AN EXAMINATION OF CURRENT RESEARCH EXPLORING THE RELATIONSHIP BETWEEN OBESITY AND HEPATOCELLULAR CARCINOMA

by

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A THESIS

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Alan J. Kelly

Over two thirds of US adults were classified as overweight in 2012. Comorbidities associated with obesity, including hepatocellular carcinoma, (HCC) are pervasive in the US population. Due to the current high prevalence of obesity, a considerable amount of research is actively being done to understand the pathophysiology of such diseases.

My intention for this thesis project is to first gain a deep understanding of the complex connection between obesity and increased risk of HCC. I then wish refine my ability to communicate complicated information about these diseases, especially to an audience without a scientific background, in preparation to practice medicine as a Physician Assistant. To accomplish these goals, I will first present a literature review of recently published, peer-reviewed journal articles examining the relationship between obesity and HCC. I will then deliver a lecture, entitled "The Relationship Between Obesity and Cancer," to fellow undergraduate students in BI123, Biology of Cancer at the University of Oregon. Alan Kelly is the instructor for the course, which has approximately 190 students enrolled. The content of fifty-minute lecture is to be derived from information collected from the literature review. The lecture materials and DVD recording are to be included in this thesis.

Acknowledgements

I would like to thank Dr. Alan J. Kelly, my thesis advisor, for helping me to fully examine the Relationship between Obesity and Hepatocellular Carcinoma and consider the various perspectives and contexts related to this subject matter. Your guidance and support has been invaluable for the last four years. I would also like to thank my parents and brother for their endless encouragement through this strenuous but rewarding process.

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List of Accompanying Materials

Biology of Cancer 123 Lecture Disk (50 min)

Introduction

In 2012 over two thirds of US adults aged 20 years or older had a Body Mass Index (BMI) at or above 25, rendering them overweight or obese (Ogden). Widespread obesity in America is a relatively new phenomenon; in a thirty-year period, from 1971 to 2001, there was a 30% increase in adult obesity, generally defined as a BMI at or above 30 (Vasan). In 2005, obesity surpassed cigarette smoking as the most common preventable cause of early mortality (Larson).

Medical conditions associated with obesity have shown concomitant increases in prevalence. Obese individuals have a higher propensity to develop a host of simultaneous chronic medical conditions, or comorbidities, including cardiovascular disease, metabolic conditions such as type II diabetes, hypertension, infertility, chronic pain, gastrointestinal disease, various pathologies of the liver, and numerous cancers (DynaMed, Bhaskaran, Renehan). Some obesity-related disorders such as atherosclerosis, hypertension, and a variety of conditions related to metabolism, can be asymptomatic in initial stages. Symptoms arising from these conditions commonly manifest in only advanced phases when they are often more difficult to treat.

In particular, non-alcoholic simple steatosis (SS) of the liver, an obesity-related complication, is common but difficult to diagnose and may progress to more severe liver pathologies (Tucker). SS is characterized by abnormal accumulation of fat in liver cells, hepatocytes, which is asymptomatic in early stages. It is estimated that 20% or more of all American adults are living with SS, but prevalence increases to 70 – 80% in obese populations. Scientists expect rates of SS incidence to continue to rise (Lall). Prolonged fat accumulation in the liver due to SS can lead to non-alcoholic fatty liver

disease (NAFLD), which encompasses a more severe series of liver pathologies, and is a known risk factor in the development of hepatocellular carcinoma (HCC), the most common cancer of the liver.

Given the current high frequency of obesity and its association with liver pathologies such as NAFLD and HCC, uncovering the mechanisms of liver disease establishment and progression has been a recent focus in research (Tucker). The purpose of this thesis is to present a literature review of recently published research articles examining the relationship between obesity and HCC. Several mechanisms that have been proposed to underlie the development of HCC as a comorbidity to obesity will be discussed.

Methods

The focus of the written portion of this thesis is to present a critical analysis of recently published, peer-reviewed journal articles examining the relationship between obesity and hepatocellular carcinoma. A literature search was performed for relevant articles published through January 2015 using PubMed. Search terms included *obesity, hepatocellular carcinoma, Non-alcoholic Fatty Liver Disease,* and *cirrhosis.* Approximately 138 articles published within the dates of interest were reviewed. 15 articles were selected for thorough analysis. Priority was given to articles discussing well-executed studies most relevant to the topic. The results of these studies are discussed in a systematic review. The analysis aims to summarize what is known and what remains unknown about the relationship between obesity and hepatocellular carcinoma.

Background Information

Anatomy and Basic Functions of the Liver

The liver is the largest internal organ of the body, positioned in the upper right quadrant of the abdominal cavity, inferior to the diaphragm (Guyton 873). The liver is a discrete organ but serves numerous critical roles including regulation of multiple metabolic functions, storage of blood and nutrients, blood purification, cholesterol synthesis, and production of bile and coagulation factors (Guyton 873). The liver plays a key role in carbohydrate metabolism and blood glucose regulation to assure a steady supply of glucose to the brain. At rest, blood glucose concentration dictates whether glucose reserves are synthesized or degraded in the liver. This activity is mediated by glucose flux through enzymatic pathways that are controlled by hormone signaling to maintain a suitable range of blood sugar (Voet 772). In addition to regulating carbohydrate metabolism, the liver plays a critical role in processing ingested fats. Liver cells are rich in mitochondria, which are cellular components responsible for generating energy through a particular type of metabolism that requires oxygen. This metabolic process, termed oxidative phosphorylation, uses fatty acids liberated from liver cells to generate energy. If energy demand is low, the liver forms excess ingested fatty acids into triglycerols. The latter are transported to adipose tissue, or fat, for storage via lipoproteins, units of lipid and protein molecules that allow non-soluble fat molecules to travel through the body's aqueous environment (Voet 773). Another feature of the liver related to metabolism is its capacity to store vitamins and minerals, such as vitamin D and iron.

The anatomy of liver circulation is critical to the blood filtering function of the liver. Chemical digestion of food in the small intestine allows nutrients to be absorbed into capillaries adjacent to digestive tract walls. The nutrient-rich, semi-oxygenated blood flows through one main vein for entry into the liver. This main vein divides into smaller and smaller diameter vessels in the liver until each liver cell is positioned adjacently to a capillary (Moore, 237). Liver tissue is highly vascularized as a result of this organization. Blood processed by liver cells undergoes purification by macrophages, white blood cells that function as part of the immune system to remove bacteria of gut origin. The liver also processes and clears pharmaceuticals, toxins, and retired red blood cells. Blood filtered by liver cells collects into central veins and eventually flows into the hepatic veins and ultimately into the inferior vena cava, which supplies de-oxygenated blood to the right atrium of the heart.

