The Cancer, Diabetes, and Heart Disease Link
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It’s common knowledge that clients and patients with type 2 diabetes have a higher risk of developing cardiovascular disease (CVD). But did you know that heart disease can be associated with an increased risk of type 2 diabetes and that diabetes can raise the risk of various cancers?

Research has shown there are interrelationships among type 2 diabetes, heart disease, and cancer. These interrelationships may seem coincidental and based only on the fact these conditions share common risk factors. However, research suggests these diseases may relate to one another in multiple ways and that nutrition and lifestyle strategies used to prevent and manage these diseases overlap considerably.

This continuing education activity will evaluate the current research showing how cancer, type 2 diabetes, and CVD interrelate with one another, and examine how nutrition and physical activity recommendations developed to reduce cancer risk intersect and can be used to care for patients who have or are at risk for diabetes and heart disease.

Interrelated Conditions
Type 2 diabetes has long been known to increase CVD risk and mortality. Even after adjusting for other heart disease risk factors, people with type 2 diabetes are at least twice as likely to develop CVD and face two to four times greater cardiovascular mortality compared with people without diabetes. Hypertension and dyslipidemia are common in diabetes, although diabetes also seems independently linked to CVD risk.

Certain medications that effectively treat components of CVD may raise the risk of developing type 2 diabetes or make the condition more difficult to control. This includes some antihypertensive medications, such as diuretics and certain beta-blockers, and LDL-lowering statins. The JUPITER trial (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin), a randomized double-blind placebo-controlled study investigating the use of rosuvastatin in the primary prevention of CVD, shows these medications are most likely to promote hyperglycemia in people with prediabetes, metabolic syndrome, or obesity.

Moreover, several meta-analyses have associated type 2 diabetes with colon, postmenopausal breast, and pancreatic cancers, three of the five leading causes of cancer mortality in the United States. The risk of liver cancer rises 250% in those with type 2 diabetes; the risk of developing endometrial and bladder cancers, and non-Hodgkins lymphoma also increases.
Among cancer patients, preexisting diabetes is associated with 30% to more than 70% higher mortality rates.\textsuperscript{17-19} Metformin may decrease cancer risk, and research is under way to examine how various diabetes treatments affect cancer risk.\textsuperscript{20,21}

Type 2 diabetes generally is associated with a 25% to 35% decreased risk of prostate cancer.\textsuperscript{22,23} However, diabetes doesn’t seem to reduce the most aggressive forms of this cancer,\textsuperscript{24} and all-cause mortality rates appear to be higher in those with both prostate cancer and type 2 diabetes.\textsuperscript{25}

In other research, the link between pancreatic cancer and diabetes is bimodal, since diabetes can be both a result of and a risk for this type of cancer.\textsuperscript{26,27}

Adult survivors of childhood cancer face an increased risk of type 2 diabetes and metabolic syndrome. Some of this risk may be associated with excess body fat or sedentary lifestyles more commonly seen in this group, but it also seems to involve some independent effect, particularly among patients treated with radiation therapy.\textsuperscript{28,29} Androgen-deprivation therapy for prostate cancer often leads to sarcopenic obesity and increases insulin resistance.\textsuperscript{30,31}

Although cancer survivors may worry most about recurrent or second cancers, heart disease is the predominant cause of death in those who have some of the most common cancers. This isn’t just a case of shared risk factors; certain types of cancer therapy can have cardiotoxic late effects.\textsuperscript{32,33}

When it comes to the interrelationship between heart disease and cancer, growing research has shifted focus from total LDL cholesterol to small-dense LDL as the source of CVD risk.\textsuperscript{34} Atherogenic dyslipidemia, defined by increased small-dense LDL with increased apolipoprotein B and higher fasting insulin or with elevated serum triglycerides and decreased HDL cholesterol, has been linked to a significant rise in coronary heart disease (CHD) risk.\textsuperscript{35-37} This lipid pattern often occurs with metabolic syndrome, which doubles the risk of CVD and also may include hypertension, increased waist circumference, and elevated fasting blood sugar. This metabolic environment of insulin resistance and inflammation greatly overlaps with the metabolic environment in which several types of cancers may develop and flourish.

**Understanding the Cancer Link**

Research has found that cancer, type 2 diabetes, and CVD have common physiological associations. These associations partially overlap with one another and all remain active areas of research.

**Obesity**

Adipose tissue consists of adipocytes and infiltrating macrophage cells of the immune system. Greater body fat, particularly with insulin resistance, tends to increase the production of the hormone leptin, a mediator that regulates energy balance. Rising leptin tends to further increase hyperinsulinemia, promote inflammation, and induce aromatase enzymes that raise estrogen production in postmenopausal women. Emerging laboratory studies suggest leptin also may directly promote cancer cell growth. Moreover, greater body fat is linked with decreased production of adiponectin, a protective anti-inflammatory hormone. In postmenopausal women, body fat becomes the primary site of estrogen synthesis, and obesity is linked with substantial increases in bioavailable estrogen.
Adipose tissue secretes cytokines such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6). These cytokines can promote the inflammation, insulin resistance, and endothelial dysfunction now linked with type 2 diabetes and coronary artery disease (CAD) as well as promote cancer development by increasing cell proliferation and decreasing apoptosis.

