Asupan Gula dan Kanker: A Literature Review

Sugar Intake and Cancer: A Literature Review

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ABSTRAK

Latar Belakang: *Kanker merupakan penyebab kematian terbesar kedua di dunia dengan jumlah kematian 9,6 juta jiwa. Prevalensi kanker di Indonesia juga mengalami peningkatan dari 1,4 per 1000 penduduk pada tahun 2013 menjadi 1,79 per 1000 penduduk pada tahun 2018. Diet diduga berkaitan erat dengan prognosis terjadinya kanker, khususnya karbohidrat yang merangsang sinyal insulin yang berpotensi menjadi mitogen kuat.*
Tujuan: *Literatur review ini bertujuan untuk menelaah asupan gula dengan kejadian kanker*
Metode: *Tinjauan literatur (traditional review) dengan menggunakan kata kunci "kanker", "gula"," karbohidrat", "insulin" dan "hiperinsulinemia" pada database dan mesin pencarian Sciencedirect dan Google . Kriteria inklusi adalah artikel ilmiah yang telah melalui peer review atau dokumen yang berasal dari lembaga nasional dan internasional yang kredibel, literatur menggunakan bahasa Inggris atau bahasa Indonesia. Kriteria eksklusi adalah literatur memiliki isi yang serupa dengan artikel lainnya.*
Hasil: *Gula meningkatkan resistensi insulin dan mengakibatkan peningkatan level bio-aktif IGF-I yang dapat mempertinggi risiko kanker. Hiperinsulinemia kronis mengakibatkan penurunan konsentrasi faktor pertumbuhan seperti insulin binding protein 1 (IGFBP-1) dan IGFBP-2 yang biasanya terikat pada IGF-I dan menghambat kerja IGF-I. Akibatnya, terjadi peningkatan ketersediaan IGF-I dan secara bersamaan terjadi perubahan lingkungan seluler yang mendukung pembentukan, proliferasi dan metastatik sel kanker.*
Kesimpulan: *Mekanisme insulin dan IGF-1 dalam darah yang merangsang dan mempercepat tumbuhnya sel-sel kanker dapat menjelaskan hubungan asupan gula dan kejadian kanker. Mengaplikasikan diet gizi seimbang dan mengurangi konsumsi gula dengan makanan yang lebih sehat disertai dengan peningkatan aktivitas fisik dapat mengurangi risiko kanker.*

Kata Kunci: *Gula, Insulin, Kanker, Karbohidrat*

ABSTRACT

Background: Cancer is the second leading cause of death after heart disease globally (total death 9.6 million). Cancer prevalence is increasing in Indonesia from 1.4 per 1000 people in 2013 to 1.79 per 1000 people in 2018. Diet is linked with cancer prognosis, particularly carbohydrate intake which stimulates insulin signals that can be potent mitogens.
Purpose: This literature review aimed to examine sugar intake and cancer incidence.
Methods: This was a literature review using the keywords "cancer," sugar", "carbohydrate", "insulin" and "hyperinsulinemia" in the Sciencedirect database and Google search engine. The inclusion criteria were peer-review articles or documents from credible national and international institutions, the literature uses English or Bahasa (Indonesian Language). The exclusion criteria were that the literature had similar content or redundant with other literature.
Results: Sugar increases insulin resistance which enhances the levels of bioactive IGF-I that contribute to raising the risk of cancer. Prolonged hyperinsulinemia reduces the production of growth-promoting factors such as IGFBP-1 and IGFBP-2 which normally bind to and inhibit the action of IGF-I with resultant increases in the levels of free, bio-active IGF-I, and concomitant changes in the cellular environment that favor cancer development, proliferation, and metastatic cancer cells.
Conclusion: The mechanism of insulin and IGF-1 stimulate and accelerate cancer cell proliferation may explain the relationship between sugar intake and cancer incidence. Adopting a balanced diet, changing or decreasing sugar intake with healthier food coupled with increased physical activity reduces the risk of cancer.