Formation of bile is another important function of the liver. Bile is stored in the gallbladder, a relatively small sac-like organ that sits just below the liver. Bile is released into the small intestine upon consumption of meals with high fat content and acts as an emulsifying agent; it allows fatty molecules to easily move through aqueous environments, which subsequently enables breakdown of dietary fat. These lipids are then able to form into lipoprotein assemblies as an initial step in triglyceride distribution to tissues of the body. This process is related to regulation of cholesterol levels, another vital function of the liver. Liver cells contain enzymes necessary for synthesis of new cholesterol if too little is available in the diet. Distribution of newly synthesized cholesterol or cholesterol derived from the diet is regulated by the liver as is the excretion of cholesterol into the digestive tract via incorporation into bile.

The liver can also act as a reservoir for blood under situations of backpressure from the heart. Healthy liver tissue can expand so that up to one extra liter of blood can be stored, beyond the nearly half liter of blood volume typically held in the liver in adults (Guyton 838).

A well-functioning liver is vital to health as it is responsible for many bodily processes occurring continuously and simultaneously. The multifunctional nature of the liver becomes apparent when the liver malfunctions (Guyton 837). Liver damage often alters many processes, which can result in a combination of different symptoms. This has major implications for individuals with liver damage.

Obesity: Classification and Associated Complications

Obesity is a medical condition that indicates excess fat accumulation, which may have adverse effects on health. Obesity most often develops as a result of chronic excess caloric intake and lack of physical activity. It is well established that a high BMI is associated with an increased risk for numerous cancers including cancers of the liver (Bhaskaran, Renehan).

Body mass index (BMI) is a ratio of height and weight used as a clinical tool to assess body fat and classify individuals as underweight, normal weight, overweight, and obese. The formula for BMI is $\frac{weight\ (kg)}{height^2\ (m^2)}$. Individuals with a BMI at or above 25 are classified as overweight. A BMI at or above 30 is considered obese (USA). BMI does not take body composition into account, and thus may misclassify individuals. Various tissue types have unique densities and therefore have different weights per unit volume. For example, adipose tissue is less dense relative to lean muscle. Therefore, individuals

who have a high muscle to fat ratio, like bodybuilders, are typically heavy relative to their height and may therefore be classified as overweight by BMI. Other simple methods of assessing obesity are used, such as height to waist circumference ratio. However, due to its ease of use and general accuracy, BMI remains a widely used figure in research and clinical settings.

Discussion

Obesity and Nonalcoholic Fatty Liver Disease

Non-Alcoholic Fatty Liver Disease (NAFLD) is a term encompassing a group of conditions related to the abnormal accumulation of lipids within small vessels of the liver, unrelated to increased alcohol consumption (Lall). Obesity along with other metabolism-related conditions such as diabetes and metabolic syndrome have been found to be risk factors for NAFLD. The term NAFLD includes any stage in this pattern of associated conditions: nonalcoholic simple steatosis (SS), nonalcoholic steatohepatitis (NASH), chronic liver fibrosis, and liver cirrhosis. Because it describes such a wide spectrum of diseases, NAFLD has appropriately been described as "the lynchpin between steatosis and cirrhosis in the spectrum of nonalcoholic fatty liver disorders" (Farrell, Lall).

Obesity and NAFLD are strongly correlated; 70 – 80% of obese individuals have the first stage of NAFLD (Lall). Liver cells processing large quantities free fatty acids over long periods of time eventually cannot maintain the level of activity required and start to accumulate abnormally high levels of intracellular triglycerides. This process can eventually result in the development of SS, the abnormal accumulation of excess triglycerides and other fats in liver cells.

The progression from SS to NASH, inflammation of the liver due to fat accumulation, has a generally accepted mechanism, but many details remain unclear. When levels of triglycerides are consumed that chronically exceed demand by cellular processes, fat accumulates in deposits around internal organs and under the skin. Large stores of adipose tissue in obese individuals release multiple signals that change the

metabolism of fats and carbohydrates, which increases the rate of fat accumulation in the liver (Rinella). SS can progress until excessive levels of triglycerides accumulate within liver cells and cause the release of oxidized lipids, which then induces an inflammatory response. As fat continues to accumulate, the inflammation cascade fails to cease, damaging liver cells. If left unresolved, acute NASH can develop, which can have significant consequences on liver function. When liver cells sustain long-term inflammation from NASH, liver tissue eventually becomes scarred and hardened, causing fibrosis. The progression of the NAFLD spectrum is dynamic and largely reversible in early stages; however when liver fibrosis progresses further to liver cirrhosis, damage to the liver is irreversible. As the degree of liver cirrhosis increases in patients, the poorer their prognosis becomes. NAFLD initiated cirrhosis can be fatal and is predicted to become the most frequent cause of liver transplant (Rinella).

Obesity is not the only risk factor in the development of liver pathology. Many medical conditions are associated with liver inflammation and cirrhosis, such as viral hepatitis. There is also evidence for a heritable factor for the development of NAFLD. Small differences in genes encoding proteins important in metabolic pathways of lipids are associated with a genetic predisposition to the development of NAFLD (Agrawal).

Diagnosis of Nonalcoholic Fatty Liver Disease

Diagnosing NAFLD poses challenges, as disease progression is dynamic and patients tend to be asymptomatic, especially in early stages. Early symptoms are usually vague, such as abdominal discomfort, fatigue, dyspepsia and nausea. Liver biopsy is the only method used to definitively diagnose the stage of NAFLD. However, there are several less invasive methods available that, when combined, can yield an accurate

diagnosis. These techniques include various biomarkers, levels of particular molecules and enzymes derived from blood chemistry, and several forms of imaging. Predictive assays are also used, which are equations that take multiple variables such as BMI and biomarker levels into account to yield a value that indicates a patient's risk for a particular stage of NAFLD.

Clinicians can also test multiple biomarkers simultaneously in a liver function panel. Levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), two biomarkers tested in liver fibrosis panels, are commonly elevated in NAFLD. These two enzymes are normally found at highest concentrations in the liver and in low concentrations in the blood. The liver releases these proteins into the blood upon sustaining damage due to fatty accumulation and cirrhosis, so a finding of high ALT and AST in the blood suggests possible NAFLD. Though ALT levels are normally elevated in patients with NAFLD, the correlation between high AST and NAFLD is weak. Gamma glutamyl transferase (GGT) is another enzyme that is commonly tested as an indicator of NAFLD in liver function panels, but is elevated in only approximately half of individuals with NAFLD (Oliviera 3). Although some biomarker levels are weakly correlated with NAFLD, if multiple abnormal tests results are observed in a liver function panel, it may serve as useful diagnostic information. Biomarkers also enable clinicians to observe levels of particular indicators over time. For example, one commonly used guideline states that if AST and ALT levels are elevated by 1.5 times normal levels for over six months, clinicians may elect to perform a liver biopsy for physical evidence to diagnose NAFLD. Biomarkers alone are not definitive; liver

function tests are sometimes found to be completely normal in individuals with early stages of NAFLD (Agrawal).