**Hyperinsulinemia and Insulin Resistance**

Hyperinsulinemia stemming from insulin resistance may exist for many years before a diabetes diagnosis, and it has wide-ranging effects. Normally, when insulin binds to its receptors, it activates two pathways: the metabolic pathway and the mitogenic pathway. Insulin resistance inhibits the metabolic pathway, which is the pathway that increases transport of glucose into cells, promotes glycogen synthesis, and suppresses liver gluconeogenesis. Without insulin’s normal postprandial inhibition of lipolysis, circulating free fatty acid levels—fundamental to the pathogenesis of insulin resistance—and liver triglyceride production rise, which contributes to atherogenic dyslipidemia.

In contrast, insulin resistance doesn't inhibit activation of the mitogenic pathway that promotes proliferation of normal and cancerous cells. Moreover, hyperinsulinemia boosts levels of bioavailable insulin-like growth factor-1 (IGF-1), another stimulus for increased cell proliferation that can promote cancer development, and decreases liver production of sex hormone-binding globulin, thus increasing estrogen bioavailability to promote cancer.

**Inflammation**

Inflammation is an inherent part of atherosclerotic plaque development, and it seems to contribute to insulin resistance. Exposure to free radicals produced in the body and externally can damage cell DNA through oxidation and strand breaks, and interfere with DNA repair. The genetic mutations that result can lead to cancer. Chronic, low-grade inflammation can result from DNA damage and create an environment in which more damage occurs. IL-6 and TNF-alpha, for example, promote cancer progression through several pathways.

**Hyperglycemia**

One of the unanswered questions about the link among cancer, type 2 diabetes, and CVD involves the effect of elevated blood glucose. Hyperglycemia is associated with increased free radical formation and may lead to the development of advanced glycation end products (AGEs), or proteins or lipids that become glycated after exposure to sugars that can increase inflammation. Some laboratory studies suggest higher circulating glucose may support malignant cell growth.

Some prospective cohort and case-control studies link elevated hemoglobin A1c and other measures of hyperglycemia with an increased risk of colorectal, pancreatic, endometrial, and other cancers. However, these studies often don’t control for insulin levels or potential confounders, such as exogenous insulin, sulfonylureas, or metformin used for diabetes treatment. A meta-analysis of intervention trials of people with type 2 diabetes shows no association between hemoglobin A1c and cancer risk or cancer mortality.
Intersection of Recommendations
Research is clear that the key to reducing the risk of developing type 2 diabetes, cancer, and CVD is to reduce excess body fat, especially around the waist. Reduction of excess body fat is a primary target for reducing cancer risk, just as it is for type 2 diabetes, prediabetes, and CVD.46,47

In the Diabetes Prevention Program and Look AHEAD (Action for Health in Diabetes) trials, even modest weight loss was linked to clinically significant improvements in multiple health metrics, such as subclinical inflammation (measured by C-reactive protein), blood sugar, blood pressure, triglycerides, and HDL cholesterol.48-50 The most recent standards from the American Diabetes Association (ADA) recommend that individuals who are overweight or obese lose 7% of their body weight.5

Excess body fat increases the risk of colon, postmenopausal breast, endometrial, kidney, esophageal, and pancreatic cancers, and probably gallbladder cancer.51,52 To reduce cancer risk, the American Institute for Cancer Research (AICR) and the American Cancer Society (ACS) recommend being as lean as possible while avoiding underweight.

Studies show the lowest cancer mortality rates in those at the lower end of the normal BMI range. For people who are already obese or significantly overweight, even modest weight loss is likely beneficial. Regardless of BMI, people with elevated body fat can have increased insulin resistance, inflammation, and metabolic syndrome. In fact, CVD mortality is significantly higher in these women.53,54

Abdominal fat particularly is linked with insulin resistance and elevated levels of inflammatory cytokines. Moreover, the combination of greater waist size and elevated triglycerides independently predicts CAD in men and women,55,56 and increases in waist circumference are directly linked with greater colon cancer risk.57

The 40-inch and 35-inch waist circumference standards from the National Institutes of Health, used to define metabolic syndrome in men and women, respectively, may not be sensitive enough to identify many people at risk of health problems related to excess body fat. So the AICR Expert Report recommends the World Health Organization limits, which call for waists to be no larger than 37 inches in men and 31.5 inches in women. These standards also are better predictors of type 2 diabetes and cardiometabolic risk.59,60 Further research is needed for standards that reflect ethnicity-based differences in body fat deposition.61

Weight-Control Strategies
Weight-management recommendations from the AICR and the ACS include limiting high-calorie foods and beverages, getting regular physical activity, and choosing appropriate portion sizes.

