Hochschule für Angewandte Wissenschaften Hamburg
Hamburg University of Applied Sciences

Hamburg University of Applied Sciences
Faculty of Life Sciences

Bachelor Thesis

The effects of a high Glycemic Index diet on pancreatic cancer

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Submitted by: Eleni Valtzis

Supervisor: Prof. Dr. Christine Behr-Völtzer

Second Examiner: Prof. Dr. Jürgen Lorenz

Abstract

Sugar and its abundance in the modern diet have long been suspected for the indirect infliction and deterioration of several diseases. From the beginning of the industrialization until today, sugar consumption has nearly increased tenfold, with the biggest growth shown in the past 50 years.
In the 1920s, a scientist named Otto Heinrich Warburg discovered that cancer cells demonstrate metabolic changes with a preference in glucose. Since then, scientists have tried to decode this metabolic phenotype and track the role of sugar in cancer.

Considering the hypothesis of Warburg, that sugar seems to be feeding cancer cells in different types of cancer, the present dissertation is trying to detect whether it could also be regarded as a risk factor for the ignition of the disease on the example of pancreatic cancer.
Pancreatic cancer is one of the most lethal types of cancer with a very poor future prognosis. To examine the connection, a hypothesis is built which connects pancreatic cancer with a diet of high glycemic index.

The results of the present research show no connection between a high glycemic index diet and ignition of the disease. However, there seems to be grave need of accessible annual screening methods for pancreatic cancer. This absence appears to interfere with the execution of well designed cohort studies.
As a result, the present dissertation suggests further research implemented on large cohorts in earlier stages of life.

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List of abbreviations

AARP	American Association of Retired Persons
ACS	American Cancer Society
AHA	American Heart Association
ASCO	American Society of Clinical Oncology
ATP	Adenosine Triphosphate
BMI	Body Mass Index
BS	Blood Sugar
CI	Confidence Interval
CT	Clinical Trial
DGE	Deutsche Gesellschaft für Ernährung

DNA	Deoxyribonucleic Acid
EBM	Evidence Based Medicine
ER	Endoplasmatic Reticulum
FFQ	Food Frequency Questionnaire
GI	Glycemic Index
GI tract	Gastrointestinal Tract
GL	Glycemic Load
GLUT	Glucose Transporter
HFCS	High Fructose Corn Syrup
HR	Hazard Ratio
IAUC	Incremental Area Under The Curve
LSTRC	Literature Selection Technical Review Committee
NADH	Nicotinamide Adenine Dinucleotide-Dehydrogenase
NCBI	National Center of Biotechnology Information
NDSR	Nutrition Data Systems for Research
NET	Neuroendocrine Tumour
NLCS	Netherlands Cohort Study
NLM	National Library of Medicine
OS	Observational Study
OxPhos	Oxidative Phosphorylation
PP	Pancreatic Polypeptide
RCT	Randomized Controlled Trial
RR	Relative Ratio
SGLT	Sodium Glucose Transporter
TCA	Tricarboxylic Acid
US	United States
USDA	United States Department of Agriculture
WHI	Womens Health Initiative
WHO	World Health Organization

1. Introduction

The present dissertation investigates the connection between pancreatic cancer and the nowadays excessive consumption of refined sugars in the form of the glycemic index (GI). Even though pancreatic cancer has low incidence rates, it is considered as one of the most lethal cancers. It has a very poor 5-year survival rate and the highest incidence is observed in western countries (Ilic, Ilic, 2016).

The first person to ever link glucose to cancer was Otto Heinrich Warburg who investigated the metabolic behavior of cancer cells in the early 20th century. Since then, scientists have been debating whether a nutrition high in glucose can play a role in the vast proliferation of already existing cancer cells, and have been trying to determine whether the findings of Warburg can be applied in the diagnostics as well as therapy of cancer (Vander Heiden, Cantley, Thompson, 2009). However, it remains unclear wether the Warburg effect is a consequence or even cause of cancer.

In the meantime, refined sugar consumption has increased within the past 200 years exponentially. Industrialization and therefore food processing have globally altered older dietary patterns. Along with sugar cane, a number of other caloric sweeteners have been invented and added to our diet within the past 50 years. Consequently, caloric sweeteners can be found in almost all processed foods and drinks.

Following the findings of Warburg, the present dissertation investigates whether sugar could potentially be regarded as a risk factor for carcinogenesis in the pancreas. Through a systematic literature research, the dissertation is trying to detect the possibility of a connection between a diet with a high glycemic index and pancreatic cancer.

First, there is an analysis of pancreatic cancer and its epidemiology. Subsequently, the Warburg Effect is introduced in order to show the dependence of cancer cells on glucose, which then leads to a demonstration of nowadays consumption of sugar in comparison to consumption in the past. Through the formation of a hypothesis and a systematic literature research of several studies, the aim is to detect whether a perennial nutrition with a high GI can possibly lead to pancreatic cancer.

The type of cancer was chosen due to the decisive role of the pancreas in sugar absorption and thus maintenance of the blood sugar in normal levels.

2. Theoretical framework

The dissertation examines the possibility of a connection between a diet high in refined sugars and the ignition of pancreatic cancer.

Cancer is a very complex disease with a behavioral pattern that can vary from one patient to another. The causes of the disease are mainly genetical and its heterogeneity is attributed to the molecular as well as cellular complexity of the human body. Due to their wide spectrum, it is impossible to demonstrate these mechanisms thoroughly within the limitations of the present thesis. Nevertheless, in their majority, these mechanisms do not serve the purpose of the dissertation and will therefore be mentioned synoptically.

According to recent studies, individuals who suffer from diabetes or obesity, have a greater risk of exhibiting pancreatic cancer. Therefore, the thesis is focusing on a higher caloric sweetener consumption without the manifestation of the above.

2.1. Pancreas Anatomy and Function

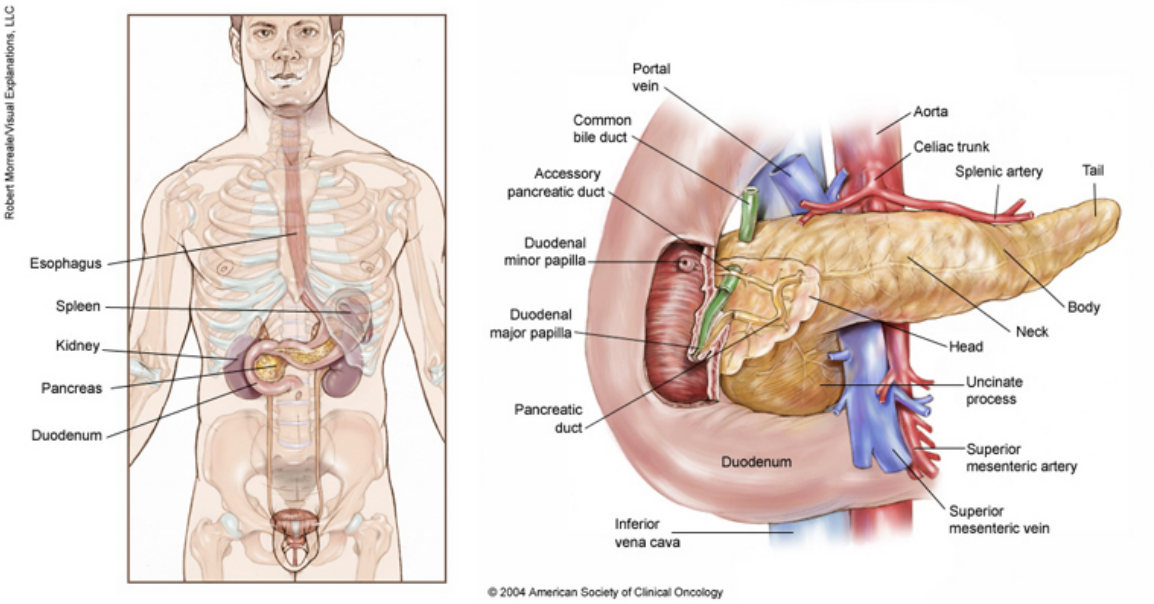

Figure 1: Location of the pancreas
Source: (ASCO) American Society of Clinical Oncology, 2018

The pancreas is a gland about 12-15 centimeters long, located deep in the upper left abdomen behind the stomach, anterior to the vertebral column. The pancreas is divided in the head, neck, body and tail, although some sources do not mention the neck. The head, the wide part of the pancreas, abuts the upper duodenum, and is connected with it via the main pancreatic duct (Fig.2). The remaining parts of the gland have a slight upward inclination and the tail extends to the spleen (Fig.1). (Standring, 2016, p.1179).