Several forms of imaging are used to diagnose NAFLD including ultrasound, magnetic resonance imagining, magnetic resonance elastography, and vibration-controlled transient elastography (fibroscan). Some imaging techniques can accurately recognize differences between stages of SS and steatohepatitis. Fibroscan imaging has been shown to accurately identify and distinguish fibrosis and cirrhosis of the liver (Rinella). Fibroscan measures the speed of waves moving through liver tissue, which can give insight into the stage of fibrosis (Oliviera 3). Ultrasound sensitivity decreases with increasing BMI, and thus obese populations can be under-diagnosed (Oliviera 3). The combination of new imaging techniques with blood chemistry biomarkers improves the accuracy of NAFLD diagnosis.

Predictive assays are tools employed to assess the risk of NAFLD. The Fatty Liver Index, NAFLD fibrosis score, and NAFLD activity score are examples of predictive assays used to assess risk. These calculations bring together a number of different values from a patient's chart such as BMI, ALT and ALS levels, and age in a calculation that can estimate the risk of NAFLD. However, there is not enough evidence to prove that the latest assay models are accurate. The NFS score has not yet been approved as a diagnostic tool of NAFLD, although use of this value as an indicator of liver fibrosis has been suggested.

Liver biopsy is the most definitive method to assess liver pathology. However, liver biopsy is invasive and carries a risk for infection or other complications. Additionally, even if liver tissue is biopsied from many areas in the liver, diseased

tissue may still be missed. In sum, despite many methods available to diagnose NALFD, drawbacks of each method coupled with mild or absent symptoms associated with disease progression lead to significant under-diagnosis (Tucker).

Nonalcoholic Fatty Liver Disease and Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most prominent form of liver cancer. HCC has been described as one of the "most lethal human malignancies, due to the difficulty of early detection, chemoresistance, and radioresistance, and is characterized by active angiogenesis and metastasis, which account for rapid recurrence and poor survival (Yang)." HCC is the most common cause of death in individuals with liver cirrhosis, and its frequency is predicted to rise. A five-year study done between 2001 and 2006 saw a 3.5% increase in incidence of HCC in the United States (Dynamed).

NAFLD is a risk factor for HCC. The pathophysiology of NAFLD and cirrhosis related to hepatocellular carcinoma is complex. Multiple mechanisms have been suggested leading to the correlation. The Multiple Hits Theory posits that disease progression can be due to the collective effect of several factors including genetic, epigenetic and environmental causes (Corte). One mechanism emanating from the Multiple Hits Theory is the upregulation of peroxisome proliferator-activated receptor alpha (PPARα). Accumulation of free fatty acids in hepatocytes in NAFLD eventually leads to cell damage and release of oxidized lipids. PPARα detects the accumulation of free fatty acids and signals for enzymes to increase rate of their disposal. Chronic activation of the PPARα receptor has been demonstrated to accelerate the development of HCC (Perumpail).

Misregulation of normal cellular pathways in hepatocytes can lead to abnormal rates of cell proliferation that can eventually develop into hepatocellular carcinoma. There are many factors that can cause regulation of cellular pathways to become faulty. For example, the presence of abnormally high concentrations of growth factors, molecules that stimulate cell growth, may increase the rate of biochemical pathways that induce abnormally high cellular proliferation, which may initiate tumor growth. Additionally some cellular receptors emit constitutive signaling upon sustaining damage, which may stimulate an increase in rate of these tumorigenic pathways. Apoptosis, programmed cell death, occurs at a normal rate in cells, but damage to pathways leading to apoptosis can reduce cell death rates. This process can also contribute to increased rates of cell proliferation.

Insulin resistance is another critical mechanism in the Multiple Hits Theory of HCC development. In obese patients with NAFLD, chronic accumulation of fat in the liver has been shown to increase insulin resistance (Oliviera 8). Insulin is a peptide hormone critical to the maintenance of blood glucose levels. The pancreas releases insulin into the blood in conditions of high blood glucose, which normally allows glucose to enter liver and muscle cells for metabolism. When insulin receptors become resistant to insulin, glucose cannot enter cells. This causes glucose to accumulate to high levels in the blood, which causes the pancreas to secrete higher levels of insulin to reduce blood glucose. This results in hyperinsulinemia, high levels of insulin in the blood relative to glucose. Hyperinsulinemia causes a decrease in production of insulin-like growth factor-1 binding protein (IGFBP-1), an inhibitor of insulin-like growth factor-1 (IGF-1), in the liver. Less IGFBP-1in liver cells causes release of IGF-1. IGF-

1 receptors on liver cells activate strong anti-apoptotic, signals in the presence of IGF-1 (Weinberg, 386). Therefore, insulin resistance can lead to strong signals that inhibit programed cell death, which ultimately promotes tumorigenesis, the development of cancerous tumors.

Insulin resistance also causes the body to rely more heavily on the metabolism of fats instead of carbohydrates due to the inability of cells to uptake glucose. The liver facilitates this transition by liberating fatty acids to generate energy through a metabolic process that requires oxygen. Heavy reliance on this type of metabolism can cause an accumulation of reactive oxygen species (ROS) in liver cells, which causes hepatic oxidative stress (Oliviera). ROS can directly damage cellular components like mitochondria and DNA. Chronic low-grade inflammation can result from cellular damage due to ROS accumulation in liver cells. Chronic inflammation promotes the development of fibrosis and cirrhosis, which have been shown as major risk factors in the development of HCC.

Obesity and Hepatocellular Carcinoma

Obese individuals with a BMI at or above 30 have a four times higher risk of developing HCC over those with a BMI less than 30 (Chen). Obese individuals have a chronic low-grade inflammation response, which promotes the development of many cancer types including HCC (Perumpail). High levels of adipose tissue signal the release of proinflammatory cytokines, small proteins that signal an inflammation response. These are important for the continuation of the inflammatory response and mediating tumor-promoting functions such as inhibiting apoptosis. Chemical signals that induce inflammation are part of normal tissue healing, which promote cell growth.

Release of pro-inflammatory cytokines and activation of cancer-causing pathways are signals for cell growth and division for tissue healing, but chronically elevated levels are associated with HCC development (Perumpail). High levels of adipose tissue in obese individuals also elevate levels of leptin, a hormone that regulates the body's level of excess fat by inducing the feeling of satiety. High leptin levels contribute to the inflammatory response and may promote the growth of new blood vessels, which is a critical process to tumor development.

