In a 2014 review, Le and Sabaté investigated three cohort studies and revealed vegetarians to have a 26-68% lower risk of death from CVD and IHD.

Even more so than a LOV diet, a vegan diet has been revealed to decrease incidence of and mortality from CVD. Additionally, a vegan diet may even reverse CVD (Fields et al., 2016). Esselstyn investigated the effects of a low-fat vegan diet on 23 CVD patients, many of whom had had failed bypass surgeries and angioplasties and were left without further treatment options. The patients' diets excluded animal products, nuts, refined oils, and avocados. Most of their diets also included vitamin B6, vitamin B12, calcium, vitamin D, and omega-3 supplements. Of the 23 patients, only 18 maintained Esselstyn's low-fat vegan diet (Esselstyn, 2007; Green, 2010). Prior to starting Esselstyn's study, the 18 lasting patients had endured over 49 cardiovascular events (stroke, heart attack, angioplasty, bypass surgery). However, during the 12-year study, 17 of the 18 continuing patients had no further cardiovascular events, and none of the 18 patients saw worsening coronary artery disease. In contrast, all six of the patients who left the study and returned to their normal diet experienced worsened CVD, including four bypass surgeries, one angioplasty, two ventricular tachycardia events, four cases of worsened angina, one diagnosis of congestive heart failure, and one death. Esselstyn therefore argued that a low-fat plant-based diet is protective against and can even reverse CVD (Esselstyn, 2007; as cited in Green, 2010).

Acne and a vegan diet. Both a cohort study of over 4,200 teenage boys and a cohort study of over 6,000 teenage girls have revealed a positive relationship between milk intake and acne (Adebamowo et al., 2006, 2008). It is thought that the hydrophilic protein fraction of milk accounts for this positive relationship. Milk intake, which is excluded from a vegan diet, has been shown to increase serum concentrations of growth factors such as insulin-like growth factor 1 (IGF-1). This increased IGF-1 is positively correlated with childhood and adult acne (Danby, 2009; Melnik & Schmitz, 2009).

All-cause mortality and a vegan diet. Both processed meat (e.g., bacon, ham, hot dogs, salami, and sausage) and total red meat consumption were associated with increased all-cause mortality in a 2014 meta-analysis (Larsson & Orsini, 2014). In this same review, unprocessed red meat (e.g., beef, lamb, and pork) was shown to increase all-cause mortality in American subjects but not in European subjects. According to their findings, the greatest increase in all-cause mortality risk was found at the border of negligible red meat and processed meat consumption and the reference ranges, indicating that even small consumption of red meat can have detrimental effects on health (Larsson & Orsini, 2014). Likewise, in a review by Le and Sabaté (2014), all 3 cohorts examined revealed a 10-20% decrease in all-cause mortality for those following a vegetarian diet. In another 2014 meta-analysis of 13 studies and over 1.5 million subjects, only processed meats were correlated with significantly increased all-cause mortality in comparison to red and white meats (Abete et al., 2014). In five of the six cohorts examined in a 2003 review, Singh, Sabate, and Fraser found a 25-50% decrease in all-cause mortality with low meat consumption compared to high meat consumption. Those who had abstained

from meat for more than 17 years were shown to have an increased life span by an average of 3.6 years compared to short-term vegetarians (Singh, Sabate, & Fraser, 2003). Conversely, both a 1998 study of over 75,000 subjects and a 2012 meta-analysis of over 120,000 subjects showed no significant association between a meatless diet and decreased all-cause mortality; however, there were inverse associations between a vegetarian diet and specific causes of mortality in both investigations (Huang et al., 2012; Key et al., 1998).

A clear association cannot yet be drawn between poultry and fish consumption on all-cause mortality. When studying white meat consumption explicitly, multiple studies point to a protective effect. In a 2009 cohort study as well as in a 2013 meta-analysis of Asian cohorts, increased consumption of white meat was associated with a significantly decreased risk of all-cause mortality (Lee et al., 2013; Sinha, Cross, Graubard, Leitzmann, & Schatzkin, 2009). Another study displayed no correlation between white meat consumption and all-cause mortality in its subjects (Rohrmann et al., 2013). However, white meat has been demonstrated to decrease mortality when used as a replacement of red meat in the diet (Fields et al., 2016).

