



Sylvia R. Karasu M.D.
The Gravity of Weight

Is There a Link Between Sugar Intake and Cancer?

Excessive sugar could produce an environment conducive to some tumors.

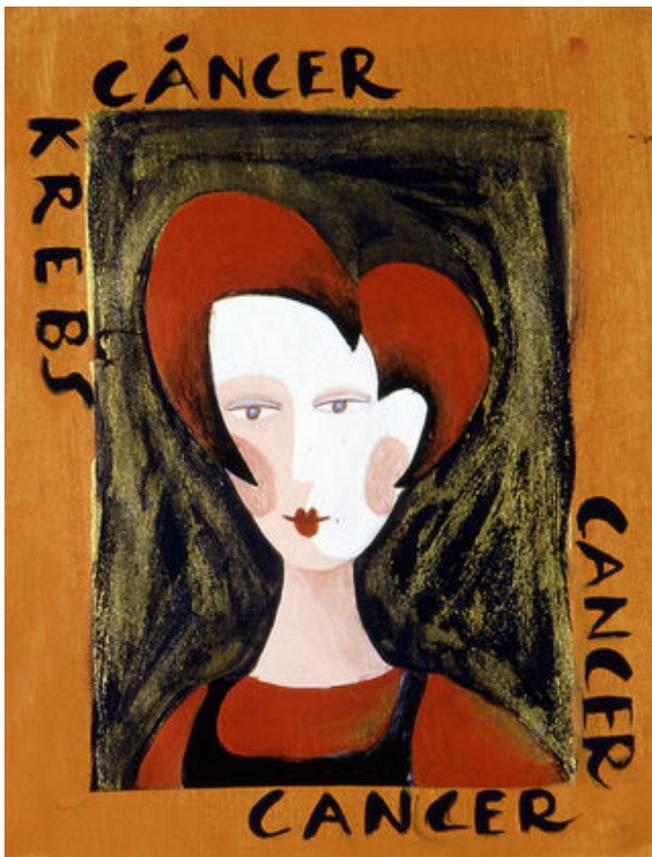
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KEY POINTS

- **Methodological complexities make the study of the relationship between diet and disease challenging.**
- **Researchers are unfortunately not able to establish direct causal links between diet and cancer or establish firm public health recommendations.**
- **Studies in animals and humans do implicate a state of chronic insulin secretion from excessive sugar intake is conducive to tumor development.**

“Is everything we eat associated with cancer?” asked researchers Schoenfeld and Ioannidis somewhat provocatively years ago (*American Journal of Clinical Nutrition*, 2013). These investigators selected 50 “common ingredients” from “random” cookbook recipes and surprisingly (or perhaps not surprisingly) found that 40 (80%) of those ingredients were linked in the scientific literature to cancer. Researchers had studied gastrointestinal cancers most commonly, but genitourinary, breast, head and neck, lung, and gynecological malignancies as well.

Schoenfeld and Ioannidis (2013) concluded that most food ingredients “were *interpreted* by their authors as offering evidence” either for some risk or some benefit even though many single studies (n=264) “highlight implausibly large effects” with weak statistical evidence. Further, they found no standardization of definitions throughout the studies.



The signs of the Zodiac: Cancer.

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The challenges of studying diet and disease

Nutritional epidemiology is the study of the relationship of diet to disease, overall health, and even mortality (Willett and Hu, in Lash et al. *Modern Epidemiology*, 4th Edition, 2021). Appreciation of the connection of diet to disease goes back at least to Hippocrates (born 460 B.C.), with his book *On Regimen*. “The complexity of the human diet represents a daunting challenge: Our foods contain literally thousands of specific chemicals,” only some of which are known and quantified. As a result, our exposure to a substance is rarely “present or absent” (Willett and Hu, 2021).

Further, there are major methodological problems inherent in nutritional studies

that limit the ability to observe any diet-disease or even specifically any diet-cancer link, including an inability to estimate diet intake accurately, rigorously control diet over long periods (Goncalves et al, *Annual Review of Cancer Biology*, 2019) or even remember what has been eaten. Patients may also deny or exaggerate “dietary misbehavior” as a way of deflecting blame or guilt for becoming ill (Hebert and Miller, *American Journal of Clinical Nutrition*, 1988).

Nutritional studies may also lead to many false-positive conclusions and even “questionable” research practices, including biases in the design and execution of a study, especially because negative findings are less likely to be published or even “misleadingly interpreted” (Schoenfeld and Ioannidis, 2013). As a result, Ioannidis and colleagues emphasize that many associations reported could not be replicated and can hardly be translated into public health recommendations (Theodoratou et al, *Annual Review of Nutrition*, 2017).