Another proposed mechanism that may contribute to the progression HCC is the effect of obesity on gut bacterial flora. Obesity has been shown to cause overgrowth of gut bacteria and a simultaneous increase in permeability of intestinal wall cells. This imbalance causes a higher concentration of bacteria to enter liver circulation. Increased gut bacteria can overwhelm the filtration mechanisms of hepatocytes, which can contribute to chronic inflammation and fibrosis (Corte).

Prevention and Treatments

Currently there are no FDA-approved drugs available to treat nonalcoholic steatosis. Two pharmaceuticals aimed at treating NAFLD have been tested in clinical trials; however, both were effective in fewer than 50% of the participants (Rinella). Probiotics and vitamin E supplements have been suggested to help slow the progression of NAFLD, but there is no evidence that demonstrates a benefit.

Lifestyle modifications designed to reduce risk factors of developing NAFLD are the main way clinicians manage at-risk patients. Weight loss is extremely helpful to diminishing the risk of developing NAFLD, hepatocellular carcinoma, and other cancers. Multiple studies have shown that restricting calories regardless of diet

composition has decreased the risk of more severe conditions like cirrhosis and HCC (Agarwal). These studies also report that the loss of 3-5% of body weight in obese persons can reverse SS. Later stages of NAFLD that involve fibrosis and cirrhosis require the loss of more than 5% of body weight to demonstrate significant improvement. Weigh loss has also been shown to decrease levels of inflammatory cytokines, which reduce chronic inflammation and risk of HCC (Perumpail). Exercise may improve liver function independent of weight loss by normalizing liver enzyme levels and preventing insulin resistance (Oliviera 8). Bariatric surgery is cited frequently as an option to treat NAFLD. Individuals who underwent bariatric surgery as a means of weight loss showed improvement in liver histology even in cases of advanced fibrosis (Corte 70).

Implications

The connection between obesity and hepatocellular carcinoma is complex, and many details have yet to be determined. However researchers agree on some basic pathways that link the two medical conditions. The Multiple Hits Theory proposes several pathways that contribute to disease progression, which is the most accurate and widely agreed upon model for HCC development among researchers. Chronic inflammation and insulin resistance in obese individuals appear to contribute to the development of HCC. There is a high likelihood that obese individuals exist somewhere on the spectrum on NAFLD, which is another strong indicator of risk for developing HCC.

There is an ongoing discussion among clinicians on the challenges that come with diagnosing individuals on the spectrum NAFLD. Healthcare providers have limited tools for diagnosis and treatment of NAFLD. Studies agree that encouraging lifestyle changes in patients is the most widely practiced method to prevent NAFLD progression.

Conclusion

With obesity as common as it is today and serving as a strong risk factor in the development of many conditions like NAFLD and HCC, understanding the mechanisms that relate these conditions is essential for designing treatments. Recently published articles on obesity and HCC have elucidated many mechanisms that contribute to disease development. Diagnosis of NAFLD poses a surprising number of challenges to clinicians. Continued development of reliable techniques will be beneficial for early detection and intervention. There currently are few pharmaceutical options available to treat and prevent NAFLD. Pharmaceuticals that slow progression of NAFLD should be developed to prevent progression to more severe conditions like HCC.

Appendices

Appendix A: BI123 Lecture Slides

The Relationship Between Obesity and Cancer

Teale Andreason

Quick Quiz:

A. Freshman
B. Sophomore
C. Junior
D. Senior
E. Super Senior

Discussion:

- **Obesity**
- **Obesity and Cancer**
- **Insulin Resistance**
- **Example: Hepatocellular Carcinoma**
- **Prevention**

Body Mass Index (BMI):

$$\frac{\textit{Weight (kg)}}{\textit{Height}^2\ (m^2)}$$

Problems with BMI measurement?

Obesity Today

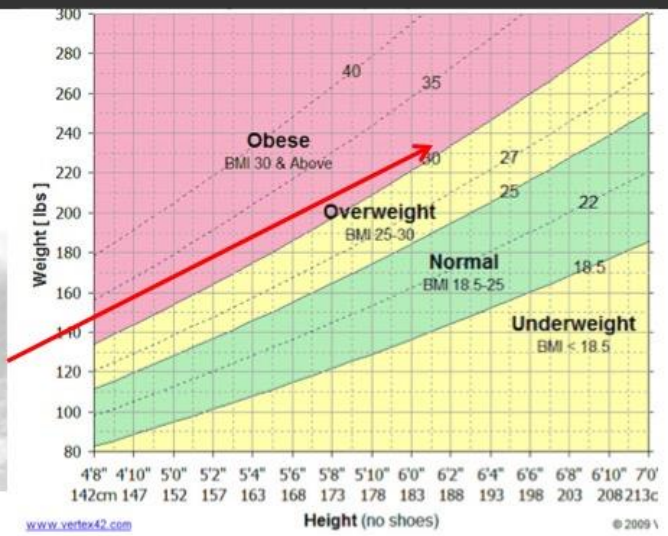
- Over two thirds of adults classified as overweight or obese in 2012
- From 1971 to 2001, there was a 30% increase in adult obesity
- Obesity often defined as Body Mass Index (BMI) above 30

Body Mass Index (BMI):

$$\frac{\text{Weight (kg)}}{\text{Height}^2\ (m^2)}$$

Problems with BMI measurement?

Body Composition



BMI is widely used to gage the severity of obesity, but is not always perfectly accurate.

Quick Quiz:

An individual is 6'7"tall and weights230 lbs.

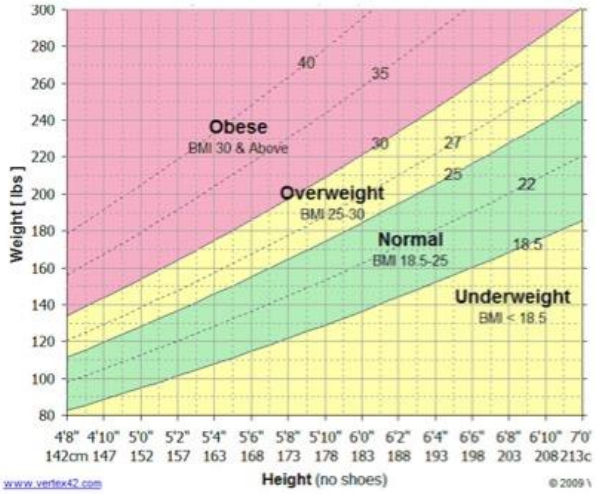
Classify this individual into the correct category based on the BMI chart.