IGF-1 and Disease

IGF-1 signaling. General control nonderepressible 2 (GCN2) is a phosphorylating protein that functions in numerous signaling cascades in the cell. GCN2 is activated in response to deficient levels of one or more essential amino acids. Once activated, GCN2 activates fibroblast growth factor 21 (FGF21). Growth hormone (GH) stimulates hepatic production of insulin-like growth factor 1 (IGF-1). FGF21 suppresses

hepatic response to GH, inhibiting synthesis of IGF-1. In addition to down-regulating its synthesis, it is also thought that FGF21 reduces IGF-1 activity by up-regulating the synthesis of the IGF-1 antagonist insulin-like growth factor-binding protein (IGFBP) (McCarty, 2014). GH deficient or GH receptor (GHR) deficient mice display low serum concentrations of IGF-1. Results are similar in studies of humans with GHR deficiencies (Levine et al., 2014).

IGF-1 activity. IGF-1 is a fundamental growth factor for cells throughout the body (Allen et al., 2002; McCarty, 1999). IGF-1 binding to its receptor (IGF-1R) results in phosphorylation of 3 proteins which then increase cellular proliferation, decrease apoptosis, and upregulate translational adaptation (Kim, Toretsky, Scher, & Helman, 2009). Low IGF-1 levels in both mice and humans is protective against numerous adverse health effects (Levine et al., 2014; McCarty, 2014). IGF-1 levels typically increase through childhood and reach a peak value during puberty (Yüksel et al., 2011). IGF-1 deficiency may lead to underdevelopment and small stature (Laron, 2001). However, this is not a large concern for vegans, as growth and development are typically within reference values (Di Genova & Guyda, 2007; Moilanen, 2004).

Low IGF-1 levels are thought to decrease inflammation and risk of autoimmune disorders (McCarty, 1999, 2014). Serum IGF-1 levels are also positively correlated with acne (Melnik & Schmitz, 2009). In mice, both IGF-1 deficiency, and FGF21 administration oppose insulin resistance and aid in diabetic control (Levine et al., 2014; Xu et al., 2009). Similar results have been found in GHR deficient, and thus IGF-1 deficient, humans (Levine et al., 2014). Additionally, FGF21 administration to obesity-

prone mice has resulted in decreased weight gain and reduced risk of obesity (Xu et al., 2009). GH and GHR deficient mice also exhibit increased lifespan in comparison to mice with normal IGF-1 levels (Levine et al., 2014; McCarty, 2014). Similarly, a positive relationship has been found between animal protein consumption in humans, IGF-1 levels, and mortality (Levine et al., 2014).

IGF-1 and a vegan diet. A vegan diet is correlated with the greatest reduction in serum IGF-1 levels, followed by a LOV diet and then an omnivorous diet (Allen et al., 2002; O'Neill, 2010). A study in the United Kingdom reported that vegans have serum IGF-1 concentrations 10% lower than non-vegans (Allen et al., 2002). A low-protein diet may decrease IGF-1 levels by directly inhibiting its hepatic synthesis, as revealed in animal studies (Isley, Underwood, & Clemmons, 1983; Prewitt, D'Ercole, Switzer, & Van Wyk, 1982). A vegan diet is also low in essential amino acids, which is thought to decrease serum IGF-1 by activating GCN2 and thus up-regulating the synthesis of IGFBP (McCarty, 1999, 2014). IGFBP antagonizes IGF-1 activity by binding to the protein and decreasing its availability (McCarty, 2014). One study found IGFBP levels to be 40% greater in vegan women than LOV and omnivorous women (Allen et al., 2002).

GH secretion and GHR expression are dependent on energy; therefore, dietary calorie restriction decreases serum IGF-1 levels. Amino acid restriction, particularly methionine and tryptophan, accounts for the IGF-1 deficiency following caloric restriction. In fact, a low-protein diet alone is sufficient to significantly decrease serum IGF-1 concentrations, independent of total calories, as exhibited in both *in vivo* and *in vitro* studies (Allen et al., 2002; Levine et al., 2014)

Levels of IGF-1 vary according to the type of protein present in a diet. In rats fed a soy-based 12% protein diet, IGF-1 levels were significantly lower compared to rats fed a casein or gluten-based diet. Addition of methionine, an essential amino acid low in vegan diets, to the rats' diets prevented IGF-1 reduction (Miura, Kato, & Noguchi, 1992). In a similar study in humans, subjects were fed equivalent amounts of either animal or vegetable protein. Those patients fed vegetable protein had 18% lower IGF-1 levels (Kontessis et al., 1995). Results are not consistent, as one study found a non-significant relationship between protein intake and IGF-1 levels (Dewell et al., 2007). Nonetheless, most evidence points to a relationship between quantity and source of dietary protein and IGF-1 concentrations (McCarty, 1999).