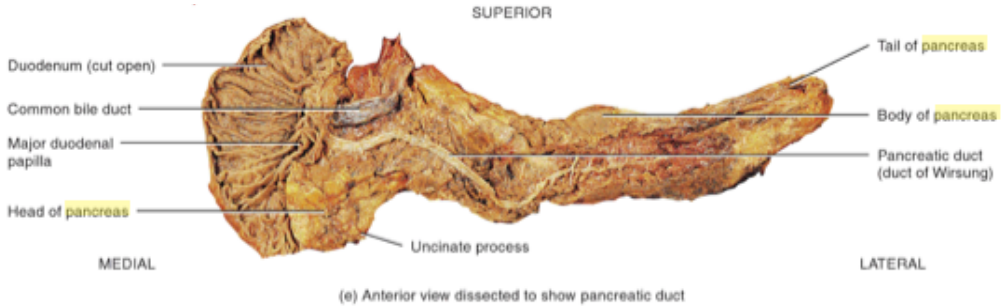

Figure 2: Anterior view of dissected pancreas
Source: Tortora, Derrickson, 2008, p.944

The pancreas is made out of 82% acinar cells, 4% ductal cells, 4% blood vessels, 2% endocrine cells and 8% extracellular matrix (Beger et al., 2008, p.71). There are two types of glands in the pancreas:

Exocrine glands: exocrine (greek: „ekso"=outside, „krinein"=secrete) glands consist of cells which secrete their product through ducts externally (The Free Dictionary by Farlex). These glands consist of acinar and ductal cells. Acinar cells form a ring structure around ductal cells. Their endoplasmatic reticulum (ER) forms and secretes digestive enzymes into the ducts which then join the main pancreatic duct that runs through the length of the pancreas. The main pancreatic duct then joins the common bile duct and together they form the ampulla of Vater which perforates to the duodenum through the major duodenal papilla (Fig.2, Fig.3). The digestive enzymes, while still in the pancreas, are in an inactive form and get activated once they reach the duodenum. There, they break down carbohydrates, fats and proteins. Another function of the exocrine tissue is the secretion of ions and water as well as bicarbonate to the gastrointestinal tract. Bicarbonate (HCO_3-) neutralizes the hydrochloric acid (HCl) from the stomach that reaches the duodenum with the rest of the nutrients. A neutral pH is

necessary for a better function of the digestive enzymes as well as gastrointestinal surface epithelial function. (Pandol, 2011, p.4-11)

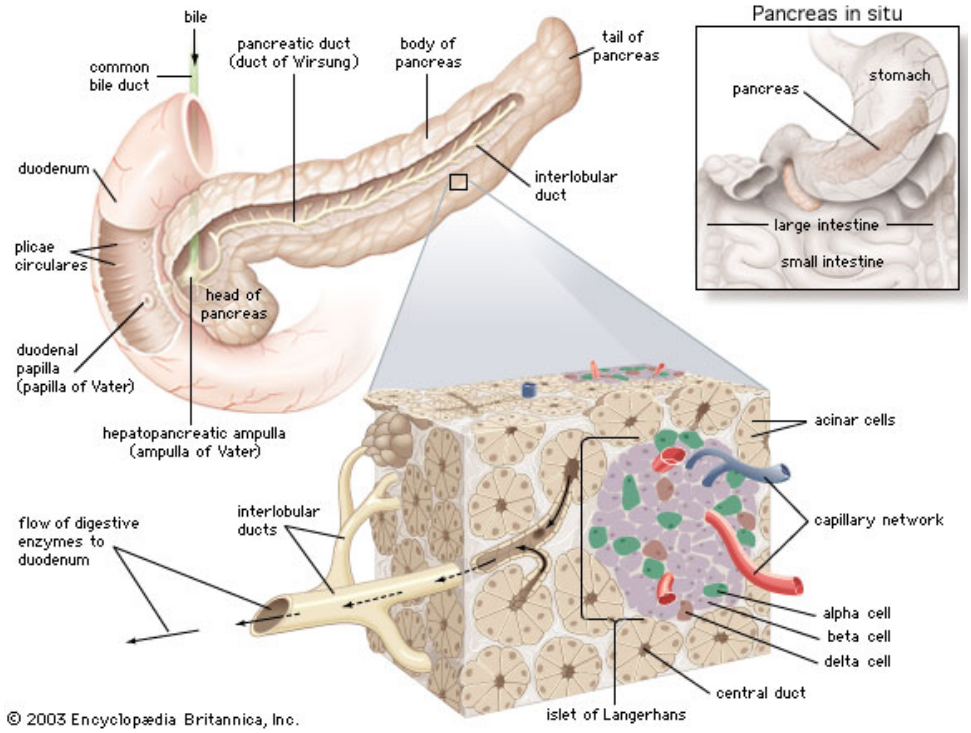

Figure 3: Exocrine and endocrine tissue of the pancreas
Source: Encyclopedia Britannica - Islets of Langerhans

Endocrine glands: endocrine (greek: „endo"=inside, „krinein"=secrete) glands consist of cells which secrete their product into the blood or lymph circulation and thus affect other parts of the body (The Free Dictionary by Farlex). They are made out of clusters called the islets of Langerhans (Fig.3). There is approximately one million islets in the human pancreas. As mentioned above, these islets secrete hormones into the bloodstream. The main two hormones are insulin and glucagon which regulate the amount of glucose in the blood, as well as somatostatin which prevents the release of the above. Insulin gets secreted by beta cells, glucagon by alpha and somatostatin by delta cells as well as the pancreatic polypeptide (PP). In humans, beta cells comprise roughly 50% of the islets whereas alpha cells 30-40% (Standring, 2016, p.1187).

Insulin and glucagon work like antagonists serving the same purpose: to keep the blood sugar in normal levels. When blood sugar (BS) is normal, insulin constantly gets secreted in a baseline amount by the beta islet cells of the pancreas. When the BS is high, beta cells get activated and release more insulin. Insulin helps glucose enter the cells to be used as fuel. When the amount of glucose becomes lower, insulin levels

decrease back to the baseline status. Glucagon is secreted by the alpha cells of the pancreas when the blood sugar levels are low (i.e. exercise, fasting, in between meals). Glucagon triggers glycogen, which is the storage form of glucose in the liver, to break off glucose molecules in order to increase blood sugar. The role of somatostatin is to inhibit the secretion of insulin and glucagon through acting as a negative regulator for alpha and beta cells (Jain, Lammert, 2009).

2.1.1. Cancer - Pancreatic cancer

Healthy tissue cells have a specific life span. They grow and divide, in order to replace themselves, and subsequently fall into apoptosis. The cell lifespan is a highly intelligent mechanism controlled by many individual factors and signals that take place within the cell as well as amongst neighboring cells. Cancer is a condition in which one or more cells of a specific tissue survive and continue proliferating, leading to an accumulation of cells that do not fall into cell death. Pancreatic cancer can arise in the cells of the exocrine as well as endocrine tissue (Longe, 2015, p. 913-914).

This uncontrollable proliferation can happen through mutation of the deoxyribonucleic acid (DNA) chain. DNA is constantly threatened by damage which occurs either from within the cell of through environmental factors, which will be listed in the next chapter. It encodes proteins, many of which are responsible for the control of cell division. A disruption of the normal DNA sequence during its self-replication can lead to the encoding of the wrong protein. The cell becomes abnormal and starts dividing itself uncontrollably, forming a tumor (Longe, 2015, p. 913-914).

However, a DNA mutation normally gets prevented by the repair mechanisms of the cell. These mechanisms control the DNA strands and, according to the extend of the damage, either correct any mistakes in the new DNA or even prevent the proliferation of the damaged cell. In case of an inherited mutation, the DNA repair system can be predisposed to certain types of cancer. These mutations usually exhibit themselves in an older age, and lead to the inability of the cell to correct the damage (Schulz, 2007, p. 47-54). Once a cell becomes cancerous, it behaves independently and starts defying its environment, exhibiting metabolic alterations which will be further analyzed in chapter 2.2..

2.1.1.1. Epidemiology

According to the prognosis of the American Cancer Society (ACS) (2018), around 55,440 people will be diagnosed with pancreatic cancer and 44,330 people will die from this disease in the U.S. in 2018. The incidence of pancreatic cancer currently lies at 3%. The same source also states that pancreatic cancer accounts for 7% of all deaths through cancer. Although pancreatic cancer is not very common, it represents an important health issue since its incidence and mortality rates are almost identical. The 5-year survival rate depends on the type and stage of pancreatic cancer. Nevertheless, for the most common type, the exocrine tumors, the survival rates are very low (ACS, 2016).

According to Bray et al., (2018) who take their information through GLOBOCAN, there is globally an average of 459,000 new cases and 432,000 people deaths each year through the disease. The highest incidence rates are in North America and Europe. According to Ilic, Ilic, (2016), the disease seems to be on a slow but steady rise in both genders.

The American Society of Clinical Oncology (ASCO, 2015) has come up with several risk factors for pancreatic cancer:

- **Age:** 90% of the cases are people are older than 55 and 70% older than 65 years
- **Family history:** may run in the family if at least two first-degree relatives have it
- **Gender:** incidence slightly higher for men than for women
- **Diabetes:** the longtime illness can cause pancreatic cancer
- **Smoking:** raises the risk 2 to 3 times
- **Ethnicity:** african-american people more likely than asian, hispanic or white
- **Obesity/Diet:** chronically overweight/chronic heavy alcohol use
- **Inflammation of the pancreas (pancreatitis):** can raise the risk according to studies
- **Rare inherited conditions:** raise risk for pancreatic as well as other types of cancer
- **Chemicals:** exposure to pesticides, benzene, some dyes and petrochemicals
- **Bacteria:** Helicobacter pylori raises risk for stomach and pancreatic cancer
- **Hepatitis B infection:** according to studies; more research needed
- **Cirrhosis:** when scar tissue develops over damaged liver cells

Nevertheless, it gets mentioned that people who develop pancreatic cancer are not always exposed to risk factors, whereas there are others who are exposed to risk factors but do not always acquire the disease.