A. Obese

B. Overweight

C. Normal

D. Underweight



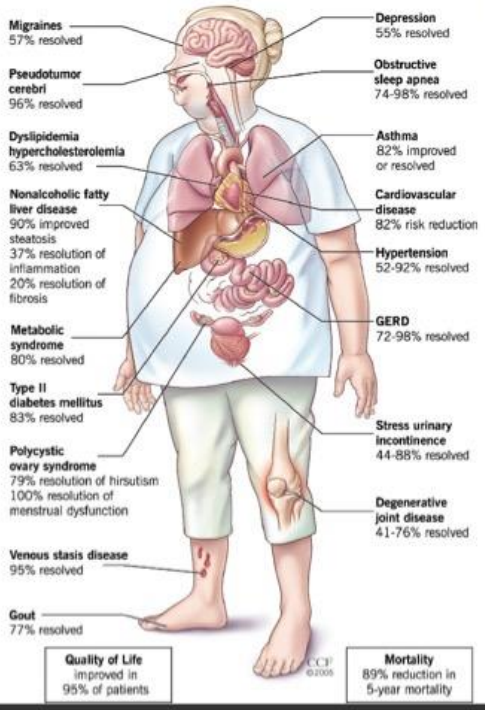
Body Mass Index (BMI):

$$\frac{\text{Weight (kg)}}{\text{Height}^2\ (m^2)} \rightarrow \frac{104\ kg}{(2m)^2} \rightarrow \frac{104\ kg}{4m^2}$$

↓

BMI of 26

What obesity-related complications do you know of?



Obesity-Related Complications

Cancer-Obesity Correlation

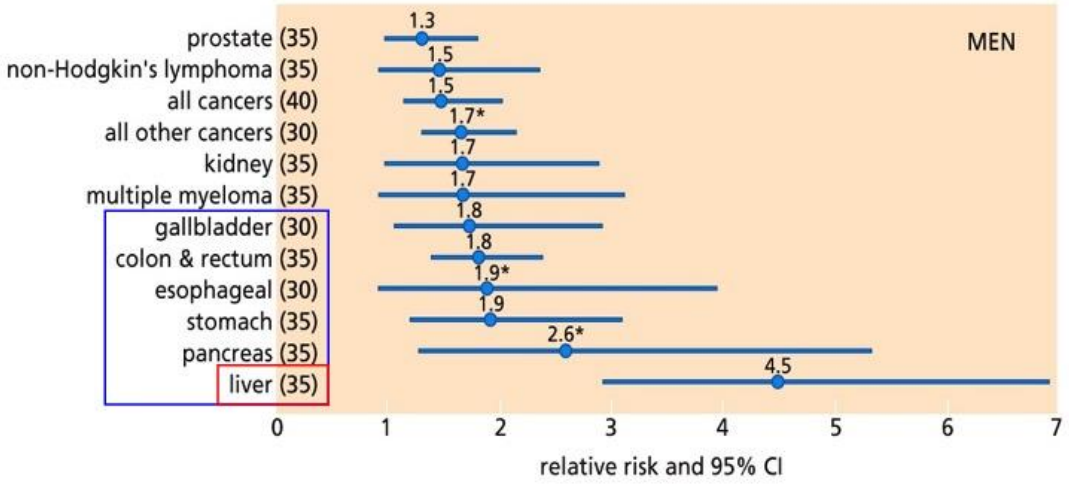


Figure 9.41a The Biology of Cancer (© Garland Science 2014)

Cancer-Obesity Correlation

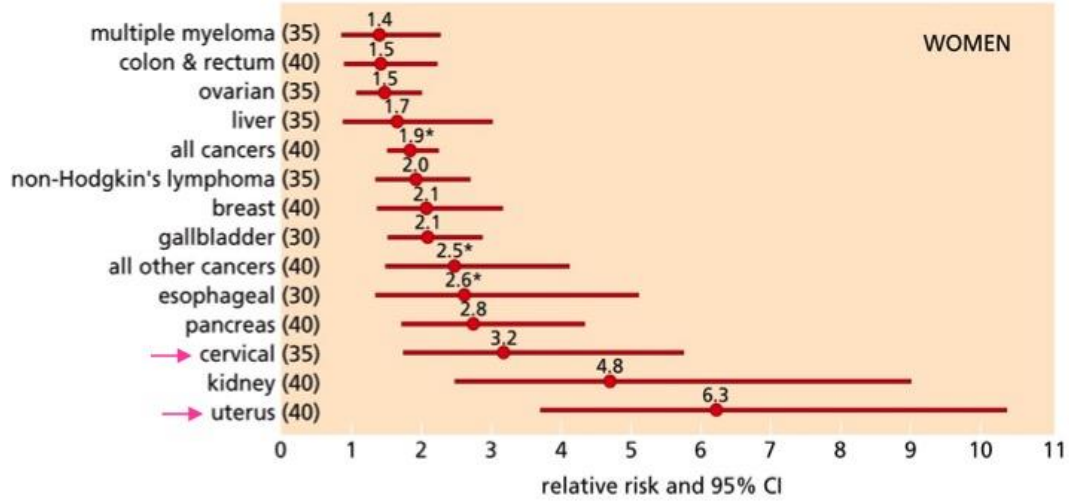


Figure 9.41b The Biology of Cancer (© Garland Science 2014)

Cancer-Obesity Causation

- Fat tissue produces high levels hormones that promote cancer development
- Increased levels of insulin
- Many other likely confounding mechanisms

Quick Quiz:

Above what BMI is considered to be obese?

A. 15
B. 20
C. 25
D. 30
E. 35

Obesity influences metabolism

Metabolism:

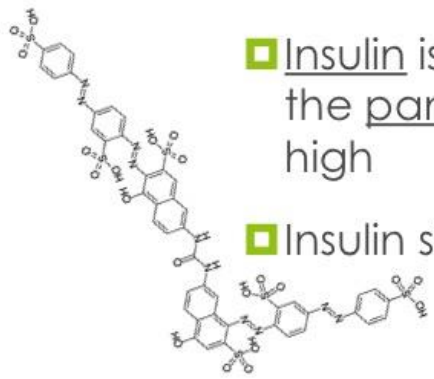
The chemical processes by which a plant or an animal uses food, water, etc., to grow and heal and to make energy

Quick Quiz:

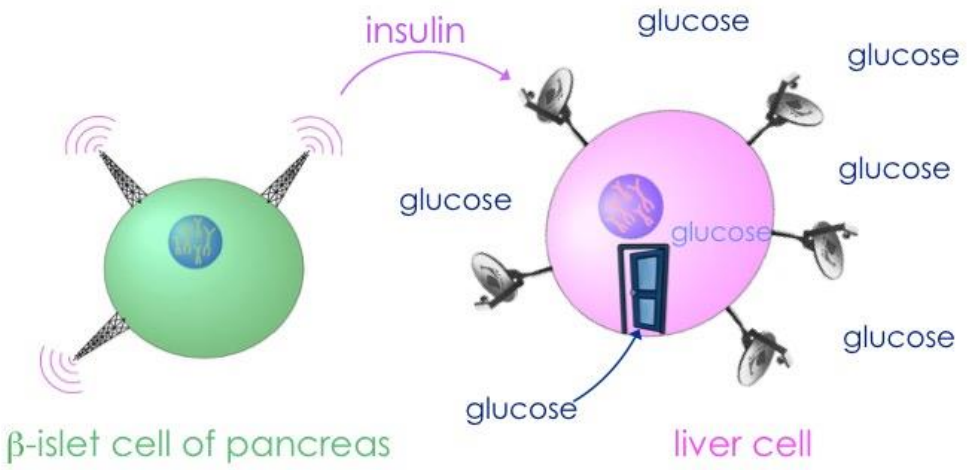
Which organ produces insulin?