Keywords: Sugar, Insulin, Cancer, Carbohydrate

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INTRODUCTION

Cancer is a condition in which cells undergo uncontrolled growth that has the potential to become malignant due to aberrant characteristics (creates own growth signals, is insensitive to anti-growth signals, unlimited replication, continuous angiogenesis, avoids apoptosis, avoids immune cells, can program cellular metabolic pathways, genetic or epigenetic instability, and tumor-induced inflammation) during development as a result of genetic and/or environmental factors[1].

Cancer is still a global public health problem and is the second leading cause of death after heart disease[2]. As many as 70% of cancer deaths occur in low- and middle-income countries. Lung cancer and breast cancer are the two most common types of cancer in the world with an estimated 2.2 million people each. Lung cancer is also the biggest cause of death (1.8 million deaths) followed by colorectal cancer (935 thousand deaths) or 18.4% and 9.2% of the total cancer deaths[3]. In Indonesia, the prevalence of cancer sufferers has also increased from 1.4 per 1000 population in 2013 to 1.79 per 1000 population in 2018[4,5]. The highest incidence of cancer in Indonesia for men is lung cancer and liver cancer, while for women, breast cancer and cervical cancer [6].

Cancer can affect human life both physically and mentally. Cancer treatment can cause fatigue, hair loss, nausea, diarrhea or constipation, infections, and weight loss. Cancer conditions can also cause fear, sadness, feelings of loneliness, isolation or anger. Cancer can affect individuals, families, and the surrounding environment[7]. The total economic loss due to cancer in 2010 globally reached 1.16 trillion US dollars. This economic loss will continue to increase along with the increase in the prevalence of cancer in the world[3].

There are modifiable (lifestyle) and non-modifiable cancer risk factors. Some risk factors for cancer related to lifestyle are smoking habits, obesity, low physical activity, and diet[8]. The results of studies related to diet and cancer risk are sometimes inconsistent and even have contradictory results. Diet is thought to be closely related to the prognosis of cancer. The relationship between diet and serum insulin levels with cancer incidence has been identified in several studies[9]. Experiments carried out on cell culture and mouse models of cancer show a relationship between carbohydrate availability, insulin stimulation, and cancer growth[10]. Carbohydrates not only provide energy but also stimulate insulin signaling which has the potential to be a powerful mitogen[9]. The synthesis of insulin and IGF-I induced by the glycemic effect of a high-sugar diet can promote tumor development [11]. Dietary restriction of carbohydrates will slow cancer growth in patients by reducing secretion and circulating insulin levels[12]. Insulin resistance is associated with continuous exposure to high levels of insulin, resulting in hyperinsulinemia[13]. In observational studies it is known that there is an increase in cancer in obese and type 2 diabetics which may be due to hyperinsulinemia, increased IGF-I, or both of these factors[14]. Until now, the relationship between cancer and diet is still being elaborated. Therefore, this article will discuss more about sugar, the etiology of cancer, and the relationship between sugar intake and the incidence of cancer.