High milk intake increases serum IGF-1 levels by 10-20% in adults and 20-30% in children and decreases IGFBP levels. In fact, milk and dairy products increase IGF-1 to a greater extent than meat or any other protein sources (Melnik & Schmitz, 2009). In a 2009 systematic review studying eight randomized controlled trials and 15 cross-sectional studies, milk intake was associated with significantly higher IGF-1 levels in all eight randomized controlled trials and in 10 of the cross-sectional studies (Qin, He, & Xu, 2009). Crowe et al. (2009) also showed dairy protein to have a significant positive correlation with IGF-1 levels and a significant negative correlation with IGFBP levels. Moreover, intervention studies have revealed that milk and dairy intake are positively correlated with IGF-1 levels in both children and adults (as cited in Crowe et al., 2009). A study of dairy-free Mongolian children given milk daily for one month resulted in a 23.4% increase in IGF-1, increased GH, and decreased IGFBP (Rich-Edwards et al.,

2007). In a study on 50 boys ages seven and eight, those administered casein protein for one week saw a 15% rise in serum IGF-1 concentrations, while those administered whey protein saw no change in IGF-1 levels (Hoppe, Molgaard, & Michaelsen, 2006). In a one-week study conducted on 24 eight-year old boys, daily consumption of skim milk increased IGF-1 levels by 19%, while daily consumption of lean meat had no effect on IGF-1 (Hoppe, Molgaard, Juul, & Michaelsen, 2004). Hoppe and Rovenna et al. (2004) further confirmed this relationship in their study on healthy toddlers, which revealed that increasing daily milk consumption from 200ml to 600ml increased circulating IGF-1 levels by nearly 30%. Other studies affirm that cow's milk increases IGF-1 levels, but there is differing research on whether intake of other dairy products is related to circulating IGF-1 (O'Neill, 2010). Additionally, formula in place of breast milk is known to increase IGF-1 (Whitehead, Metayer, Wiemels, Singer, & Miller, 2016).

The essential amino acids present in dairy protein are thought to account for the association between dairy products and increased IGF-1 levels. Cow's milk also contains bioactive IGF-1 and growth hormone, which could also account for its association with increased IGF-1 levels after consumption (Crowe et al., 2009; Davoodi, Esmaceli, & Mortazavian, 2013). Organic milk may contain slightly lower levels but still considerable amounts of IGF-1 (Vicini et al., 2008). The IGF-1 present in cow's milk is similar to that synthesized in humans and can therefore bind to human IGF-1R and elicit the same effects, even after digestion. High concentrations of active IGF-1 are still measurable in cow's milk even after pasteurization and homogenization (Melnik & Schmitz, 2009).

Furthermore, most cows are given recombinant GH to aid in milk production, this GH then further increases the IGF-1 levels in cow's milk (Key, 2011a).

Calcium intake is positively correlated with IGF-1 levels (Crowe et al., 2009; Holmes, Pollak, Willett, & Hankinson, 2002). However, Crowe et al. (2009) did not find a significant correlation between IGF-1 and nondairy calcium sources. Likewise, Holmes et al. (2002) found little association between calcium supplement intake and IGF-1 levels.

A Vegan Diet and Cancer Prevention

Mechanisms of Cancer

Cancer is a disease characterized by malignant neoplasms. Hallmarks of cancer include uninhibited cell division, absence of cellular apoptosis, diversion of nutrients from surrounding healthy cells, metastasis, and tumorigenesis (O'Neill, 2010). In normal growth and development, cells in the body must go through a series of checks and balances in order to divide. Any alteration to this tightly regulated process can lead to cancerous cells (Davidoff, 2010).

Incidence of Cancer

As of 2007, it is speculated that cancer causes 13% of deaths worldwide (O'Neill, 2010). In the United States, cancer is the second most prominent cause of mortality. It is estimated that over 1/3 of American women and about 1/2 of American men will be diagnosed with cancer at least once within their lives (Campbell, 2017).

Childhood cancer accounts for only about 2% of all cancer cases (Davidoff, 2010). Although its incidence is low, childhood cancer is still the second most common cause of fatality in children above age one, and the most common disease-related childhood death

in the United States and Canada (Davidoff, 2010; Mosby, Cosgrove, Sarkardei, Platt, & Kaina, 2012). Leukemia is the most commonly diagnosed cancer in children, accounting for over 30% of all childhood cancer cases (Davidoff, 2010). Other common childhood cancers include neuroblastoma, lymphoma, Wilms tumors, Hodgkin disease, germ cell tumors, soft-tissue sarcomas, retinoblastoma, and osteosarcoma (Davidoff, 2010).