A. Stomach
B. Gallbladder
C. Liver
D. Pancreas
E. Spleen

Insulin

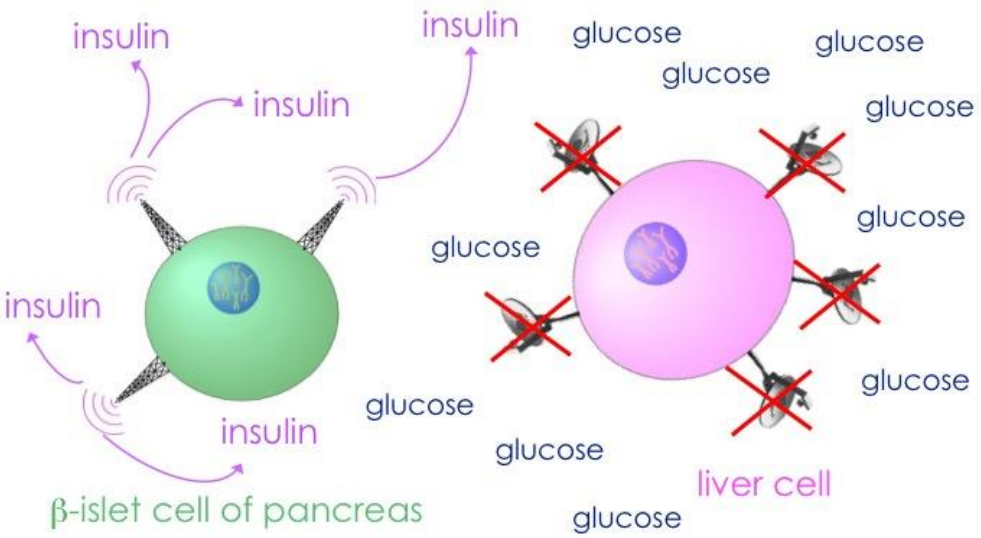


- Cells rely on the sugar glucose for energy (Metabolism)
- Insulin is released into bloodstream by the pancreas when blood glucose is high
- Insulin signals cells to uptake glucose



Insulin Resistance

- If receptors become resistant to insulin, glucose cannot enter cells
- In response to even higher blood glucose, insulin production increases



Hyperinsulinemia

Insulin Resistance

- **Hyperinsulinemia** is high insulin in the blood relative to glucose
- High levels of insulin stimulate the production of some **mitogens**

Insulin Resistance

- A **mitogen** is a chemical that promotes cell growth
- **Hyperinsulinemia** causes more of a **mitogen** called insulin-like growth factor-1 (IGF-1) to become available, which promotes cell proliferation

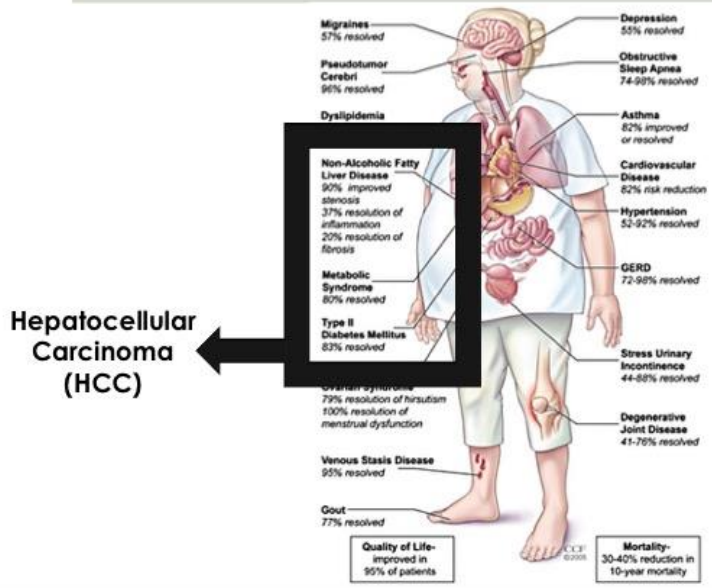
Quick Quiz:

Which of the following are mitogens?

A. Estrogen
B. IGF-1
C. Glucose
D. A and B
E. All of the above

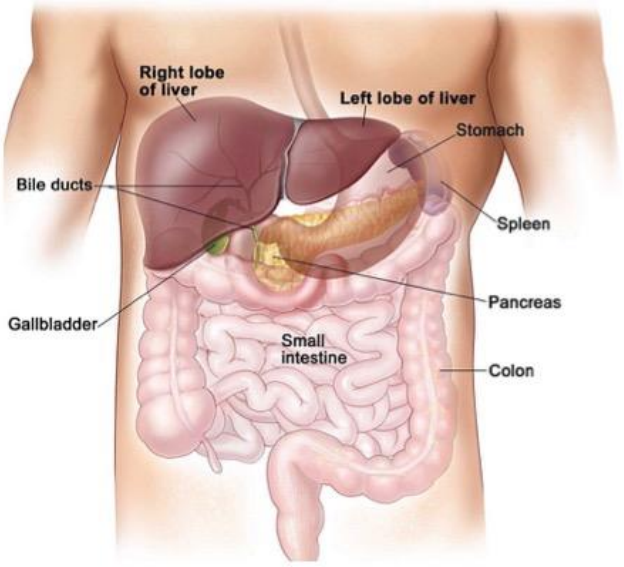
Type II Diabetes

- Type II diabetes is a separate medical condition in which individuals become resistant to insulin
- Obesity is a risk factor for type II diabetes
- Research has indicated that some cancers including liver, pancreas, and breast cancer appear more commonly in individuals with type II diabetes