2.1.1.2. Types of pancreatic cancer

The following table lists the two different types of pancreatic cancer and their subcategories according to the specific cell type infected by cancer:

Type of pancreatic cancer	Categories	Types	Characteristics
Exocrine	pancreatic adeno-carcinoma	ductal: starts in the duct acinar: starts in the cells	95% of all exocrine cancers and usually ductal
	less common types	adenosquamous carcinomas squamous cell carcinomas signet ring cell carcinomas undifferentiated carcinomas undifferentiated with giant cells	
	carcinoma of the ampulla of Vater		starts at ampulla of Vater where bile and pancreatic duct come together technically not pancreatic cancer but treated the same
Endocrine (pancreatic neuroendocrine tumors/islet cell tumors)	functioning NETs	gastrinomas	from cells that make gastrin
		insulinomas	from cells that make insulin
		glucagonomas	from cells that make glucagon
		somatostatinomas	from cells that make somatostatin
		VIPomas	from cells that make vasoactive intestinal peptide
		PPomas	from cells that make pancreatic polypeptide
	non-functioning NETs		don’t cause symptoms and grow large before they are found
	carcinoid tumors		

Table 1: Overview of the types of pancreatic cancer
Source: own representation after the American Cancer Society (2016)

Exocrine cancers are by far more common than endocrine ones. Most often pancreatic cancer starts in the ducts that carry pancreatic juices. Specifically, pancreatic ductal adenocarcinoma is with a frequency of 90% the most common type of pancreatic cancer. Endocrine cancers make up for less than 5% of all pancreatic cancers (Beger et al., 2008, p.601). No literature source has been found stating the reason of the higher frequency of exocrine cancers in comparison to endocrine ones, although a possible explanation could be the percentile majority of acinar and ductal cells according to chapter 2.1..

2.1.1.3. Diagnosis

Pancreatic cancer usually does not exhibit any symptoms in early stages and thus does not get treated early enough. According to the ACS (2016), for people of average risk, routine screening is usually not recommended mainly due to the fact that no screening has yet contributed to a lowering of the mortality rates. Nevertheless, upon suspicion, there is a variety of imaging as well as biopsy tissue tests that can be used for the detection of pancreatic cancer. Depending on the symptoms, age, medical condition and previous test results of the patient, the doctor will decide which test is more appropriate (ASCO, 2018).

Once diagnosed with pancreatic cancer, surgery seems to be the sole palliative treatment. However, even after a successful resection, the 5-year survival rate remains below 20% (Matsuoka, Selby, Genyk, 2012).

2.2. The Warburg Effect

As already mentioned in chapter 2.1.1., cancer cells exhibit metabolic changes. Otto Heinrich Warburg was the first scientist to discover in the 1920s that cancer cells have a different metabolic behavior from healthy tissue (Wittig, Coy, 2007). Several scientists presume that through researching the Warburg effect, a better understanding of the metabolism of cancer cells can be gained as well as ways to cease their proliferation.

The first step in understanding the Warburg Effect and its appliance is to gain a better insight of the cell respiration and proliferation as well as the role of nutrition.

In order for cells to proliferate, they need energy. When food is consumed, the cells need to convert food molecules into their form of energy, adenosine triphosphate (ATP). One of the ways for cells to convert biochemical energy from nutrients into ATP is through cellular respiration.

There are two forms of cellular respiration; aerobic and anaerobic. In aerobic respiration, when oxygen is abundant, cells convert one glucose molecule to carbon dioxide (CO_2) through the oxidation of pyruvate in the tricarboxylic acid (TCA) cycle. Through the reaction, nicotinamid adenin dinucleotide-dehydrogenase (NADH) is produced, which gives energy to the oxidative phosphorylation (OxPhos) in order boost ATP production. Through OxPhos the energy produced is 36 ATP moles and only a small amount of lactate. In anaerobic conditions though, when oxygen has decreased, cells produce large amounts of lactate. Through the metabolism of glucose to lactate only 2 ATP moles per glucose molecule are produced (Vander Heiden, Cantley, Thompson, 2009).

Otto Warburg demonstrated that cancer cells, regardless of the presence or absence of oxygen, prefer to live in an anaerobic environment and to metabolize glucose and produce large amounts of lactate instead of producing more energy through OxPhos. He named this metabolic phenotype "aerobic glycolysis". Aerobic glycolysis was observed especially in very aggressive tumors compared to benign ones or healthy tissues (Wittig, Coy, 2007).

The preference of glucose metabolism in cancer cells has raised the question whether the abundance of refined carbohydrates, especially in western diets, and specifically glucose as the product of carbohydrate digestion, may be a factor which can promote cancer initiation or growth.

According to nutrigenomics, nutrition and environment can affect gene expression (Mead, 2007). Consequently, a person with a genetical predisposition to a certain disease might be able to inflect its expression through diet. In other words, a person predisposed to pancreatic cancer, might avoid or enhance the expression of the disease, through perennial nutrition patterns.

Following the lead of this idea, the present dissertation is trying to detect whether sugar and its vast increase through the past decades might have played a role in the incidence of the disease.

2.3. Sugar

Sugars, are a subgroup of carbohydrates. Alternative descriptions for sugars are "caloric sweeteners", and "refined" or "simple" carbohydrates due to their fast absorption. Carbohydrates are one of the most controversial group of nutrients nowadays. Nevertheless, they play a very important role in cell life and are fundamental for any kind of cell connection and communication (Nelson, Cox, 2005, p.238).

As for human nutrition, carbohydrates can be received mainly through plants and dairy and are often responsible for their sweet taste. Sugar, as the refined form of carbohydrates, is vastly used nowadays in the industrialization of food production. Sugars are not only used for the enhancement of sweet taste but according to Hanover, White (1993), also contribute to a variety of sensory aspects that are favorable to consumers such as flavor enrichment, viscosity, ability to retain water and keeping moisture, microbial inhibition, color, lowering of the freezing point, texture, fermentation as well as adding body to drinks.

Apart from the typical sugar extracted from cane or beet, there is a variety of caloric sweeteners such as corn syrups, juice concentrates, honey, molasses, agave nectar as well as the semi-caloric sugar alcohols that can be used by the food industry to enrich meals, snacks and drinks. Each of these caloric sweeteners is used in different types of foods in accordance with the attribute needed in order to achieve the maximum taste and sensory experience (Grembecka, 2015).

2.3.1. Carbohydrate Digestion and Absorption

The digestion of carbohydrates in the gastrointestinal (GI) tract begins in the buccal cavity. The polysaccharide chains get coarsely hydrolyzed by the enzyme alpha-amylase in saliva, also known as "ptyalin" or salivary amylase. The mix moves to the stomach where the action of ptyalin is stopped through the acidic pH of the gastric juice. The acidic chyme then moves to the duodenum, the first part of the small intestine. There it gets neutralized by the alkaline juices of the bile and intestine as well as the pancreas, which, as mentioned before, contains bicarbonate (HCO_3-). The pancreatic juice, which is produced in the exocrine glands of the pancreas, also contains pancreatic alpha-amylase which is more powerful than the amylase in the buccal cavity. It hydrolyzes the glycosidic bonds and breaks down polysaccharides into di- and oligosaccharides. These

get further disintegrated into monosaccharides by enzymes of the intestinal juice such as intestinal amylase, sucrase, maltase, isomaltase, lactase and limit-dexrtinase (Verma, Pandey, 2012, p.366-367).

The monosaccharides then get absorbed by the walls of the small intestine to the blood and provide our cells with energy. Glucose and galactose enter the epithelial cells of the small intestine though the protein sodium glucose transporter 1 (SGLT1) and exit through diffusion glucose transporters (GLUT2). Fructose however, is not getting transported by SGLT1. It is taken from the walls of the small intestine by GLUT5 transporters, then gets intracellularly converted into glucose and exits the cells also though GLUT2 (Goodman, 2010). As already mentioned in chapter 2.1., the endocrine pancreas is responsible for the absorption of monosaccharides by the cells through releasing insulin and glucagon. It is thus clear that the pancreas is very much involved both in carbohydrate digestion as well as absorption.

More complex carbohydrates (fiber) such as cellulose, which are complex polysaccharides do not get hydrolyzed and move to the large intestine where they get moderately metabolized by bacteria of the colon (Vander et al., 2001, p.562).

2.3.1.1. Natural vs. refined sugar metabolism

As already mentioned, sugars are digested and absorbed easily by the human body and are thus referred to as „simple carbohydrates“. According to the Cancer Treatment Centers of America (2016), the body metabolizes natural sugars differently than refined ones. Natural sugars from fruit are accompanied by fibers, minerals, vitamins and sometimes proteins which slow down the digestion, contribute to the feeling of satiety, promote a steady absorption and steadily increase blood sugar. On the other hand, refined sugars have no further nutritional value other than providing calories and thus get absorbed very fast. This results to a belated feeling of satiety and drastic increase of blood glucose. Nevertheless, once sugar of any source reaches the duodenum, it gets metabolized and absorbed by the body exactly the same.

2.3.1.2. Glycemic index and Glycemic Load

Since sugar, as a form of carbohydrates, is a nutrient and not a trace element or vitamin which will simply get washed out of the body in case of satiation, it seems to be a

challenge to set coordinates of how much sugar is adequate and how much could be abundant or even lead to health problems and weight gain.

Over time scientists have developed formulas in order to roughly estimate glycemic response after the injection of carbohydrates. These formulas are the glycemic index (GI) and glycemic load (GL) and are used as guidance and evaluate quantity as well as quality of carbohydrates.

The GI is a way to value how fast the blood sugar rises after consumption of carbohydrates. It measures the increase of blood glucose within two hours after the consumption of a specific amount of food. The formula for the GI is:

$$GI = (IAUC_{food}/IAUC_{glucose}) \times (Wt\ glucose/Wt\ available\ carbohydrate\ in\ food) \times 100\%$$

where IUAC: the incremental area under the blood glucose response curve (Monro, Shaw, 2008). It is thus safe to assume that the higher the GI, the richer is a food in simple carbohydrates.

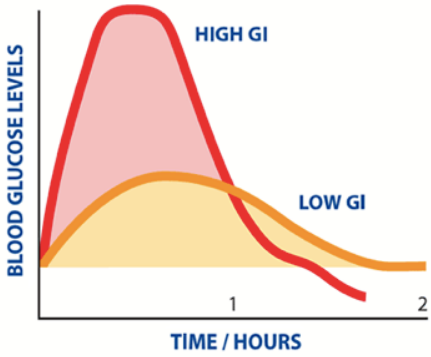

Figure 4: Blood glucose response curve
Source: http://glycemicindex.com/about.php, 2017

The result then gets compared to the same amount of a reference food which is either glucose or white bread. Foods with a high GI get very fast absorbed by the body and lead to fluctuations of the glucose due to the rapid rise and fall of the concentration in blood. Foods with a low GI need more time to get digested and lead to a more steady postprandial glycemic response which in longterm seems to be more beneficial (Sheard et al., 2004).