METHODS

This article was a literature review involving the results of research or reviews about sugar intake and cancer. The databases used in the literature search were Sciencedirect and Google. Inclusion criteria were scientific articles that have gone through peer review or documents originating from credible national and international institutions, literature using English or Indonesian. Literature was excluded if it contained similar content to other articles or without a clear source of reference. Literature was obtained with the keywords "cancer", "sugar", "carbohydrate", "insulin" and "hyperinsulinemia". Article search technique by entering the words: cancer AND sugar AND carbohydrates AND insulin AND hyperinsulinemia. The bibliography of the literature used was reviewed and used if it was deemed appropriate for the purpose. The literature was used to answer several questions, namely "What was the meaning of sugar?", "What was the etiology of cancer?" and "How was sugar and cancer related?". The complete literature search strategy is shown in **Figure 1.**
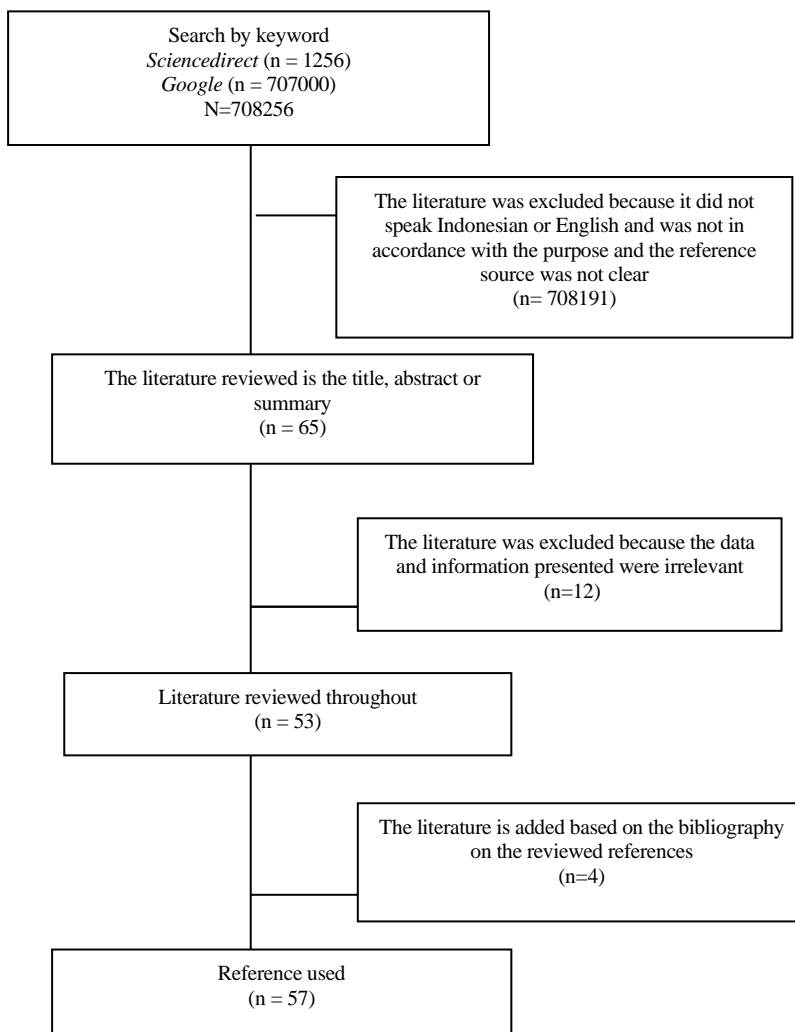
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Figure 1. Literature search strategy

RESULTS AND DISCUSSION
Sugar

Carbohydrates are polyhydroxy aldehydes, ketones, alcohols, acids and their simple derivatives which have polymers related to the acetal type. Carbohydrates can be divided according to the degree of polymerization into three main groups, namely sugars, oligosaccharides and polysaccharides[15]. The three groups above are further divided based on the monosaccharide composition of each carbohydrate, namely sugars consisting of monosaccharides, disaccharides, and polyols (sugar alcohols), oligosaccharide groups consisting of malto-oligosaccharides derived from starch hydrolysis and other oligosaccharides such as raffinose, stachyose and fructo. -oligosaccharides while the last group of polysaccharides includes starch (β-glucan) and non-starch polysaccharides such as cellulose, hemicellulose and pectin[16,17]. Sugars conventionally describe mono and disaccharides. The use of the word sugar also refers to pure sucrose as well as the terms added sugar and refined sugar. The definition of sugar and some examples of food and beverage sources can be seen in Table 1.

WHO recommends that sugar consumption from all food and beverage sources is less than 10% of total energy intake to avoid various health problems[18]. Indonesian balanced nutrition guidelines recommend limiting added sugar to a maximum of four tablespoons per day (50 grams) for adults[19]. Excessive sugar intake can be harmful to health. However, the intake of natural sugars from whole vegetables and fruits as well as lactose in milk and dairy products has a lower risk or does not harm health[20]. High intake of sugar (sweetened foods and drinks) is associated with an increased risk of obesity [21-23], dental caries[24,25], and non-communicable diseases such as type 2 diabetes[26], heart disease[27,28], and cancer[29,30].