Obesity-Related Complications

Location of the Liver

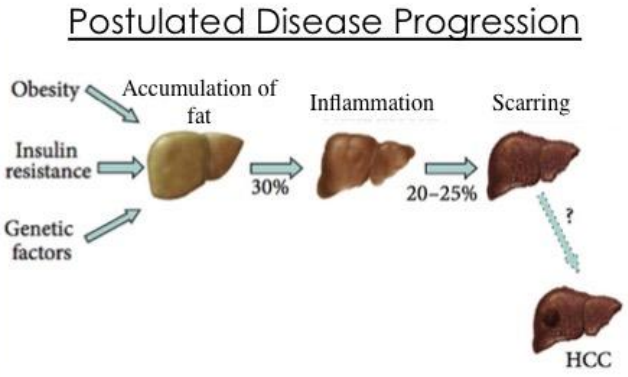


Basic Functions of the Liver

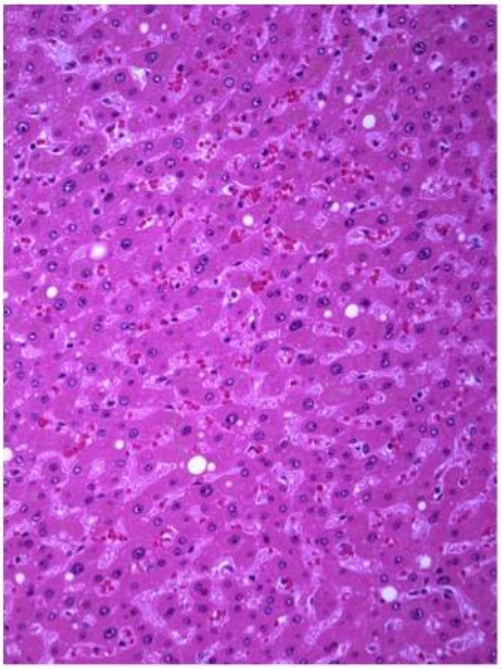
- Large regulator of metabolism
- Storage of blood and nutrients
- Blood purification
- Cholesterol synthesis and regulation
- Production of bile and coagulation factors

Hepatocellular Carcinoma (HCC)

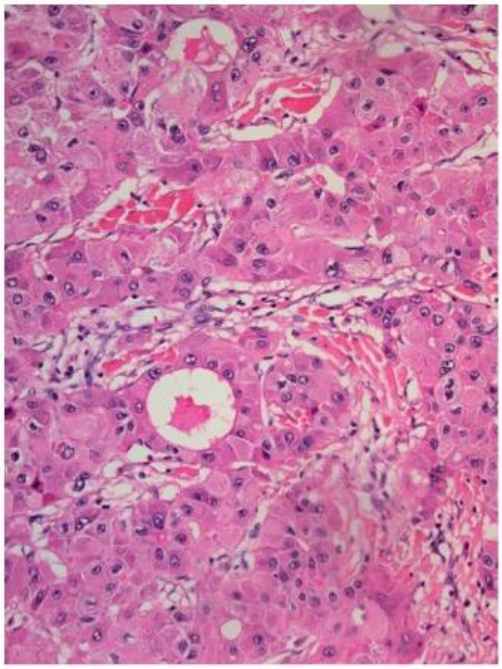
- HCC is the most common type of liver cancer
- When this progression happens, it can be hard to detect because the liver has so many functions



Normal Liver



Liver cancer



Obesity → Fat Accumulation in the Liver

- Insulin resistance causes our metabolism to shift from sugar to fat breakdown for energy
- High levels of free fatty acids accumulate in the blood
- Abnormal fat accumulation in liver cells

Hepatocellular Carcinoma (HCC)

- Fat accumulation in liver cells can cause inflammation, which eventually causes scarring and hardening
- Inflammation and scarring cause release of chemicals promote tissue healing
- One process of healing is cell proliferation. This is a step towards HCC

Prevention

- Weight Loss
- Diet
- Exercise
- Stop Smoking

The Relationship Between Obesity and Cancer:

Media coverage of threatening diseases like Ebola causes the public to become very concerned. However, far more people in the US die from largely lifestyle-mediated causes such as use of tobacco, high alcohol consumption, and obesity. Obesity is a risk factor for the development of cancer, which is the main topic of this presentation.

Obesity Today

Obesity is clearly a large and growing problem in the United States today. Over two thirds of adults were classified as overweight or obese in 2012.

- From 1971 to 2001, there was a 30% increase in adult obesity.
- Obesity often defined as **Body Mass Index** (BMI) above 30.

Body Mass Index (BMI)

- The equation for BMI is: $\frac{\text{Weight (kg)}}{\text{Height (m}^2\text{)}}$

BMI is a widely used tool in medicine and research used to classify the severity of obesity. However, BMI is not always a perfectly accurate gage of extra body fat. For example, Arnold Schwarzenegger, former Mr. Universe, would be considered obese using this calculation. Schwarzenegger was just over six feet tall and about 235 pounds, which results in a BMI of 31. Recall that

a BMI of over 30 is considered obese. The range of BMI from 18.5 to 24.9 is considered normal weight.

Obesity-Related Complications

Obesity affects all body systems in complex ways and has a big impact on metabolism. Obesity is a risk factor for the development of many cancers.

Cancer-Obesity Correlation

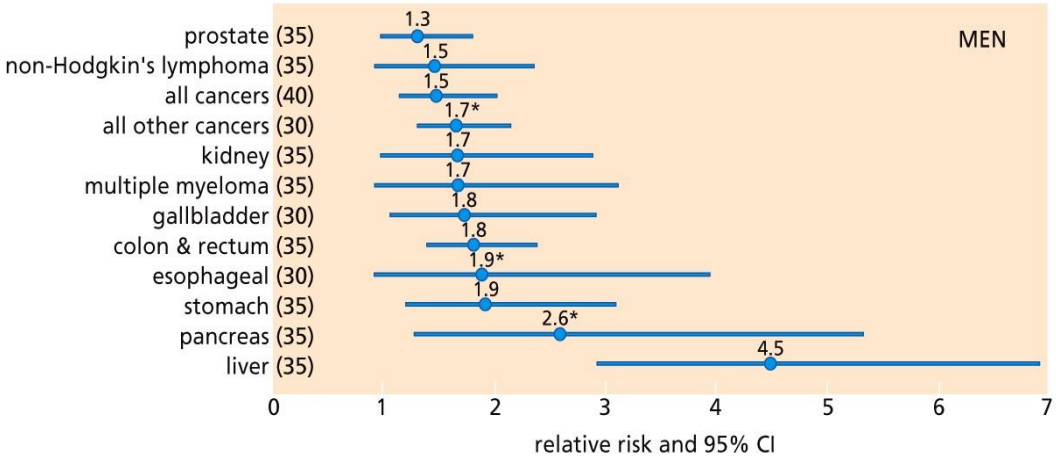


Figure 9.41a The Biology of Cancer (© Garland Science 2014)

This graph examines relative risk of various cancers in obese men. This graph has brought together information from many studies. On the Y-axis, there are different cancer types and BMI at which researchers examined. The X-axis represents relative risk and confidence intervals (CI), which shows how statistically significant the values are. For example, men with a BMI of 35 have about double the risk of developing stomach cancer relative to men with a BMI in the normal rage. According to this graph, men develop the highest risk of

getting cancers that affect organs of the gastrointestinal tract at high BMIs.