Still the comparison is not realistic if the amount of usual consumption is not included in the calculation. Therefore, scientists have invented a formula to calculate the glycemic load (GL). Foods with a GL ≤10 are considered low GL, whereas foods with GL ≥20 high GL (Barclay, Brand-Miller, Wolever, 2005). The formula for the GL is:

GL= GI/100 x P x weight of food

where P: the proportion of available carbohydrates in food

(Monro, Shaw, 2008)

In other words, GI measures the quality of the carbohydrates whereas GL takes also into account their quantity. Even though both GI and GL are only a rough estimate of the overall glycemic effect of food, they provide valuable information on the effect of specific carbohydrate consumption on glycemic response.

2.3.2. History of sugar consumption

It is difficult to find literature about sugar consumption in the past. Nevertheless, according to Cordain et al. (2005), who adapted a graphic from Cleave T.L. (1974) in his research, within 150 years after the industrial revolution (1760-1830) the consumption of sugar rose nearly eight times (Fig.5). Although it shows only the consumption in England, the source assumes that, due to the already expanded trade at the time, the rest of the western countries were consuming approximately suchlike amounts. According to Cleave T.L., in 1815 around 6,8kg (19gr per day) of sucrose were consumed each year per capita. By 1970 the consumption had reached 54,4kg per year (149gr per day).

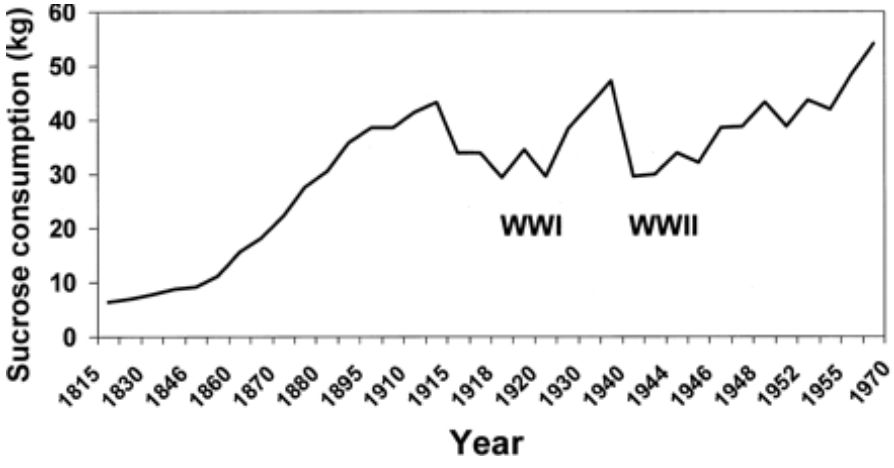

Fig. 5: Rise of sucrose consumption in the UK, 1815-1970
Source: Cordain et al. (2005)

However, the same source points out that sugar from cane and beets was for technological and geographical reasons not very reliable, making its price fluctuate. In

response to that, the industry had to come up with another alternative. Scientists managed to extract fructose and glucose out of corn. In the late 60s to 1970, high fructose corn syrup (HFCS) was finally introduced into the market and started steadily taking the place sucrose.

The next graphic (Fig.6) shows the availability of caloric sweeteners per person in the United States between 1970 and 2014. Since availability is not equal to consumption, the United States Department of Agriculture (USDA) included in their calculations all production losses and therefore assume that the numbers are close to consumption.

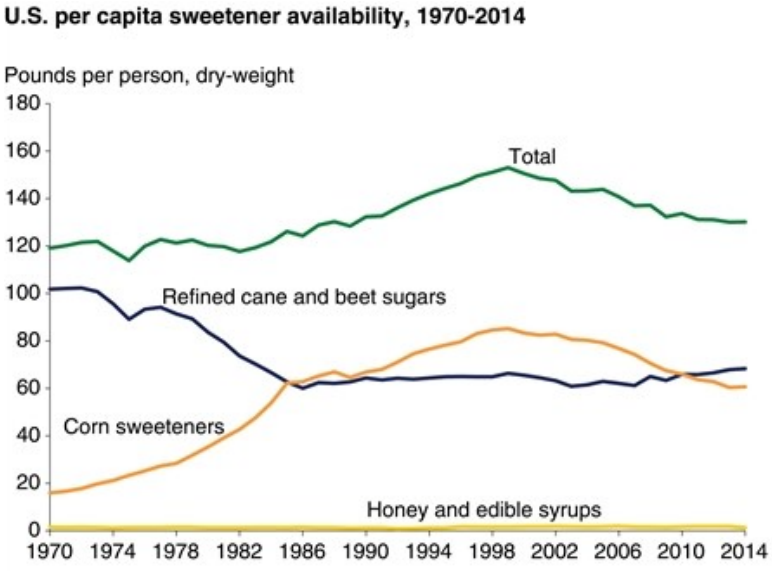

Fig. 6: Per capita sweetener availability in the U.S. between 1970-2014
Source: USDA, Economic Research Service, Food Availability Data (2014)

After 1970 the total annual per capita availability of caloric sweeteners started increasing, reaching its peak in 1999 with 153.1 lb (69kg) per person. Since then, the availability of corn sweeteners and total sweeteners has been slowly decreasing, going down to 131 lb (approx. 59kg) in 2014, mainly due to so far unsubstantiated health concerns.

According to Popkin, Nielsen (2003), in the forty years prior to the publication date of his research, there had been an immense increase of caloric sweetener consumption worldwide. In the U.S., approximately 80% of the caloric sweetener increase is through soft drinks and sugared fruit drinks, whereas added sugar intake from food has stayed roughly the same. The same source states that, worldwide there has been a shift towards consumption of caloric sweeteners and away from more complex carbohydrates.

2.3.3. Guidelines for sugar intake

According to Shu Wen, Slining, Popkin (2012), 75% of all foods purchased within 2005 and 2009 in the U.S. contained sweeteners, most of which were caloric. These data seem alarming considering that although sugar has no nutritional value, it seems to have taken the place of other beneficial nutrients. Guthrie and Morton (2000) suggest that, through the vast consumption of caloric sweeteners, the average calorie intake of the population has increased. As a result of suchlike studies, in 2015 the World Health Organization (WHO) published a guideline manual for children and adults urging them to reduce the intake of free sugar to less than 10% of their daily intake. WHO further recommends a reduction of less than 5%.

The American Heart Association (AHA) (2018) suggests a total sugar intake of maximum six teaspoons (24 grams) for women and nine teaspoons (36 grams) for men per day. The AHA also advises to decrease the consumption of soft drinks depending on evidence which holds them responsible for their contribution on weight gain and obesity.

Furthermore, the nowadays vast consumption of sugars has been suspected of enhancing several health issues, one of which is also cancer. Following the leads of the already presented theoretical framework, the present dissertation will examine the possible connection of pancreatic cancer and a diet rich in caloric sweeteners through a set up of a hypothesis.

3. Methodology

In this chapter a hypothesis is formed as milestone of what is searched for in the studies chosen and presented in chapter 4, and further analyzed in the discussion chapter 5. Concurrently, the precise research methods are demonstrated in order for the reader to comprehend the choice of these studies.

3.1. Hypothesis assembly

Through the combination of the information of the theoretical framework in chapter 2., one hypothesis was built:

- **Hypothesis: There is a connection between high sugar intake and the ignition of pancreatic cancer.**

Through this hypothesis the effects of the nowadays high consumption of refined carbohydrates on pancreatic cancer will be analyzed in the studies presented in the next chapter. Due to the fact that the contribution of sugar to health damage is still highly ambiguous, there is no definition of a high intake and no limit dose. Therefore, the only comparison that can be made is between people who consume more and those who consume less.

3.2. Literature research

The literature research was the first segment that was completed for this thesis and was first composed in May 2017. The objective was to gain a better insight of the current data surrounding this subject as well as finding the most valid scientific information. Back then, it had still not been decided in which way sugar intake would be measured.

The main database used was PubMed. PubMed is a database of the U.S. National Library of Medicine (NLM) and was built from the National Center for Biotechnology Information (NCBI). Through the set up of an account there is free access to MEDLINE and thousands citations of full-text life science journals, online books and biochemical literature (U.S. National Library Medicine, 2016).

The research in PubMed happens through a set up of keywords. When more than one keywords are being searched for, they have to be connected with the word "and".

Prior to composing this thesis, a more general research was conducted in order to assess the scientific stand point on the topic. Up to that point, the aim was to find studies that were measuring sugar consumption and comparing it to pancreatic cancer. Nevertheless, research such as "pancreatic cancer and sugar", or "pancreatic cancer and glucose" led to a confusing variety of results, most of which seemed to be irrelevant to the topic. This led to the conclusion that "sugar" or "glucose" are vague terms and that something more specific was needed for the research, since filters such as "Meta-Analysis" or "Systematic Reviews" did not change the outcome. After trying "pancreatic cancer and fructose“, the results were more apparent, although half of the studies were older than ten years and the rest consisted of some relevant studies which were based on a more genetical aspect of the disease and hence could not be used. The keywords "pancreatic

cancer and Warburg effect" did only lead to scientific reviews instead of population studies and were not brought into connection with nutritional aspects. Hence, it became evident, that a more dose-oriented measurement was needed for sugar. Therefore, it was decided to use the glycemic index.