Table 1. Definition of Sugar and Sources of Food and Drinks Containing Sugar[19,31]

Sugar	Definision	Food Sample
Total sugar	Total free monosaccharides (glucose, fructose, and galactose) and disaccharides (lactose, sucrose, and mannose) both naturally found in food and beverages or added. Total sugar includes natural sugar and added sugar.	Bread, cereal products, fruit, sweet foods, sweet drinks.
Natural Sugar	Sugar that is naturally found in food or drink.	Fruit, honey, milk and dairy products, 100% fruit juice.
Added Sugar	Sugar and syrup added during the production or processing process.	Sugary drinks, cakes, sweet foods, sweetened fruit products, candy, baked goods, and cereal products.
Fructose	Monosaccharides naturally found in fruits. Fructose is a constituent of sucrose and high-fructose corn syrup.	Main sources of sugary foods and drinks with added artificial sweeteners from high-fructose corn syrup, fruit juices, fruits, vegetables, and nuts.
Sucrose	Disaccharides made of glucose and fructose, also known as table sugar.	Sugar beet, cane sugar, and some fruits.
Sweet Food	Foods high in sugar (total and added).	Desserts made of milk, sweet snacks, candies and sweet chocolate.
Sweet Drink	All drinks containing sugar. Drinks such as sugary drinks and fruit juices.	Fizzy/non-soda drinks, 100% fruit/vegetable juices, liquid and powder concentrates, flavored drinks, sports drinks and energy drinks, ready-to-drink teas, ready-to-drink coffee, and milk with added sugar. Sweetened fruit juice, lemon drink.

Cancer and Etiology

Cancer is a disease related to body cells. The body is made up of billions of cells. Normal cells grow and divide into two. When dead cells are replaced by new cells, but in some cells there are errors that cause cells not to die and divide out of control[32]. In cancer cells, the normal control systems that prevent cell overgrowth and invasion of other tissues are deactivated. These altered cells divide and grow at a signal that normally inhibits cell growth. Therefore, these cells no longer need special signals to promote cell growth and division. These cells grow and develop new characteristics, including changes in cell structure, decreased cell adhesion, and production of new enzymes[33] .

Cancer is caused by a combination of genetic and non-genetic changes caused by the environment. These factors trigger the activation or inactivation of certain genes that cause neoplastic transformation, or abnormal cell growth[34]. Risk factors for cancer are divided into non-modifiable risk factors and modifiable risk factors[33]:

Non-modifiable risk factors for cancer include age[35,36], ethnicity[37], descendants[38], gender[39], chronic health conditions[40] and chromosomal anomalies[41]. A person's probability of developing cancer increases with advancing age. Starting at the age of 60 years the percentage of cancer probability increases to 13.3% in men and 10.2% in women or almost double that of the previous age group[42]. Cancer rates vary by ethnic group. Melanoma was highest in whites compared to blacks at 95% and 90%, respectively[42]. Inherited mutations or

deletions of genes cause 5-10% of cancers[33]. The proportion of cancers 30 - 40% may be due to cancer gene susceptibility plus exposure to carcinogens[33]. Some chronic diseases or medical conditions over time cause cancer. Inflammation of the colon, which is a series of colon inflammations, is associated with a 30% risk of colon cancer[33]. Risk factors for chromosomal anomalies in the incidence of cancer, among others, are indicated by a 10-20-fold increased risk of lymphoblastic leukemia, acute myeloid leukemia and acute megakaryocytic leukemia in children with Down syndrome[33].

Modifiable risk factors include the use of cigarettes, alcohol, infectious agents, ultraviolet radiation, ionizing radiation, occupational exposure, environmental pollution, drugs, environmental pollution, drugs, food contaminants, obesity, physical activity low and unhealthy diet[33]. Alcohol and cigarettes account for more than 80% of squamous carcinomas of the mouth, pharynx, larynx, and esophagus in the United States[43]. The use of large amounts of alcohol is also associated with an increase in the number of breasts cancers[43]. Infectious agents such as hepatitis B virus (HBV) and C (HCV), Epstein-Barr virus (EBV), human papillomavirus (HPV), human immunodeficiency virus type 1 (HIV-1), Helicobacter pylori (H. pylori) and Streptococcus bovis (S. bovis) contributes to various cancers such as hepatocellular carcinoma, Burkitt's lymphoma and nasopharyngeal carcinoma[44]. Long-term exposure to sunlight and other forms of ultraviolet radiation increases the risk of skin cancer[45,46]. Excessive exposure to ionizing