It is estimated that only 5-10% of cancer incidence is due to genetic mutation, with the remaining 90-95% due to lifestyle, infection, and environment. It is predicted that nutritional intake accounts for roughly 30-40% of cancer cases (Davoodi et al., 2013; O'Neill, 2010). Campbell (2017) affirmed through his work on rodents that nutrition has a greater impact on cancer development than the amount of carcinogen one is exposed to. Foods are composed of numerous substances and nutrients, each of which impact genes throughout the body, affecting numerous bodily functions (Campbell, 2017).

IGF-1 and Cancer

IGF-1 is a growth factor that inhibits apoptosis and promotes cell division, metastasis, and avoidance of apoptosis in stem cells, pre-neoplastic lesions, and tumors (Badr, Hassan, Tarhony, & Metwally, 2010; McCarty, 1999). Additionally, IGF-1 activates mammalian target of rapamycin complex 1 (mTORC1), which is a protein known to promote cellular proliferation and cancer (McCarty, 1999, 2011). Multiple studies have revealed IGF-1 deficient mice to exhibit decreased risk of cancer incidence and cancer-related mortality (Ikeno et al., 2009; Levine et al., 2014). Similarly, humans with GHR defects exhibit near immunity to cancer incidence, affirming the notion that IGF-1 is a universal cancer promotor (McCarty, 2014; Shevah & Laron, 2007).

Prospective studies have revealed a positive correlation between IGF-1 and breast cancer incidence in premenopausal women (Hankinson et al., 1998). Likewise, a collaborative study by the Endogenous Hormones and Breast Cancer Collaborative group found that subjects with the highest IGF-1 levels had a 28% higher risk of breast cancer incidence than those with the lowest levels (Key, Appleby, Reeves, & Roddam, 2010).

A positive relationship between IGF-1 and prostate cancer risk has also been found (Key, 2011a). IGF-1 acts as a growth factor for prostatic tissue as shown in studies of animals with decreased IGF-1 synthesis and administration of IGFBP (McCarty, 1999). In studies on humans, subjects with the highest IGF-1 levels had a 38% higher risk of prostate cancer incidence than those with the lowest levels (Key et al., 2010).

The relationship between IGF-1 and cancer is less studied for other types of cancers besides breast and prostate (Key, 2011a). Some studies have revealed IGF-1 to be an autocrine growth factor for lung cancer, but other studies report no relationship (Bhatavdekar et al., 1994; Reeve, Payne, & Bleehen, 1990; Tisi et al., 1991). IGF-1 can also moderately but significantly increase risk of colorectal cancer (CRC) incidence (Rinaldi et al., 2010). Ovarian and pancreatic cancers grow in response to IGF-1 as revealed in cell culture, animal models, and human tissue models (Beck et al., 1994; McCarty, 1999; Ohmura et al., 1990; Szende, Srkalovic, Groot, Lapis, & Schally, 1990).

While much has been studied regarding adult IGF-1 levels and cancer, only a small number of studies have examined the relationship between IGF-1 and childhood cancer. However, Badr et al. (2010) studied IGF-1 levels of 50 healthy children and 50 with cancer. Badr found that IGF-1 levels were significantly higher in children with

cancer than those who were healthy. Significant differences were not found in IGF-1 levels of hematological malignancies versus solid malignancies or in IGF-1 levels of tumors in different stages of development (Badr et al., 2010)

Specifically, IGF-1 is positively correlated with childhood leukemia risk, as IGF-1 promotes proliferation of bone marrow cells (Ross, Perentesis, Robison, & Davies, 1996). IGF-1 receptors are present on the surface of leukemic lymphoblasts, and *in vitro* studies reveal IGF-1 to promote growth of leukemia (Badr et al., 2010; Sanders, Sorba, & Dainiak, 1993). In a case-control study in Greece, Petridou et al. (1999) found no significant relationship between childhood leukemia risk and IGF-1. However, increasing IGFBP levels by 1 µg/ml was significantly correlated with 28% reduction in childhood leukemia risk. These findings therefore suggest that the amount of bioavailable IGF-1 is correlated with childhood leukemia incidence (Petridou et al., 1999). Increased levels of IGF are also correlated with lymphoma, osteosarcoma, neuroblastoma, Wilms tumor, retinoblastoma, and hepatoblastoma (Badr et al., 2010; El-Badry et al., 1991; Giuliano et al., 1996; Gjerset et al., 1990; Gray et al., 2000; Kim et al., 2009; Pollak, Sem, Richard, Tetenes, & Bell, 1992; Werner et al., 1993).