The first step was to add specific filters required for the studies:

Article types: Clinical Trial, Controlled Clinical Trial, Randomized Controlled Trial

Species: Humans

Text availability: Free full text

After typing in "pancreatic cancer and glycemic index“, a more apparent amount of results came up.

The following graphic shows the steps and results of the research.

Literature research in PubMed:

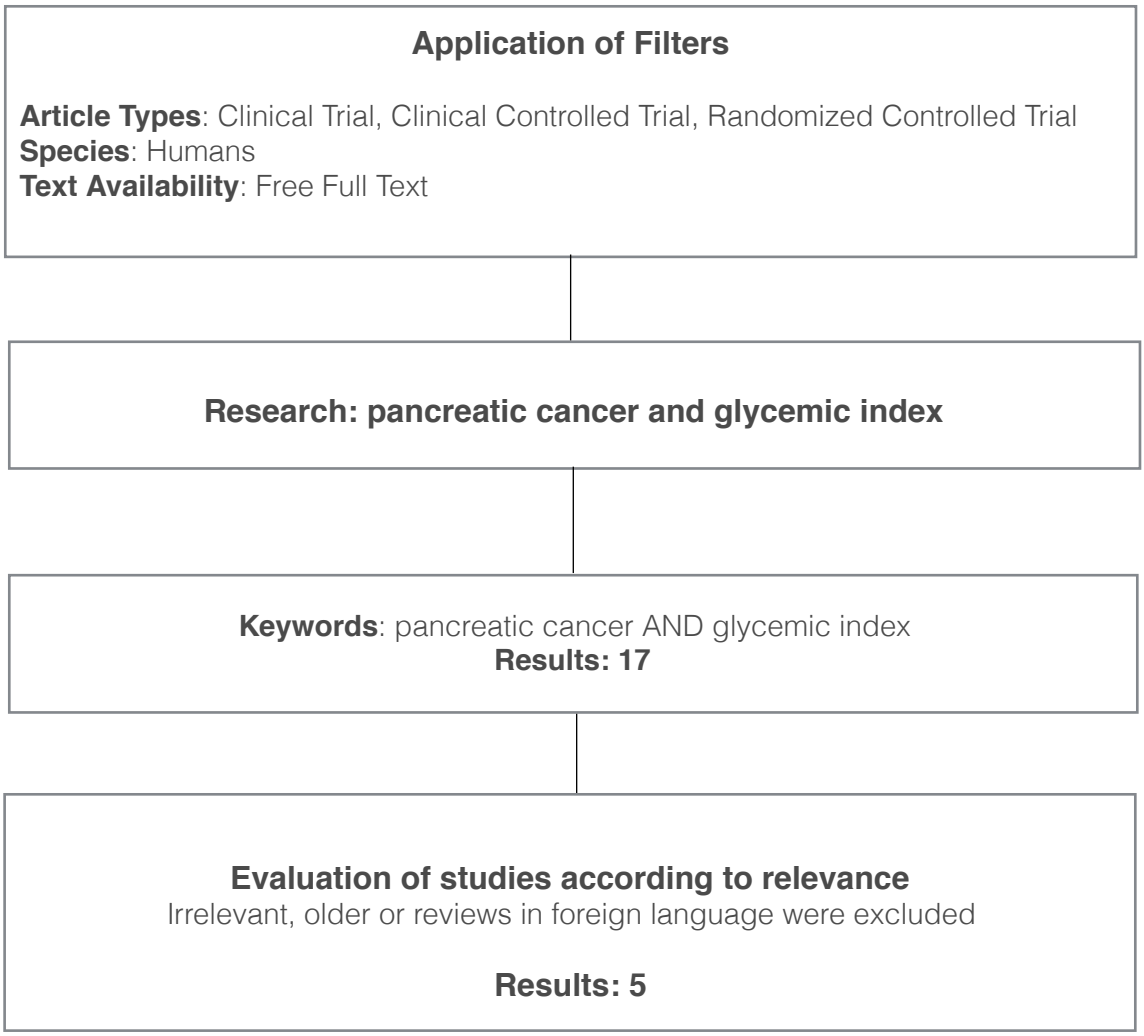

Figure 7: Sequence of literature research

The next step was to go through the titles and abstracts of all the studies and decide which were the most relevant. Three of the studies were irrelevant to the topic, one was in foreign language and two were older than 10 years. Another study was examining pancreatic cancer and diabetes which, as already mentioned, is not the focus of the present dissertation. Three studies were examining high glycemic index and its effects on cancer in general, and were thus discarded as well. The last rejected study was examining the effects of the insulin index on pancreatic cancer. Insulin index should not be confused with the glycemic index.

The remaining results were about seven studies. Two of these studies are already included in both meta-analyses found, and were hence not presented separately but mentioned synoptically within the results of one of the two.

3.3. Assessment of the studies via levels of evidence

The critical elements which form the scientific validity of most studies on PubMed is already reviewed by the Literature Selection Technical Review Committee (LSTRC) (U.S. National Library of Medicine, 2017).

However, in order to assess the studies from the research in chapter 3.2., they were compared to the evidence classification system.

The evidence classification system is an essential element of the evidence-based medicine (EBM) which helps prioritize information. It is a hierarchical system which encourages scientists to answer clinical questions through the use of the highest possible evidence level (Burns, Rohrich, Chung, 2011).

Since the present thesis is focusing on intervention/therapy and not on prognosis, the highest possible evidence level are randomized controlled trials (RCT) and the lowest are case series and expert opinions.

The levels of evidence seem to have been altered through the years in order to become more applicable and understandable.

Since the present dissertation is written in English but is part of a german degree, it was decided to translate the levels of evidence according to the guidelines of the "Deutsche Gesellschaft für Ernährung" (DGE) for prevention of chronic diseases in English.

Level	Type of study
1a	Systematic review (meta-analysis) of randomized controlled trials (RCTs)
1b	Individual RCT
1c	Non randomized/non controlled studies
2a	Systematic review (meta-analysis) of cohort studies
2b	Individual cohort study
3a	Systematic review (meta-analysis) of case-control studies
3b	Individual case-control study
4	Non analyzed studies or expert opinions

Table 2: Levels of evidence
Source: Evidenzbasierte DGE-Leitlinien zur Prävention chronischer Krankheiten, DGE 2014

During the research, articles of the highest possible evidence class were searched for. Due to the fact that the amount of studies found was very limited, all studies were used and analyzed hierarchically from greater evidence to lower as well as from older to newer.

4. Results

In this chapter, the results of the chosen studies are cited based on the hypothesis built in chapter 3.1. First, there is a table including basic information of the selected researches which deal with the topic together with some basic information about each study. Afterwards, each selected study gets described and analyzed extensively.

4.1. Study overview and analysis

The following table contains some basic information about each study: the authors and the title as well as the study design and the duration. Next to the study design, the level of evidence is listed. The number of participants in each study is listed and divided by sex.

No RCTs were found but three cohort studies instead as well as two meta-analyses of cohort studies.

As already mentioned, the studies are listed according to their level of evidence from higher to lower as well as chronologically from older to more recent. Most of the studies about pancreatic cancer that are included in the two meta-analyses of the research are the same. The two meta-analyses only differ from two studies and were therefore analyzed separately. These two studies came up as results during the original research and have therefore been synoptically mentioned and described in the second meta-analysis of Mulholland et al. (2009).

Authors	Studies	Study design and evidence class	Duration	Participants (n)
Gnagnarella et al. 2008	Glycemic index, glycemic load, and cancer risk: a meta-analysis	meta-analysis of cohort studies and case-control studies, 2a	multiple	multiple
Mulholland et al. 2009	Glycemic index, glycemic load, and risk of digestive tract neoplasms: a systematic review and meta-analysis	clinical review and meta-analysis, 2a	multiple	multiple
Jiao et al. 2010	Glycemic index, carbohydrates, glycemic load, and the risk of pancreatic cancer in a prospective cohort study	prospective cohort study,2b	8 years	280,542 men 201,820 women
Simon et al. 2010	Glycemic index, glycemic load, and the risk of pancreatic cancer among postmenopausal women in the women's health initiative observational study and clinical trial	observational study and clinical trial, 2b	8 years	161,809 postmenopausal women
Meinhold et al. 2010	Available carbohydrates, glycemic load, and pancreatic cancer: Is there a link?	prospective cohort study,2b	9 years	109,175 men and women

Table 3: Overview of the results

Gnagnarella et al. (2008)

This meta-analysis investigates the connection of GI and GL with several cancer types. It analyzes the scientific standing point up until 2007 through 39 cohort, case-control and cross sectional studies found through the databases PubMed, Embase and Web of Science. It was marked as 2a, since for pancreatic cancer, the analyzed studies were only cohort studies and no case-control studies.

In all analyzed studies, the participants had filled out food frequency questionnaires (FFQ). Along with the portion sizes, and with the help of the national food-composition tables, the usual dietary intake of the participants had been measured. In order to assess the GI and GL quota, the researchers of the original studies had used various kinds of international tables.

Results: Five studies have examined the connection of GI and GL with pancreatic cancer. The participants had been divided into quintiles according to their GI and GL measures. The results of the research were presented in a forest plot containing the relative ratios (RR) of the lowest versus the highest quintile as well as 95% confidence interval (95%CI). Unlike other types such as colorectal or endometrial cancer, which showed positive association, no association was found for pancreatic cancer.