radiation, such as X-rays and radiation therapy, has been linked to an increased risk of leukemia and bone cancer[47]. Cancer cases are caused by air, water, and soil pollution by 1 - 4% which occurs mainly in developed countries compared to developing countries[33]. Certain drugs, such as alkylating agents used for chemotherapy, can increase the risk of leukemia, and use of angiotensin receptor blockers increases the risk of lung cancer[48]. Obesity is a significant risk factor for cancer in developed countries associated with unhealthy diet and physical inactivity. Obesity is associated with an increased risk of endometrial, kidney, gallbladder, and breast cancer[33]. A sedentary lifestyle is linked to an increased risk of colon cancer and breast cancer[49]. Physical activity with moderate to vigorous intensity for 30-60 minutes per day significantly reduces cancer risk[50]. 30% of cancer in developed countries is caused by an unhealthy diet that is high in saturated fat and low in fruits and vegetables[33]. Sugar intake has a relationship with cancer risk[29,51].

The Relationship between Sugar and Cancer

Sugar consumption is increasing worldwide. In Indonesia, the percentage of people who like to eat sweet foods is also increasing[4]. The percentage of the population aged more than 10 years with the habit of consuming sweet drinks in 2018 increased to 60.4% compared to the percentage of the habit of consuming sweet foods and drinks in 2015 which was 53.1%[4,5]. 11.8% of the Indonesian population consumes sugar >50 grams per day or higher than the limit set by WHO[52]. This fact needs attention because sugar intake is not only closely related to weight gain, obesity, type 2 diabetes, hypertension and heart disease[53-57] but also associated with the incidence of cancer[29,51,58].

Makarem et al's systematic review of sugar intake and cancer risk of 37 longitudinal studies (15 studies on total sugar, 14 studies on fructose and sucrose, five studies on added sugars, and 15 studies on sugary foods and beverages) indicated that the relationship between between sugar intake and cancer is quite variable depending on the location of the cancer. However, when analyzed as a whole, there was no relationship between consumption of total sugar and sucrose with cancer risk. Several studies have found that the intake of added sugar, fructose, and sugary drinks has a potential negative impact on the etiology of cancer[24]. The Prinz Review (2019) stated that sugar intake was only associated with an increase in obesity when consumed in excess (excess calories) and was ultimately associated with an increased risk of diet-related diseases[25].

The debate regarding the relationship of carbohydrates, especially sugar intake with cancer, has been going on for a long time. In the 1920s, Otto Warburg and colleagues described that cancer cells prefer anaerobic glycolysis to produce energy for their cellular processes (Warburg effect)[59]. In cancer cells, glucose uptake and lactate production increase drastically. Although, the availability of oxygen is sufficient, and the mitochondria are functioning properly. These metabolic-type changes provide the substrate required for cancer cell proliferation and division, which involves tumor

growth, metastatic development, and longer survival[45]. Tumor cells need to be able to survive in the presence of drastic changes in the microenvironment such as hypoxia, low nutrient stores, and acidic pH levels. Cancer cells have remarkable plasticity to metabolic adaptations. The reprogramming of glucose metabolism enables cancer cells to meet their high proliferative needs. In addition, the reprogramming of glucose metabolism is also beneficial for the survival and growth of cancer cells, including as the main carbon source for anabolism and providing fast ATP to supply energy. The amount of lactic acid will increase the oxidation reaction status (NADPH) through the glycine-serine pathway[45]. This is in contrast to normal cells which are more dependent on oxidative phosphorylation in mitochondria. This Warburg effect then encourages the assumption to reduce glucose intake. Decreased glucose intake will result in tumor cells such as starvation (glucose deficiency) and also has the potential to decrease insulin-related cell growth (as a result of decreased blood sugar levels)[25].

Sugars in carcinogenesis tend to be site-specific. Insulin and IGF-I synthesis induced by the glycemic effect of a high-sugar diet may promote tumor development by increasing cell proliferation and inhibiting apoptosis, stimulating sex steroid synthesis, or by stimulating vascular endothelial growth factor production[11]. These factors support tumor growth and promote the migration of these cells. Another potential mechanism is increased oxidative stress caused by postprandial hyperglycemia[60].