Nutrition and Cancer Prevention

Animal products and cancer prevention. Research is nearly consistent with the idea that animal product consumption is linked to increased risk of Western cancers (McCarty, 1999). Western cancers are those which are more prevalent in modern and urban societies and include cancers of the breast, prostate, colon, endometrium, ovaries, and pancreas (McCarty, 1999). In multiple short-term and long-term animal model

studies, Campbell and colleagues have affirmed that animal products promote tumor growth and plant products inhibit tumor growth (Appleton & Campbell, 1983; Campbell, 2017; Campbell & Campbell, 2006; Youngman & Campbell, 1992a, Youngman & Campbell 1992b). Replacement of animal products with soy protein has been shown to prevent cancer (Hawrylewicz, Zapata, & Blair, 1995; McCarty, 1999). Moreover, a vegan diet can reduce serum IGF-1 concentrations by up to 30% (McCarty, 2014).

The China Study began in the 1970s and investigated mortality rates of 12 cancers in over 2,400 Chinese counties (Campbell & Campbell, 2006). This study found a localized trend in cancer rates, as cancer incidence was higher in wealthier populations and lower in more rural, traditional populations. Genetic background was ruled out for cause of any disparity. Of the 2,400 counties, 65 were then further investigated. Results revealed a plant-based diet to better prevent cancer incidence than a standard Western diet (Campbell & Campbell, 2006).

A vegetarian diet may reduce total cancer incidence by 8% according to an Adventist cohort review (Le & Sabaté, 2014). A vegan diet may decrease total cancer incidence by 15%, as concluded by a recent meta-analysis of 86 cross-sectional studies and 10 cohort studies (Dinu et al., 2017). Some researchers have reported that vegetarian diets decrease risk of breast, colon, gastrointestinal, respiratory, and prostate cancers. Other studies have revealed no association between vegetarianism and risk of breast, respiratory, and uterine cancers (Dinu et al., 2017; Le & Sabaté, 2014). A vegan diet has been revealed to increase risk of urinary cancer (Le & Sabaté, 2014). Additionally, some

research has revealed dairy to have a protective effect regarding certain cancers, and some studies have revealed fish to be protective (McCarty, 1999).

There is differing opinion within the vegan scientific community on whether minimal amounts of animal products are harmful or whether traces of animal products are acceptable (Green, 2010). Campbell and Campbell (2006) have argued that the greatest health benefits are associated with the lowest but non-zero quantities of animal products. Esselstyn, on the other hand, has argued that every bit of animal product is harmful (Esselstyn, 2007).

Protein and cancer prevention. Dietary protein has been shown in numerous studies to support cancer growth. Multiple studies in which animals were induced with aflatoxin carcinogen revealed 20% dietary protein intake to promote tumor growth and 5% dietary protein intake to inhibit tumor growth (Appleton & Campbell, 1983; Campbell, 2017; Campbell & Campbell, 2006; Youngman & Campbell, 1992a). In a two-year study, 100% of animals given a 20% protein diet developed cancer while 0% of animals given a 5% protein diet developed cancer (Youngman & Campbell, 1992b). Moreover, these studies utilized one of the most common dietary proteins, casein, and administered it in amounts typical of human daily consumption (20%) (as cited in Campbell, 2017). In a 39-day study on mice, those fed a high protein diet had 78% greater tumor growth than those fed a low protein (Levine et al., 2014). In animals initially given aflatoxin and fed a 5% protein diet for 9 weeks, no cancer formation occurred, but mutations were able to be recalled even after switching to a 20% protein diet nine-weeks later (Youngman & Campbell, 1991).

The association between a high-protein diet and cancer development is mainly attributed to consumption of animal protein, as revealed by studies administering equal amounts but different sources of protein (Fontana et al., 2013; Levine et al., 2014). Additionally, a high-protein diet increases IGF-1 levels (Levine et al., 2014). Not only does a low protein diet decrease bioavailable IGF-1 levels, but it also reduces reactive oxygen species and diverts energy away from cancer growth (Campbell, 2017; Kritchevsky, 1985; Youngman, Park, & Ames, 1992).

Meat and cancer prevention. Both red meat and processed meats are associated with cancer incidence (Ferguson, 2010; Mosby et al., 2012). Processed meats include meats treated with smoking, grilling, salting, curing, or preservatives (Ferguson, 2010; Mosby et al., 2012). Studies on maternal intake of meat products and childhood cancer risk have revealed a positive correlation as well (Petridou, Ntouvelis, Dessypris, Terzidis, & Trichopoulos, 2005; Whitehead et al., 2016). Replacement of meat with soy protein delayed cancer progression in animal studies (Hawrylewicz et al., 1995; McCarty, 1999).