Further, there is often “considerable uncertainty” about the timeframe involved between diet exposure and the development of disease. Schoenfeld and Ioannidis (2013) found in their sample of 36 meta-analyses that some “were often forced to merge data” from studies that had used different exposure times.

Even whether a low-carbohydrate diet is more efficacious for some than a low-fat diet, i.e., the so-called “perpetual diet wars” now raging (Ludwig et al, *Cell Metabolism*, 2019), may be affected by the length of time that participants are followed. With consideration of total calories expended for these different diets, Allison and colleagues (Ludwig et al, *The Journal of Nutrition*, 2020) reanalyzed meta-analyses of 29 controlled-feeding studies that spanned a period from 1982 to 2020. Studies varied considerably in duration. The researchers, though acknowledging the possibility of subjects' non-adherence to diet protocols (another major limitation in nutritional research), found that shorter-term studies may be examining *different* physiological states: longer trials, for example, may allow for “adequate adaptation” whereas shorter-term trials may miss these adaptations and yield conflicting results (Ludwig et al, 2020).



Girl tasting sugar from a barrel. Many researchers believe there is a link between sugar consumption and cancer. Unknown artist, private collection.

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A purported link between something we eat and cancer often seductively produces considerable hype and draws widespread media attention. Those in the media and even research scientists themselves may have underlying *righteous* intentions but their enthusiasm may lead, sometimes intentionally, sometimes unintentionally, to misrepresentation and distortion of the data, a phenomenon Cope and Allison have labeled *White Hat Bias* (*International Journal of Obesity*, London, 2010). When this



Go Western Parade in Billings, Montana, 1939. "White Hat Bias" is a term to describe the misrepresentation and distortion of research, often with righteous intentions.

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occurs, "passions inflame rather than inform" and they may lead unfairly to the "demonization" of some foods and the "sanctification" of others (Cope and Allison, 2010).

Dangers of added sugars in processed food

"What you really need to know is what's been done to the food, even more than what's in the food. A food label does not tell us that," says Robert H. Lustig, in his new book, *Metabolics: The Lure and the Lies of Processed Food, Nutrition, and Modern Medicine* (2021). "What's

important is the alchemy of how the food itself has become poison," he adds. Almost all food has some processing (e.g. olives to olive oil), but for Lustig, ultra-processed food is the poison, and "sugar is both the marker and the hook for processed food."

Most Americans consume high levels of sugar daily, usually in the form of sugary foods and beverages made from table sugar and high fructose corn syrup, and added sugars typically account for 270 calories of daily intake (Makarem et al, *Annual Review of Nutrition*, 2018). Some researchers believe this excessive intake of carbohydrates is so noxious to human health, they have coined the term *carbotoxicity* (Kroemer et al, *Cell*, 2018).

High insulin levels and cancer risk

Malignant cells thrive on blood glucose for their growth and proliferation (Makarem et al, 2018). Insulin, with both central and local effects, is secreted by the pancreas in response to elevated glucose levels and "ultimately controls systemic metabolic homeostasis" (Hopkins et al, *Nature Reviews Endocrinology*, 2020). A state of hyperinsulinemia produces an environment conducive for tumor development, and Dr. Lewis C. Cantley, Director of the Meyer Cancer Center at Weill Cornell Medicine,

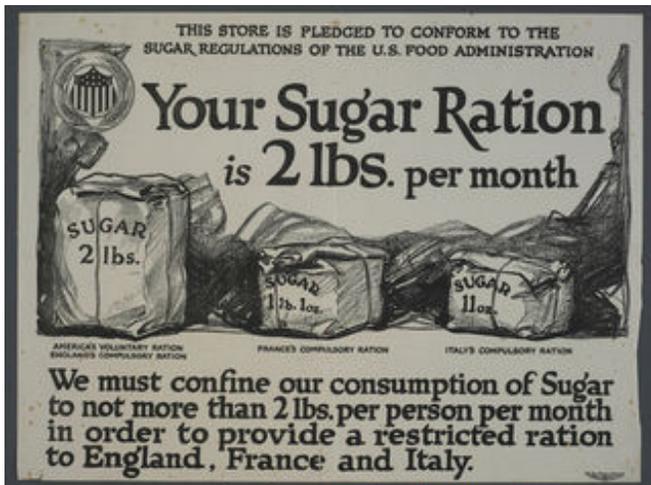
suggests that insulin is a "protumorigenic factor" (Hopkins et al, 2020). With excessive intake, ambient insulin levels remain high all the time, and "sugar may be the most dangerous food we eat" (Cantley, *CBS television interview*, 6/7/21).