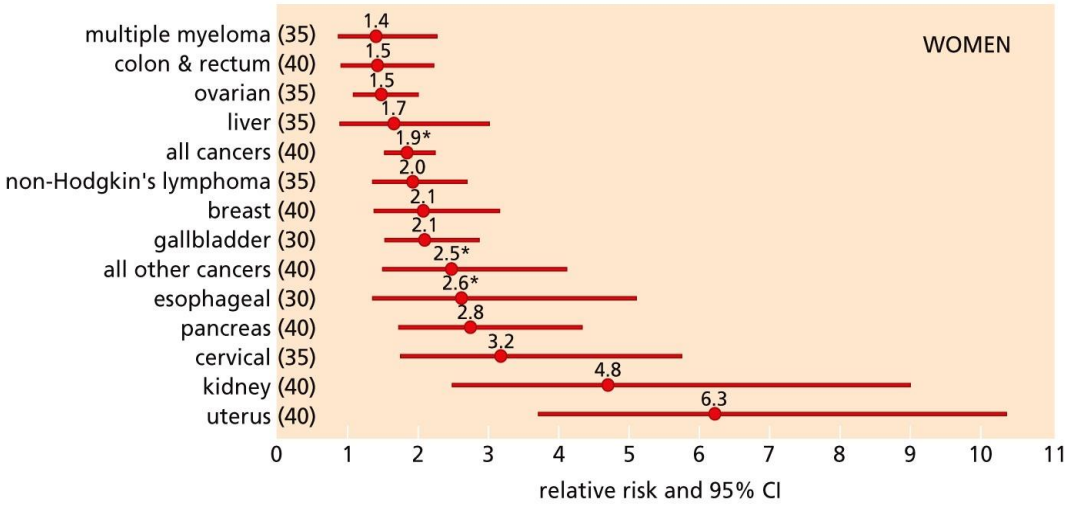


Figure 9.41b The Biology of Cancer (© Garland Science 2014)

This examines relative risk of various cancers in obese women. A similar trend between obesity and risk of cancer is observed in women for different cancer types than men. Notice that obese women are at especially higher risk of developing cervical and uterine cancers, which is related to high levels of estrogen as explained further below.

Cancer-Obesity Causation

There are many complex physiological mechanisms that contribute to causation. Fat tissue produces high levels hormones that promote cancer development. For example, obesity can induce high levels of estrogen production, which is associated with increased risk of breast, uterine, and cervical cancers. Another molecule, leptin, is higher in obese populations and promotes cell proliferation. Increased levels of insulin also promote the development of various cancers, which will be discussed further. Again, many

other likely confounding mechanisms exist. For example, low-grade chronic inflammation in obese individuals causes release of inflammation mediators that yield mutations in important genes. These mutations give cells survival advantage, but if too many accumulate, tumor development can occur.

Obesity Influences Metabolism

- **Metabolism:** The chemical processes by which a plant or an animal uses food, water, etc., to grow and heal and to make energy.

  Metabolic rate is how quickly the body is using food to produce energy.

Insulin and Insulin Resistance

Cells rely on the sugar glucose for energy (Metabolism)

- Insulin is released into bloodstream by the pancreas when blood glucose is high Insulin signals cells to uptake glucose. However, if receptors become resistant to insulin, glucose cannot enter cells. In response to even higher blood glucose, insulin production increases.
- **Hyperinsulinemia:** high levels of insulin in the blood relative to glucose
- High levels of insulin stimulate the production of some mitogens.
- A **mitogen** is a chemical that promotes cell growth
- Hyperinsulinemia causes more of a mitogen called insulin-like growth factor-1 (IGF-1) to become available, which promotes cell proliferation

Type II Diabetes

- Type II Diabetes is a medical condition in which individuals become resistant to insulin. Obesity is a risk factor for type II diabetes.

Research has indicated that some cancers including liver, pancreas, and breast cancer appear more commonly in individuals with type II diabetes. “The relative risks imparted by diabetes are greatest (about twofold or higher) for cancers of the liver, pancreas, and endometrium, and lesser (about 1.2–1.5 fold) for cancers of the colon and rectum, breast, and bladder.” http://care.diabetesjournals.org/content/33/7/1674.long

The Liver

Basic functions:

- Large regulator of metabolism
- Storage of blood and nutrients
- Blood purification
- Cholesterol synthesis and regulation
- Production of bile and coagulation factors

This is only five, but the liver performs hundreds of functions!

Hepatocellular Carcinoma (HCC)

- Hepatocellular Carcinoma (HCC) is the most common type of liver cancer. When the progression from fat accumulation in the liver to liver hardening to

liver cancer occurs it can be hard to detect because the liver has so many functions.

Insulin resistance causes our metabolism to shift from sugar to fat breakdown for energy. High levels of free fatty acids accumulate in the blood. Abnormal fat accumulation occurs in liver cells.

- Fat accumulation in liver cells can cause inflammation, which eventually causes scarring and hardening. Inflammation and scarring cause release of chemicals that promote tissue healing.
- One process of healing is cell proliferation. This is a step towards HCC.

Prevention

- Weight Loss – Weight loss has been shown to reduce the risk of cancer.
- Diet – Consuming a healthy diet rich in antioxidants has also been shown to reduce the risk of cancer.
- Exercise – Cardiovascular exercise can help stabilize insulin levels, which can contribute to its cancer risk-reducing affect.
- Stop Smoking! – Smoking doesn't only promote lung cancer! As we have seen, there are many complex physiological mechanisms that contribute to the development of cancer. Obesity and smoking are big cancer promoters, so addressing both is necessary for big-picture cancer prevention.

The Relationship Between Obesity and Cancer

- From 1971 to 2001, there was a _____ increase in adult obesity.
- Obesity often defined as **Body Mass Index** (BMI) above _____.
- The equation for BMI is: _____
- **Metabolism:** The _____ processes by which a plant or an animal uses food, water, etc., to grow and heal and to make _____
- _____ is released into bloodstream by the _____ when blood glucose is high
- **Hyperinsulinemia:** high levels of _____-_____ in the blood relative to _____
- High levels of _____ stimulate the production of some _____.
- A **mitogen** is a chemical that promotes _____
- _____ causes more of a mitogen called _____ to become available, which promotes _____.
- _____ is a medical condition in which individuals become resistant to insulin.
- _____ (HCC) is the most common type of liver cancer.
- Fat accumulation in _____can cause _____, which eventually cause _____
- Inflammation and scarring cause release of chemicals that promote _____. One process of healing is cell proliferation. This is a step towards _____.

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