Meat products are typically high in fat, nitrates, nitrites, *N*-nitroso compounds (NOCs), and heme iron, all of which are confirmed to promote cancer (Ferguson, 2010; Mosby et al., 2012). Additionally, cooking of meat often leads to production of carcinogenic polycyclic aromatic hydrocarbons and/or carcinogenic heterocyclic amines (HACs) (Ferguson, 2010; Mosby et al., 2012). Furthermore, amino acid restriction, in conjunction with decreased IGF-1 levels, can reduce mTORC1 activity, and thus reduce risk of cancer (McCarty, 2014).

The main cancer type correlated with meat consumption is CRC (Ferguson, 2010; Norat, Lukanova, Ferrari, & Riboli, 2002; Sandhu, White, & McPherson, 2001). An increase of 100g of total meat or red meat per day has been shown to increase CRC risk by 12-17%, while an increase of just 25g of processed meat has been shown to increase CRC risk by almost 50% (Sandhu et al., 2001).

In a study by Sarasua and Savitz (1994), maternal intake of one or more hot-dogs per week was correlated with increased risk of childhood brain tumor. Sarasua and Savitz also found that childhood intakes of hamburgers and hot dogs once or more per week were associated with increased risk of leukemia and brain tumors, respectively. A similar case-control study by Liu et al. (2009) found a positive link between childhood cured/smoked meat and fish consumption and leukemia incidence. Frequent consumption of these meat products was associated with a near tripling in risk of leukemia in comparison to rare consumption. Conversely, consumption of plant-based meat substitutes significantly reduced childhood leukemia risk (Liu et al., 2009).

Additionally, red meat intake may increase risk of esophageal, lung, liver, kidney, pancreatic, breast, and prostate cancers (Cross et al., 2007; Daniel et al., 2012; Kabat et al., 2009; Sinha et al., 2009; Stolzenberg-Solomon et al., 2007). Other studies show no association between red meat intake and cancers of the prostate, lung, and breast (Koutros et al., 2008; Tasevska et al., 2011). Multiple studies point to a positive relationship between childhood red meat intake and premenopausal breast cancer risk (Farvid, Cho, Chen, Eliassen, & Willett, 2015).

Conversely, substitution of red and processed meats with poultry has been revealed to reduce risk of lung, esophageal, liver, colorectal, and breast cancers (Abid, Cross, & Sinha, 2014; Cross et al., 2007; Daniel et al., 2011; Farvid et al., 2015). Childhood consumption of poultry is also associated with decreased risk of adult breast cancer (Farvid et al., 2015). Chicken contains niacin, a cancer-inhibiting vitamin. Chicken also contains selenium, which aids in DNA repair, providing protection from cancer. However, processing of poultry can lead to production of carcinogenic compounds such as HACs, nitrates, and nitrites (Mosby et al., 2012). Although substitution of red meat for poultry decreases risk of some cancers, poultry intake has been associated with breast and endometrial cancer incidence (Bandera, Kushi, Moore, Gifkins, & McCullough, 2007; Bissonauth, Shatenstein, & Ghadirian, 2008).

Fish are rich in n-3 fatty acids, which are known to decrease inflammation and decrease risk of cancer. Additionally, fish are high in vitamin D, which is protective against cancer (Mosby et al., 2012). Studies reveal fish intake to be inversely correlated with CRC incidence (Gonzalez, 2006; Mosby et al., 2012).

Fat and cancer prevention. Total fat and saturated fat consumption have been confirmed to increase risk of certain cancers (McCarty, 1999). Dietary fat intake has been shown to promote pancreatic and breast cancer incidence in animals administered carcinogens (Campbell, 2017; Carroll, Braden, Bell, and Kalamegham, 1986; O'Connor, Roebuck, & Campbell, 1985). A typical vegan diet is lower in saturated fat and higher in unsaturated fat, which is thought to increase synthesis of IGF1BP, thus decreasing levels of available IGF-1 and decreasing cancer risk (Campbell, 2014).

Dairy and cancer prevention. In conclusion to a series of experiments, Campbell claimed casein to be the most powerful carcinogen ever known (Campbell, 2014). Previously mentioned, Youngman and Campbell (1992b) conducted a two-year study on casein intake and tumor formation in aflatoxin administered animals. None of the 58 animals in the low-casein group exhibited tumor growth, while all 60 of the high-casein group, given casein in percentages comparable to average human daily intake, exhibited tumor growth (as cited in Campbell, 2017; Youngman & Campbell, 1992b). A separate experiment compared the effects of aflatoxin dose (200-350 $\mu\text{g}/\text{kg}/\text{day}$) and casein consumption (4-20%) on tumor growth in rats. Results indicated intake of casein to be more rate-limiting in tumor growth than the dose of carcinogen (Dunaif & Campbell, 1987). Adelaiye et al. (2013) had similar results in their study on mice fed either a 20% plant-based protein diet, 10% plant-based protein diet, 20% dairy protein diet, or 10% dairy protein diet following tumor implantation. Replacing dietary casein with soy protein in animal models has also been proven to impede cancer growth (Hawrylewicz et al., 1995; McCarty, 1999).