Sugar increases insulin resistance and increases levels of bio-active IGF-I which increase the risk of cancer. Chronic hyperinsulinemia due to decreased concentration of growth factors such as insulin binding protein1 (IGFBP-1) and IGFBP-2 which leads to increased availability of IGF-I and simultaneously changes in the cellular environment that supports tumor formation[61].

Insulin plays a central role in regulating blood glucose levels during periods of eating and fasting. Insulin is an anabolic hormone involved in the metabolism of glucose, lipids, and proteins. Insulin is released by pancreatic -cells when glucose levels rise. Insulin also plays a role in inhibiting glucose synthesis (gluconeogenesis) by the liver. Another role of insulin is to bind to specific insulin receptors on the cell membrane, which causes GSV to be translocated to the cell membrane. The insulin-responsive transporter is GLUT4 which is synthesized on the endoplasmic reticulum ribosomes and then transferred to the Golgi apparatus, where GLUT4 combines into GLUT4 storage vesicles (GSV). The end result of the effect of insulin on the cell membrane causes the translocation of GLUT4 to the cell membrane until it is available to transport glucose into the cell[62].

Insulin resistance is a condition when the insulin level is higher than expected for the glucose level. In insulin resistance there is a decrease in the response of target cells or organisms to the concentration of insulin that is exposed. This condition of increased insulin levels is also known as hyperinsulinemia[63]. Insulin resistance is associated with continuous exposure to high levels of insulin. Hyperinsulinemia conditions can cause persistent

insulin resistance in the body. Continuous hyperinsulinemia over 40 hours in humans results in significantly reduced glucose utilization and glucose metabolism at sub-maximal and maximal plasma insulin concentrations[13]. Decreased concentration of growth factors such as insulin binding protein 1 (IGFBP-1) and IGFBP-2 also causes hyperinsulinemia which leads to increased availability of IGF-I[61].

The IGF system is a complex network molecule composed of two ligands (IGF-I and IGF-II), two receptors (IGF-IR and IGF-IIR), six high-affinity binding proteins (IGFBP-1-IGFBP-6) and several proteases. protein binder[64]. IGF-I, IGF-II and IGFBPs are present in high circulating concentrations and can be measured. Total circulating IGF-I depends on growth hormone (GH). IGF-I binds with high affinity to IGF-IR in terms of receptor activation and with low affinity for insulin receptor (IR)[61,65].

IR activation by insulin triggers an intracellular signaling cascade in the extracellular signal-regulated kinase (ERK) and phosphotidylinsositol 3-kinase (PI3K) pathways[65]. This insulin signal has the potential to be mitogenic and anti-apoptotic. Conventionally, insulin is thought to be mitogenic only at a supraphysiological level, possibly mediated via the IGF-I receptor or the hybrid IR-IGF-I receptor[61].

Several cellular actions of IGF-I support tumor growth, including mitogenic in almost all human cells, inhibiting apoptosis induced by gamma radiation, cytotoxic agents and TNFa. IGF-I also induces the production of hypoxia-inducible factor-1-mediated vascular endothelial growth factor (VEGF), induces tumor-associated lymphangiogenesis, and promotes integrin- and E-cadherin-mediated cell migration[66].

IGF-I also plays a role in the regulation of differentiation, cell size and cellular cytoskeleton[66]. IGF-I stimulates pathways that are key to early tumor initiation such as -catenin and has potential stimulatory effects on other cell growth including estrogen[67].

CONCLUSION

Sugar intake and cancer can be explained through the mechanism of insulin and IGF-1 in the blood which stimulate and accelerate the growth of cancer cells. Reducing sugar consumption does not mean stopping carbohydrates because these components are an important part of the human diet. Less IGF is secreted allowing a lower risk of cancer growth. Consumption of protein, fat, and fiber along with simple sugars helps the body produce less insulin. A balanced nutritional diet and reducing sugar consumption with healthier foods along with increased physical activity can reduce the risk of cancer.

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