GI: RR= 1.11

GL: RR=1.00

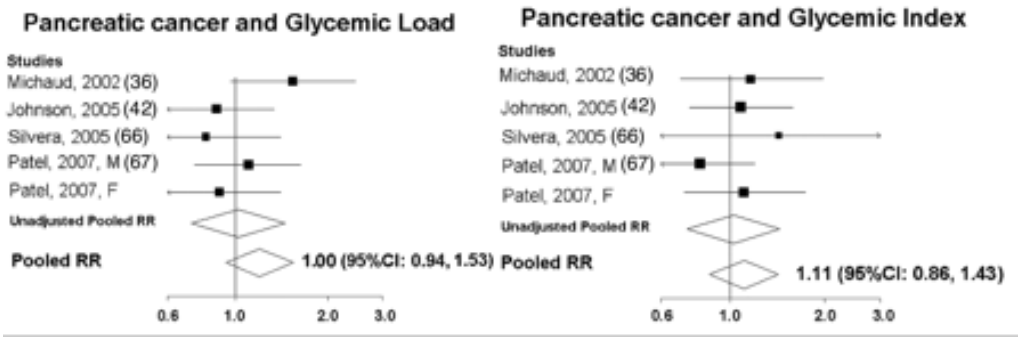

Figure 8: Forest plot of GI and GL and pancreatic cancer risk

Mulholland et al. (2009)

This meta-analysis compares high GI and GL with colorectal and pancreatic cancers after gathering information from studies published until 2009. The analyzed studies

were found through Ovid Medline and Embase databases. Reviews and animal studies were excluded. The meta-analysis includes 48 studies, of which n=6 are prospective cohort studies and describe the correlation between pancreatic cancer and GI and GL. Most cohorts were in north America and one in Europe. Only three of the studies included men. Risk factors such as age, smoking and energy intake were standardized whereas in most studies diabetes was regarded as a disturbance factor due its relevance both to cancer as well as high GI and GL.

Most of the studies included in the meta-analysis seem to be cohort studies. Two of the studies were also found during research. One (**Nöthlings et al. 2007**) is a multiethnic cohort study conducted in Los Angeles and Hawaii. It includes people of African-American, Japanese-American, Latino, Native-Hawaiian and white lineal descent and investigates the effects of specific lifestyle factors on cancer. Participants were over 215,000 men and women in the age of 45-75 at the beginning of the study. The other one (**Heinen et al. 2008**) is the Netherlands Cohort Study (NLCS) which lasted 13.3 years. The NLCS started in September 1986 including 58,279 men and 62,573 women aged 55-69 years and ended in December 1999.

In brief, after reading the two studies included in this meta-analysis, it becomes apparent, they both have a very similar set up. At baseline, participants fill out a food frequency questionnaire (FFQ) including general information about their weight, height, health, diet and lifestyle. Participants with dubious information and inconsistent data about their diet or body mass index (BMI), or ones with history of cancer are automatically excluded from the study. The studies lasted for many years with annual follow ups. Pancreatic cancer cases are identified either through telephone or email correspondence or even death. By the end of the study participants are divided into smaller groups, quintiles, according to their GI and GL measures. The quintiles are then compared with each other, the highest with the lowest in order to come up with any results.

The **results** as shown in figure 7 and 8, showed no significant connection between high GI or GL with pancreatic cancer risk:

GI: RR=0.99

GL: RR=1.01

There was only little evidence of heterogeneity of estimates and the results did not change even when specific individuals were moved or when the female-only studies

were examined. Unfortunately, there were no sufficient data to conduct an analysis only on the male participants.

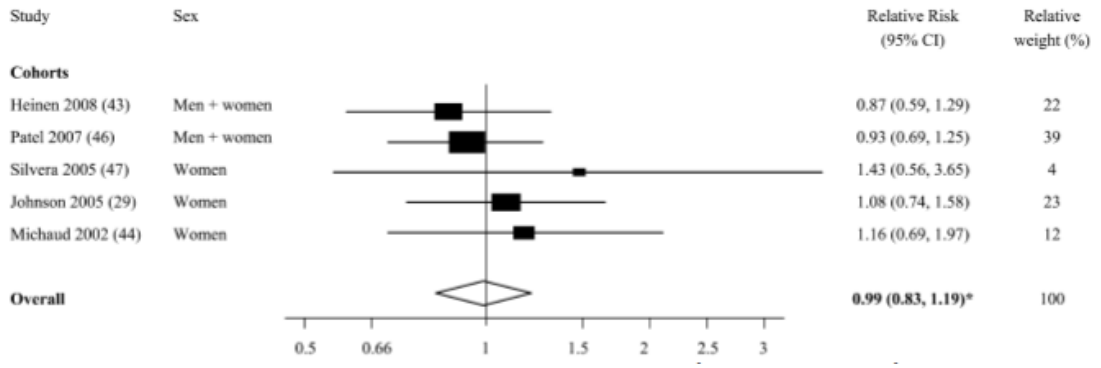

Fig. 9: Forest plot of glycemic index and pancreatic cancer risk

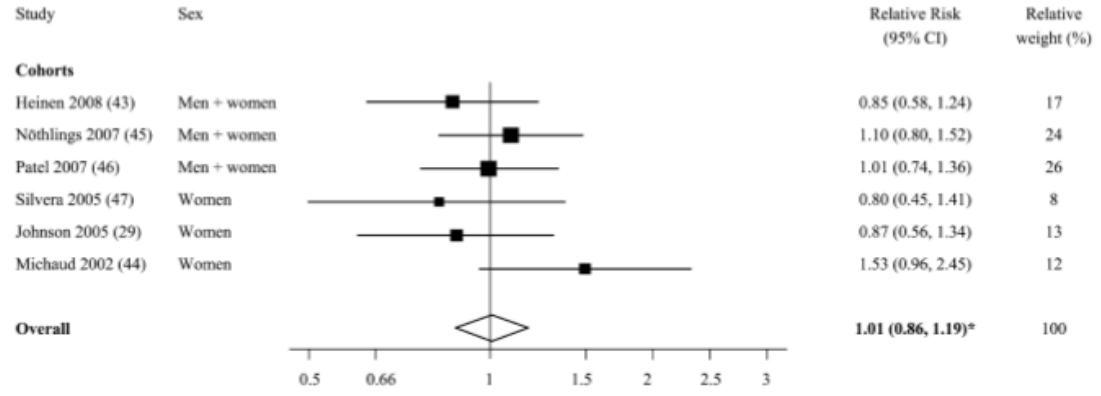

Figure 10: Forest plot of glycemic load and pancreatic cancer risk

Jiao et al. (2009)

This is the largest cohort study included in this thesis. The population for this study was collected in 1995/1996 through the National Institute of Health - American Association of Retired Persons (NIH-AARP) Diet and Health Study.

A self-administered FFQ was mailed to 3.5 million members of the AARP aged between 50-71 years who lived in six U.S. states and two metropolitan areas. Although more than 600,000 questionnaires were returned, 482,362 were finally included in the study due to demographic reasons as well as other reasons such as vague responses, extreme energy intake or self-reported diabetes. The study consisted of 282,262 men and 201,820 women. The duration of the study was one year after the FFQ distribution until

diagnosis of pancreatic cancer, death from any cause, change of residency and out of the study areas or December 31, 2003. The FFQ inquired on the demographic as well as the nutritional status of the participants. Age, sex, race, educational level, history of diabetes, BMI, smoking and physical activity were inquired. The average GI and GL as well as intake of monosaccharides, disaccharides and starch were determined through questions about portion size of 124 different food items as well as 225 food groups which were listed in an international table of glycemic index values.

The results were assessed according to quintiles of glycemic index, glycemic load, total carbohydrate intake and available carbohydrate intake, starch, disaccharides, monosaccharides and total simple sugar.

Results: By the end of the follow-up, 733 men and 418 women had been diagnosed with pancreatic cancer. In comparison to the lower quintiles, people from the higher quintiles of glycemic index were more likely to have a higher BMI, be smokers, be less active and consume more total energy, red meat and saturated fats. Nevertheless, people of higher quintiles of glycemic load had a considerably healthier lifestyle.

There was no correlation between glycemic index, glycemic load, total and available carbohydrate intake and the incidence of pancreatic cancer.

The only positive association with pancreatic cancer was found through free fructose and glucose:

fructose: RR=1.29

glucose: RR=1.35

Nevertheless, the was no association of sucrose with the disease.

Simon et al. (2010)

Simon et al. have used data from the Women's Health Initiative (WHI) cohort. The participants of this initiative were divided in two groups; one clinical trial (CT) and one observational study (OS). The CT examined the connection between a low fat diet and the prevention of breast, colorectal cancer, and coronary heart disease; hormone replacement therapy and its role in the reduction of the risk of coronary heart disease and fractures with an adverse risk of breast cancer as a possible outcome; and calcium and vitamin D supplementation for hip and other fractures, as well as colorectal cancer.

The participants of the OS were the ones that either refused or were ineligible to take part in the CT. Based on the FFQ distributed three months prior to the beginning of the WHI, Simon et al., have derived the GI and GL values, and have formed a retrospective study, which examines the connection of sugar intake and pancreatic cancer.

The initiative included 161,809 postmenopausal women in the ages between 50-79. Through an FFQ of 122 food items, the dietary habits of the participants were assessed three months prior to their enrollment. The food questionnaire enlisted usual frequency of food intake, preparation and portion size. Physical exams, demographic, medical as well as lifestyle characteristics were provided through questionnaires. The height and weight of the participants were also measured at baseline.

Within 8 years of annual or semiannual follow up, 332 women had been identified with pancreatic cancer. The diagnosis was made after contacting the participants via telephone or mail.

A large amount of the WHI participants were excluded from this study for many reasons, such as unknown or already known history of cancer, unreliable FFQ results and extreme values of body mass index (BMI). The remaining group consisted of 139,503 non-cases and 287 cases of pancreatic cancer.

GI, GL, total carbohydrates, as well as sucrose and fructose levels were not calculated in the original study and were therefore developed for all items in the questionnaire. The data from the FFQ were later processed through Nutrition Data Systems for Research (NDSR, version 5).