Beyond elevating IGF-1 levels, dairy protein consumption has been found to increase mTORC1 activity and thus promote tumor growth (Adelaiye et al., 2013). Additionally, cow's milk contains 5 α -reduced compound 5 α -pregnenedione (5 α -P), which is linked to some cancers (Chagas, Rogero, & Martini, 2012; Danby, 2009). Potential carcinogenic compounds commonly found in cow's milk include 35 different hormones, 11 different growth factors, pesticides, antimicrobial drugs, and toxic sweeteners and preservatives (Davoodi et al., 2013; Green, 2010).

Majority of studies indicate a positive relationship between dairy intake and prostate cancer risk; however, inconsistent results are reported (Chagas et al., 2012; Schwedhelm, Boeing, Hoffmann, Aleksandrova, & Schwingshackl, 2016). Both the NIH-AARP cohort and the 2007 WCRF/AICR reports revealed a positive relationship between dairy intake and prostate cancer risk (Abid et al., 2014; Park, Leitzmann, Subar, Hollenbeck, & Schatzkin, 2009). The 5α -P contained in cow's milk is a direct precursor of dihydrotestosterone, which is known to promote prostate cancer (Chagas et al., 2012; Danby, 2009). It is also thought that calcium intake could account for a positive relationship. Small but insignificant increases in prostate cancer risk have been found to be associated with calcium intake (Chagas et al., 2012).

In many studies, a potent link has been established between dairy consumption and breast cancer risk. Both the IGF-1 and 5α -P found in cow's milk have been linked to this relationship (Chagas et al., 2012; Danby, 2009; Davoodi et al., 2013). However, a 2004 review did not find a significant association between dairy consumption and breast cancer incidence (Moorman & Terry, 2004). Some studies have suggested a negative association between childhood milk consumption and adult breast cancer risk (Michels, Rosner, Chumlea, Colditz, & Willett, 2006; Pryor, Slattery, Robison, & Egger, 1989).

Additionally, infant formula feeding, compared to breast feeding, is associated with increased serum IGF-1 levels and increased risk of childhood leukemia (Whitehead et al., 2016). A recent review of 18 studies determined that breast feeding beyond six months of life reduced risk of childhood leukemia by almost 19% (Michie, 2016).

In contrast, dairy intake decreased risk of CRC in the majority of studies (van der Pols et al., 2007). In a recent meta-analysis of 19 different cohorts, dairy intake was associated with decreased CRC incidence (Abid et al., 2014). Calcium is thought to account for the protective effect of dairy consumption on CRC risk (Abid et al., 2014; O'Neill, 2010). However, a 65-year follow-up of the Boyd Orr cohort revealed that high childhood dairy intake was correlated with a near-tripling increase in risk of adult CRC (Kesse, Boutron-Ruault, Norat, Riboli, & Clavel-Chapelon, 2005; Larsson, Bergkvist, Rutegard, Giovannucci, & Wolk, 2006; van der Pols et al., 2007).

Dairy intake has been associated with decreased risk of bladder cancer in multiple studies (Mao et al., 2011; Park et al., 2009). However, some studies have found no significant association (Li et al., 2011). A Swedish cohort study found no change in bladder cancer risk for patients who consumed less than 3.5 servings of dairy per day versus patients who consumed seven or greater servings of dairy per day (Larsson, Andersson, Johansson, & Wolk, 2008). Further research is still needed to understand how dairy intake affects risk of certain cancers, as there are great inconsistencies between research on how dairy affects prostate, breast, colorectal, and bladder cancers (Abid et al., 2014; Chagas et al., 2012; Moorman & Terry, 2004; Park et al., 2009; Li et al., 2011; van der Pols et al., 2007).

Eggs and cancer prevention. Little research has been conducted on the relationship between eggs and cancer. There is no clear evidence affirming either an inhibitory or promotional role of egg consumption on cancer risk. However, eggs are rich in selenium, vitamin D, and choline, which are known to decrease risk of some cancers.

Choline deficiency is thought to contribute to DNA damage in immune cells and is associated with breast cancer incidence (Mosby et al., 2012).