Interest in the connection between carbohydrate intake and cancer dates back to the work of Nobel-Prize winning researcher Otto Warburg in the early 1920s, who investigated how cancer cells generate energy *differently* from normal cells, i.e., by a process of aerobic glycolysis, aptly named the *Warburg effect* (Vander Heiden et al, *Science*, 2009). This effect is considered the "hallmark of cancer" (Klement and Kämmerer, *Nutrition & Metabolism*, 2011).



Jose Raphael Aragon, Holy child of Atocha, c. 1840. Christ, dressed as a pilgrim, brought food to Christian prisoners.

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"Your Sugar Ration." American School, 20th century. Museum of New Zealand, Wellington, NZ. Printed by The Carey Company.

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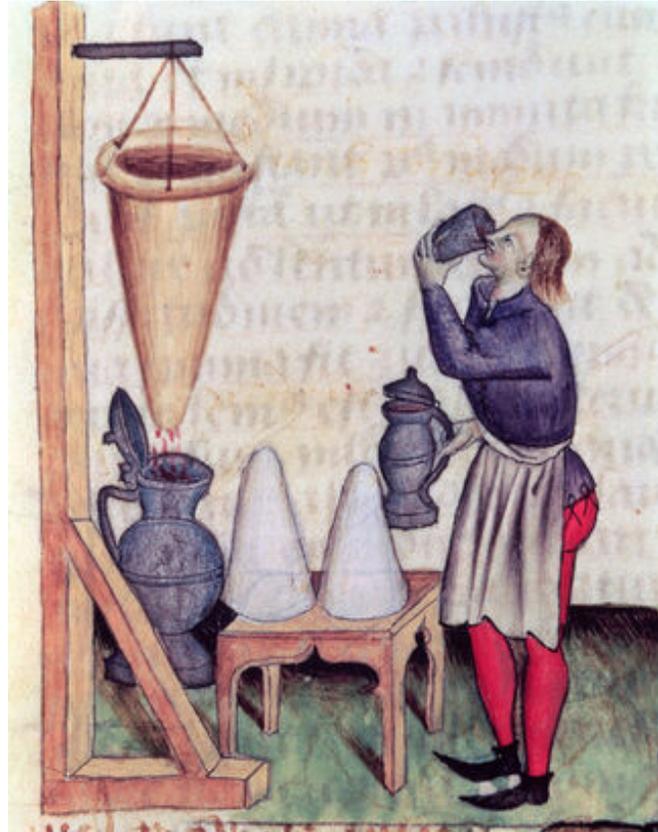
For a fascinating account of Warburg, see Sam Apple's newly published book, *Ravenous: Otto Warburg, the Nazis, and the Search for the Cancer-Diet Connection* (2021).

Researchers have appreciated that intake of excessive sugar (including total sugars and added sugars) is associated with obesity, type 2 diabetes, and cardiovascular diseases, particularly through pathways involving oxidative stress, inflammation, and insulin. There is now sufficient evidence that obesity

increases the risk of developing 13 different cancers, possibly partly driven by high, but ineffective insulin levels, i.e., insulin resistance (Goncalves et al, 2019). Data from trials to establish a connection between diet and cancer have generally been less consistent (Debras et al, *American Journal of Clinical Nutrition*, 2020) and “may be dependent on tumor, patient, and context” (Goncalves et al, 2019).

One 10-year prospective French study, NutriNet-Sante, including over 100,000 volunteers studied for a median follow-up of almost 6 years, found that total sugar intake was associated with higher overall cancer risk, particularly for breast cancer, even when adjusting for weight gain. Researchers concluded that though they could not establish causality, sugar intake “may represent a modifiable risk factor for cancer prevention” (Debras et al, 2020).

Establishing a causal connection between diet and disease, including between diet and cancer, is not possible, particularly because of the methodological complexity of nutritional research. Studies in both animal models and humans indicate, though, that persistently high levels of insulin (i.e., chronic hyperinsulinemia) from excessive sugar intake produce an environment conducive for the proliferation of some tumors.



Ms Lat 993, Making sugar syrup from 'Tractatus de Herbis' by Dioscorides. Italian School, 15th century. Biblioteca Estense, Modena, Italy.

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About the Author



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