According to their GI and GL levels, participants were divided into tertiles and quartiles. Specific hazard models were used in order to determine the hazard ratios (HR) and 95% confidence intervals (CI) and compare dietary factors with indicator variables. Indicator variables were age, race, income, BMI, frequency of moderate or strenuous physical activity, history of diabetes, alcohol and smoking in order to measure the exposure to risk factors and the risk of pancreatic cancer.

Due to the large sample size, $p \leq 0.01$ results were considered to be statistically significant, whereas $0.01 < p \leq 0.05$ of minimal statistical significance.

The **results** showed that there was no statistical evidence between pancreatic cancer and a diet high in carbohydrates:

- for the GI p=0.94

- for the GL p=0.31

The results were the same for women with a history of diabetes mellitus.

Meinhold et al. (2010)

In this prospective study, Meinhold et al. collected the participants of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial which investigate whether screening tests can reduce mortality for the above types of cancer. The population of the study consisted of 109,175 men and women, aged 55-74, who were collected and randomized out of one of ten US centers of the trial, between 1993 and 2004. Participants with missing or extreme BMI or total energy values were excluded as well as participants with history of any of the above mentioned types of cancer.

At the beginning of the study a baseline questionnaire about lifestyle, demographics, medical and screening history was distributed. The GI and GL were determined after the completion of the Diet History Questionnaire (DHQ) of 124 foods and supplements.

The annual follow up began after the completion of both questionnaires and ended either after pancreatic cancer diagnosis, death or on December 31, 2006 after a research at the National Death Index. The study population was divided into quintiles and percentiles in which the highest was compared to the lowest. The population was observed on glycemic load, glycemic index, available carbohydrate intake as well as specific carbohydrate intake (starch, sucrose, fructose) within their diet.

Results: within 9 years of follow up, 162 men and 104 women suffered from pancreatic cancer. Due to the fact that sex did not change any outcome, the results represent both male and female participants.

After comparing the highest with the lowest quintile, the results were the following: A high GI did not show a correlation with pancreatic cancer.

- GI: HR= 1.00, 95%CI= 0.69, 1.47, P_{trend}= 0.54

Nevertheless a high GL as well as the available carbohydrate intake were associated with a higher risk of pancreatic cancer.

- GL: HR=1.41 , 95%CI=0.97, 2.07, P_{trend}=0.03
- available carbohydrate intake: HR=1.56 , 95%CI=1.06, 2.30 , P_{trend}=0.004

Furthermore, with a HR of 1.55 and 95%CI of 1.06, 2.27, a positive association was found between sucrose and the risk of pancreatic cancer although P_{trend}=0.12 was not statistically significant.

After the follow up periods were divided into 3 categories (<2, 2–<4, and ≥4) and comparing the highest (90th) with the lowest (10th) percentile, the results were the following:

- GI: HR=1.08 , 95%CI=0.78, 1.49
- GL: HR=1.45 , 95%CI=1.05, 2.00
- available carbohydrate intake: HR=1.47 , 95%CI=1.05, 2.06

These results were similar to the ones of the comparing the quintiles. The association of a high GL and available carbohydrate intake was stronger in the first 2 years of follow up, reduced in the time bracket between 2 to 4 years and none after 4 years.

5. Discussion

In this chapter the results of the research are discussed under a more objective point of view. Researchers who conduct studies based on specific assumptions are often biased and fail to interpret their results impartially. Therefore, the results of the five studies which were analyzed in the previous chapter, as well as the validity of the methods used for the present dissertation will be discussed. The objective of this thesis is to examine the possibility of a connection between a diet with a high GI and the ignition of pancreatic cancer based on the hypothesis made in chapter 3.1..

The first part of the discussion includes the general limitations and validity of the present research. Since the studies found in the research follow a very similar pattern, the collective points of discussion will be argued afterwards. Eventually, the discussion emphasizes on each study individually.

Unfortunately, by using these keywords, only a small variety of studies was found. Therefore, all relevant studies, that were found, were analyzed. The studies include two meta-analyses of cohort studies which present the scientific standing point up until 2008 and 2009, and three cohort studies published in 2010. Additionally, it would have been

preferred to use more recent studies, not older than five years. The age of these results demonstrates the most major limitation of the present research, since the possible scientific advancements on the topic, that might have taken place in the meantime are disregarded.

The absence of recent studies does not imply a conclusion on the topic due to negative results but, as it will be discussed subsequently, it is assumed that scientists changed the methods of research.

To quantify sugar intake in the form of glycemic response, the present dissertation used the glycemic index. Since the GI does not include the calculation of typical serving sizes, all of the studies also measured the GL. Nevertheless, the utility of the glycemic index seems controversial.

The glycemic index is derived after studying foods in isolation. As already mentioned in chapter 2.3.1.1., it is essential to observe how carbohydrates get injected. Usually people do not eat foods in isolation but instead accompany them with several other nutrients, either at the same time, right before or right after. This is a factor which is impossible to include in FFQs and can throw off the GI and consequently the GL readings.

Another aspect which seems to have been partially disregarded by the FFQs in the studies above, is that the GI varies according to preparation, processing, as well as subtypes of specific food categories (Pi-Sunyer, 2002). Although some FFQs included preparation and processing, some subcategories, such as brown rice or whole wheat pasta, were not taken into account. Additionally, fruit consumption was often not divided between fresh or canned and the ripeness was not considered either.

Furthermore, a recent study showed that the glycemic response can vary from one person to another. According to Matthan et al. (2016), who conducted repeated randomized controlled tests on 63 individuals for 12 weeks, the blood sugar levels varied up to 20 percent in each subject each time they ate the same food in the same amount. An even greater variation was observed when the blood glucose levels were compared among individuals. In other words, the same dosage of the same food triggered different glycemic responses between the participants. Although it is understandable that GI illustrates an average figure, a variation of 20% seems too high.

The unreliability of the glycemic index might also be the answer of the limited variety of recent studies found in this research. As already mentioned, the latest study, that was found, was conducted in 2010. Since then, no other research using the glycemic index was found. This leads to the assumption that a growing skepticism about the reliability of the GI might have led researchers to cease using it as a measurement for their studies.

Regarding the validity of the studies in this research, no randomized controlled trials were found, but instead, only cohort studies which are not regarded as the highest level of evidence. This might lead to the assumption that the evidence is not strong enough to come to a certain conclusion. RCTs are of such high validity due to their design which eliminates bias (Kabisch et al. 2011). However, in defense of the results found through the research, RCTs would be very difficult to apply on this topic. As already mentioned in the theoretical part of the dissertation, cancer is usually multifactorial and does not develop of a short-term dose-response relationship. According to the existing scientific status quo, cancer is a genetic disease acquired through heritage or lifestyle factors and gets usually demonstrated in an advanced stage of life. It is also assumed that it can often be a result of genetical predisposition in combination with at least one lifestyle factor. This combination makes the research considerably more complicated. In order thus to observe any apparent results through an RCT, a high dosage of glucose would have to be supplemented for a time frame of many years. Participants would have to be very committed and follow the same instructions of physical activity and nutrition, and further exposures to risk factors would be almost impossible to trail.
Furthermore, it is a matter of scientific ethics. It is unlikely to find participants who will endure the above in risk of acquiring cancer and even less probable for people who have already acquired the disease, to follow a diet high in sugar or no sugar at all. Since the focus of RCTs is intervention, participants take part in trials in order to find the cure and not the disease.

The above leads to the conclusion that, cohort studies might seem more applicable for this topic, since, due to their design, they focus on dietary habits acquired through many years. However, the validity of the studies presented in this dissertation remains questionable.

With only very few exceptions, most of the results between the studies have come to similar conclusions. The results show no connection between a nutrition with a high GI or GL and pancreatic cancer. Nevertheless, after examining each study individually, several collective arguments regarding the validity as well as execution of the studies above came into focus.

As a principal, cohort studies, which measure nutritional facts, rely on FFQs in order to come up with certain results. However, this method is not always very objective since participants might alter the actual facts as a mistake of recall. Considering the fact that the FFQs focus on assessing the average weekly consumption of a variety of foods, the amounts stated might be often wrong due to false recall or calculations.

Furthermore, most of the above studies seem to take into consideration all parameters which could throw off the results, such as demographics, smoking, diabetes and obesity. However, without a single exception, these cohort studies focus on the dietary habits of people in the ages between 50-75 years. Having accessed the time in life showing the most incidence in cancer, the participants take part in the studies without previous screening for this specific disease. One can argue that, there is no annual screening available for this form of cancer. Nevertheless, the lack of it at the beginning of the studies, as well as during follow-up, makes it impossible to value the timing between food intake and pancreatic cancer ignition. According to Yachida et al. (2010), who have studied the annual progression of pancreatic cancer, more than 10 years can pass between the first mutation in the pancreas and the development of cancer cells. Moreover, the same source states that approx. another six years can pass between the creation of the cancer cell and its ability to invade neighboring organs. Since there seems to be a wide time gap between the acquiring of pancreatic cancer and its manifestation, it becomes very difficult to determine the role of nutrition as well as the extend of it without screening. Considering that the cohorts lasted approx. 8-9 years, it is highly possible that several participants might have had cancer even before entering the study. Furthermore, even though it is not clear whether the Warburg effect is demonstrated in all types of cancer, it could also be hypothesized that, through the lack of awareness of the disease and the simultaneous consumption of sugar, the medical condition might have even deteriorated.