Fruits and vegetables and cancer prevention. Several case-control studies have revealed fruit and vegetable intake to protect against cancer incidence, with many exposing a near 50% decrease in cancer risk with high intake (Key, 2011b). In a review on cancer risk and vegetable and fruit intake, 19 of the 20 cohorts affirmed an inverse association between cancer incidence and fruit and vegetable intake, with 12 of these showing statistical significance. Many studies in rodents have revealed that fruit and vegetable intake decrease tumor incidence, DNA damage, and metastasis and increase activity of detoxification enzymes (Steinmetz & Potter, 1996).

Steinmetz and Potter (1996) reviewed 174 case-control studies, the majority of which found an inverse relationship between fruits and vegetable intake and risk of lung, stomach, and esophageal cancer. One 2005 survey claimed that daily fruit and vegetable intake of 600g can decrease risk of lung, stomach, and esophageal cancers by 12%, 19%, and 20%, respectively (as cited in O'Neill, 2010). Research from Steinmetz and Potter (1996) also suggests, but less consistently, an inverse relationship with breast, pancreatic, bladder, oral, pharyngeal, and colon cancers. At least 20 case-control studies have revealed fruit and vegetable intake of four to six servings per day to decrease oral, pharynx, and larynx cancer risks by half, in comparison to one to two servings per day (Terry, Terry, & Wolk, 2001).

Of the 174 case-control studies reviewed by Steinmetz and Potter (1996), 85% concluded raw vegetables to be protective against cancer, and over 70% reported allium

vegetables to be protective. The allium family includes vegetables such as onions, chives, scallions, and garlic, and these are known to increase activity of detoxification enzymes and to decrease carcinogenic nitrites in the body (Steinmetz & Potter, 1996). Cruciferous vegetables (e.g., broccoli, cauliflower, cabbage, brussels sprouts) and citrus fruits, among other fruits and vegetables, have also been shown to upregulate enzymes which detoxify carcinogens (Key, 2011b; Steinmetz & Potter, 1996). Fruits and vegetables also contain antioxidants such as vitamin C, vitamin E, lutein, flavonoids, and beta carotene, all of which reduce nitrite levels and reduce oxidative damage to DNA (Steinmetz & Potter, 1996; Terry et al., 2001). Folic acid is another component of fruits and vegetables shown to prevent cancer, particularly CRC, as it aids in DNA repair (Steinmetz & Potter, 1996; Terry et al., 2001). Additionally, vitamin A present in fruits and vegetables promotes cell differentiation. The large fiber content in such foods is thought to act as a barrier between carcinogens and the intestinal wall, protecting against CRC (Steinmetz & Potter, 1996).

On the other hand, fruits and vegetables may contain pesticides, aflatoxin, and nitrate, all of which are cancer-promoting. However, the majority of pesticides are non-carcinogenic, and their residues can be washed off or avoided by purchasing produce grown without pesticides. Aflatoxin levels are regulated in the United States. And although vegetables and fruits contain harmful nitrates, they also contain antioxidants that reduce nitrite levels. Moreover, pickled vegetables have been associated with increased cancer incidence in some Asian studies (Steinmetz & Potter, 1996).

In their case-control study, Liu et al. (2009) concluded that frequent childhood vegetable consumption decreased childhood leukemia risk by 40%. Fruit and vegetable

consumption during pregnancy has been revealed in several studies to significantly reduce risk of childhood and infant leukemia risk as well (Jensen et al., 2004; Kwan et al., 2009). Maternal intake of folic acid, which is present in fruits and vegetables, promotes DNA repair and has also been shown to decrease risk of childhood leukemia incidence (Whitehead et al., 2016). In a large study by the Childhood Leukemia International Consortium reviewing 12 studies and over 17,000 subjects, maternal folic acid intake prior to conception or during pregnancy was inversely associated with childhood leukemia risk (Metayer et al., 2014).

Conclusion

A well-planned vegan diet is suitable to meet the dietary needs of growing children and adults alike. A vegan diet not only promotes healthy growth and development, but it has also been shown to prevent a number of childhood and adult ailments including, but not limited to, obesity, cardiovascular disease, diabetes, and cancer. The increased intake of fruits and vegetables as well as the decreased intake of protein, fat, meat, and dairy have been revealed to decrease inflammation, decrease serum IGF-1 levels, and up-regulate anti-cancer mechanisms in the body, thus decreasing tumor growth and cancer risk. However, conflicting data still remains for site-specific cancers, and further research is needed to clarify the relationship between a vegan diet and pediatric cancers.

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