The lack of screening mechanisms is a major limitation not only for the purposes of the present dissertation, but also for the purposes of any potential research connected to this

type of cancer. However, there seems to be no screening for any of the other types of cancer mentioned in the studies and the health assessment is left up to the participants.
Additionally, as it will be mentioned further on, many of the analyzed studies had originally no focus on pancreatic cancer. It seems highly ambiguous to take the results of a study that was made for specific types of cancer and implement them on another type. The study should be formed according to the needs of the specific type of cancer monitored.
As already mentioned above, participants of the studies are already in an advanced stage of life. Taking into account the theory of nutrigenomics, that the longterm environmental exposure and nutrition can accordingly restrain or promote cancer growth, it seems more suitable to conduct studies on cohorts of younger age, and continue until they reach the point in life considered to be more precarious. Even without the availability of screening mechanisms, this would at least help in the documentation of longterm nutrition patterns as well as changes and their effect. It is understandable that the long duration, the big cohorts and the continuous monitoring, are financially prohibiting, however, it seems to be the only way in order to come up with more certain results.

Another point that stands out after reading each study, is that most of the original cohort studies are not focusing primarily on pancreatic cancer. The cohorts used, are from big studies such as the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, the Women's Health Initiative and the NIH-AARP. These large studies did not originally compare nutritional facts to pancreatic cancer, or in the case of the NIH-AARP, compared many nutritional facts to many types of cancer. This leads to the assumption that, if the original study has another focus, the data used are designed to give answers to other issues. Therefore, the results might not be representative.
Even though it can be argued that the cohort studies had primarily a focus on other types of cancer and are therefore a suitable groundwork to accommodate even more types of cancer such as pancreatic, there are several factors of this disease that have to be taken into account while researching. Meinhold et al. mention that, people with pancreatic cancer often have symptoms of dyspepsia which may lead to an avoidance of fatty foods and result to a preference of foods with a higher content in carbohydrates. As a result of this, research was conducted in order to assess the validity of this

information. Several older studies mention dyspepsia as a symptom of pancreatic cancer. Even though no recent studies were found, it is a factor that ought to be taken into consideration by all studies researching pancreatic cancer.

As already mentioned above, the studies found through this research, all follow a very similar pattern. Nevertheless, regarding each study individually, several points of discussion came into focus. For each study, the percentage of follow-up was calculated, following the lead of Dettori (2011) as well as Howe et al. (2016). Since the studies included in the meta-analyses were not all accessible, only the follow-up rates for the two accessible ones were measured.

The meta-analysis of **Gnagnarella et al. (2008)** go through case-control and cross sectional studies. The authors of the study have evaluated 39 different studies and calculated the GI and GL since the original reports did not use these readings. However, it focuses on different types of cancer and does not show the same emphasis on pancreatic cancer as on types of cancer with a positive association to GI and GL.

In the meta-analysis of **Mulholland et al. (2009)**, six studies examine the connection between high GI and GL and pancreatic cancer. The conclusion of the meta-analysis is that there is no connection between the two. Nevertheless, through the research two of the included studies were found and examined more closely. Both Nöthlings et al. (2007) and Heinen et al. (2008) focus not only on the connection between pancreatic cancer and GI and GL readings, but also on mono- and disaccharide intake. Although Nöthings et al. (2007) shows so association between the disease and GI or GL, a correlation is shown with fructose. The research comes to the conclusion that fructose is associated with 37-42% of pancreatic cancer risk.

Another point regarding the two meta-analyses above, is that, half or more of the studies included were conducting research only on women. From the theoretical part of this dissertation it became clear that men are slightly more incidental. Therefore, the choice of women based studies becomes questionable.

Jiao et al. (2009) have used data from the NIH-AARP. After calculating the percentage of follow-up, the results were 85%. This percentage is considered satisfactory according to the source stated above. The results of the study found a positive association with fructose and glucose consumption, the association to sucrose was negative. Nevertheless, as already mentioned above, it needs to be taken into account that

participants might have had pancreatic cancer which had not been manifested even at the start of the study. The FFQs were mailed to AARP members who then mailed them back. It becomes apparent that no physical screening was done at the beginning of the study nor at follow-up and its results can thus be assumed as highly ambiguous.

Even though **Simon et al. (2010)** is a well established research, it is a retrospective cohort focusing solely on female population. The researchers of this study have used data from the Women's Health Initiative and have found no connection between pancreatic cancer and high GI, GL, carbohydrates, fructose or sucrose. The follow-up rate in this research was 86%. Nevertheless, after careful reading of the design of the WHI, no physical screening was mentioned. Once again, the lack of screening can lead to misleading results. Another critic point on this research is that as already mentioned in the theoretical part of the dissertation, men have a slight higher chance of acquiring the disease than women. It would be thus preferable and more accurate to conduct studies including both sexes.

Lastly, **Meinhold et al. (2010)** took their data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. This study has a very satisfactory follow-up rate of 97% and has come to the conclusions that pancreatic cancer risk is associated with high glycemic load, available carbohydrates and sucrose. However, as mentioned above, the focus of the original study was not pancreatic cancer. Although participants were screened before, the screenings were done for those specific types of cancer. This leads to the conclusion that the cohort had not undergone any prior screening on pancreatic cancer and thus the results cannot be certain since their pancreatic cancer status had not been determined at baseline.

6. Conclusion

Although it is considered a fact that nutrition patterns have shifted and that refined carbohydrates have taken the place of more complex carbohydrates, it remains doubtful whether sugar consumption can be regarded as a risk factor for pancreatic cancer. It still remains uncertain whether the metabolic alteration described by Warburg is a result of a mutated gene or whether an increased consumption of refined carbohydrates can through the years be regarded as a risk factor for the ignition of pancreatic cancer. Fact

remains that pancreatic cancer is mainly a result of age. Unfortunately, through this dissertation a contribution of sugar to the disease could not be demonstrated.

In the meanwhile, although cancer research and treatment have made big improvements within the past decades, improvements on pancreatic cancer seem to have become stagnant. The disease remains as one the most fatal types of cancer with a very grim future prognosis. Although more rare than other types, the prognostic number of new cases for 2018 almost collides with the number of deaths expected (ACS, 2018), which has been the case according to a graphic of the National Cancer Institute for many decades (NIH, 2015). These figures show a dire need for early detection mechanisms as well as improvements in treatment.

Since pancreatic cancer usually gets manifested at more advanced stages, the absence of early detection mechanisms has also been evident through the results of the research. In the examined studies, the absence of screening of the participants at the beginning of the studies leads to doubtful results, since it remains unclear whether participants had acquired the disease before entering. Additionally, since pancreatic cancer gets detected when advanced, it is difficult to measure the contribution of sugar and whether a high GI diet had any effects on pancreatic cancer ignition, deterioration or no effects at all.

The present dissertation has come to the conclusion that there is not enough evidence linking a nutrition high on refined carbohydrates to pancreatic cancer. The hypothesis formed, of a connection between a diet with a high GI and the ignition of pancreatic cancer, could not get confirmed. First of all, the number of studies found are not enough to come to a more certain conclusion. Additionally, there have not been any new studies regarding the matter since nine years. Furthermore, the choice of GI and GL as a quantification of sugar intake does not seem accurate, since these readings show severe ambiguity. However, a few studies show a connection with fructose and glucose consumption. Therefore further research on the topic is recommended.

For future observation and research, it would be recommended to conduct cohort studies solely focusing on pancreatic cancer. The population of the cohort should be approx. 30-40 years old and be screened and followed-up until it reaches the age considered more perilous. These studies should be lasting for a longer period of time than the ones above, measuring solely mono- and disaccharide intake as well as physical activity. Additionally, the examined cohort should be as large as possible, always according to budget. Large cohorts from multiple cultural and socioeconomic classes are

recommended. When analyzing the results the cohort should be divided between people with pancreatic cancer incidents in the family and those with no previous history. This would help narrow down the group of people with a higher potential of inheriting the disease, and compare their nutritional behavior with the one of people less likely to acquire the disease. Monitoring of nutritional behavior at an earlier stage of life and regular follow-up, would then allow the documentation of changes in nutrition as well as physical activity and their effects on a subgroup with a higher potential of acquiring the disease.

Another approach for future observation would be through the help of genetic testing. The advancements in genetic testing can help encode genes that can lead to pancreatic cancer later in life. This could help track down people that carry these genes as well as people with no such occurrence. These cohorts could then be monitored on their dietary patterns from an early stage in life on to the stage considered more precarious.

A meta-analysis of suchlike studies could then provide more conclusive results on the contribution of sugar as well as possible information about recommended dosage.

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Glossary

adenosine triphosphate (ATP)	main energy form in cells; drives core processes in body
aerobic respiration	production of cellular energy involving oxygen; produces carbon dioxide and water
alcohol	organic compound (contains carbon) with a hydroxyl (-OH) functional group
anaerobic respiration	production of cellular energy without the involvement of oxygen; produces alcohol and lactic acid
apoptosis	cell death
biopsy	examination of tissue removed from living body
buccal cavity	oral cavity / mouth cavity
carcinogenesis	formation of cancer
carcinoid	type of neuroendocrine tumor
cellulose	complex carbohydrate / polysaccharide with a linear chain of glucose units
deoxyribonucleid acid (DNA)	molecule carrying genetic instructions
duodenum	first section of the small intestine
epithelial cells	types of cell that line the surfaces of the organs
gastrointestinal tract (GI)	mouth, esophagus, stomach, intestines
gene expression	information of a gene used in the synthesis of a gene product
glycemic response	effect of a meal on blood sugar after consumption
glycosidic bond	bond that connects carbohydrate molecule to another group, carbohydrate or not
hydrolysis	molecule bond break through water
lactate	lactic acid; forms when body breaks down carbohydrates
nutrigenomics/nutrigenetics	focus on the relationship between human genes and nutrition
oxidative phosphorylation (OxPhos)	metabolic pathway; cells use enzymes to oxidize nutrients and release energy to produce adenosine triphosphate (ATP)
pyruvate	made from glucose through glycolysis; supplies energy to cells through citric acid cycle in presence of oxygen or lactate in lack of oxygen
tricarboxylic acid cycle (TCA)	series of chemical reactions used by all aerobic organisms in order to release stored energy derived from carbohydrates, proteins and fats

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