AICR recommendations also encourage people to limit calorie-dense foods. Decreasing calorie density can reduce calorie consumption.62,63 This fits well with eating patterns linked with a lower risk of cancer, diabetes, and CVD. For example, one of the primary ways to lower calorie density is to increase vegetable consumption.63,64
Research suggests foods low in calories should be substituted for foods high in calories rather than simply added to the diet. The goal of an overall eating pattern low in calorie density doesn’t exclude modest amounts of foods high in calorie density, such as oils, nuts, and seeds, which add nutritional value.65

**Physical Activity**

Regular exercise is key to reducing the risk of and controlling type 2 diabetes and CVD, and is linked with lower cancer risk, especially colorectal, endometrial, and postmenopausal breast. Recommendations for physical activity to lower cancer risk are similar to those promoted for overall health, which include a minimum of 30 minutes of moderate activity daily, and preferably 60 minutes of moderate or 30 minutes of vigorous activity daily.

Emerging research suggests that aside from the time individuals spend exercising, limiting the amount of time they’re inactive provides yet another means of improving biomarkers of cardiovascular health, reducing insulin resistance, and likely lowering cancer risk.66-68 Research shows that interspersing short bouts of light exercise within periods of sedentary activity seems beneficial to glucose and fat metabolism and waist size.69,70

Although one of the expected benefits of regular exercise is maintaining a healthy weight, physical activity can beneficially affect abdominal fat, insulin resistance, and estrogen levels, and increase HDL cholesterol without weight loss. Because direct effects of exercise on insulin last 24 to 72 hours, it’s best to go no more than two consecutive days without being active.5,71,72

**Vegetables, Fruits, Whole Grains, and Beans**

Just as vital as physical activity for the reduction of type 2 diabetes, cancer, and CVD are the types and variety of foods individuals eat. Plant foods are encouraged because they supply dietary fiber, nutrients, and phytochemicals that seem to impact the process of cancer development.

Dietary fiber is associated with lower colorectal cancer risk,57 and a meta-analysis links dietary fiber with reduced breast cancer risk.73 The current dietary fiber recommendation for people with diabetes is no different from that of the general public: 14 g/1,000 kcal, with higher amounts possibly beneficial.5

Not all fiber is the same, but both types (soluble and insoluble) seem to offer cancer-protective benefits. Viscous soluble fiber helps reduce LDL cholesterol and slow postprandial blood sugar increases, while fermentable fiber provides the substrate for gut bacteria to produce short-chain fatty acids. These fatty acids seem to promote normal colon cell differentiation and have anti-inflammatory effects.

It isn’t clear, however, whether some of the health benefits seen in studies of people with high fiber consumption come from other qualities of foods high in fiber. The choice of whole grains vs. refined grains provides an example of this. Analysis in the AICR/WCRF (World Cancer Research Fund) continuous update project shows a reduction in colorectal cancer linked to cereal fiber. Yet reduced colorectal cancer risk associated with whole grains may come from more than fiber alone, since whole grains are higher than refined grains in several nutrients and provide antioxidant phytochemicals such as polyphenols.74
Legumes are a concentrated source of dietary fiber. They also provide significant amounts of resistant starch and flavonoid phytochemicals that may function as antioxidants and have cancer-inhibitory effects.

Vegetables and fruits are important because they're low in calorie density and likely contribute directly to reducing cancer risk. Besides fiber, they provide nutrients vital for DNA production and immune function. What’s more, research is only beginning to reveal the role of phytochemicals in produce. Many are antioxidants and, at least in laboratory studies, they have the potential to reduce cancer development. For example, allyl sulfur compounds in garlic and onion, and isothiocyanates formed from compounds in cruciferous vegetables may promote epigenetic changes that activate tumor suppressor genes.51,75

**Dietary Recommendations**
Because of the cancer-fighting compounds found in fruits, vegetables, and whole grains, the AICR recommends at least two-thirds of the food individuals eat come from plants.

The 2010 Dietary Guidelines for Americans say at least one-half of grain products should be whole grain, and people should aim for at least three servings per day. Yet recent reviews that focus on decreasing insulin resistance and ACS recommendations concur with the AICR’s advice to eat more than three servings per day of whole grains if possible and “minimize consumption of refined grains.”

For greater health benefits, clients can use dried beans and peas in place of all or part of the meat in some dishes. When it comes to fruits and vegetables, research shows individuals can eat smaller amounts than what’s recommended to reduce heart disease and still lower cancer risk. ACS recommendations call for a total of at least 2 1/2 cups of vegetables and fruits daily. The AICR recommends at least five standard-size servings daily of nonstarchy vegetables and fruits, which means potatoes and legumes don’t count toward the total.

Fruit and vegetable targets should focus not only on the amount but also on a variety of choices. To help control or decrease hypertension risk, dietitians can suggest clients include choices rich in potassium. To reduce cancer risk, variety also refers to selections rich in carotenoids and vitamin C as well as cruciferous vegetables, garlic-onion family vegetables, and berries, among other foods.

**Limiting Red Meat**
In addition to eating more plant foods, limiting red meat consumption also is important. Heart-health messages usually focus on saturated fat and group together poultry, seafood, and lean cuts of red meat as recommended choices. However, research on cancer suggests these foods aren’t all the same.

A meta-analysis conducted as part of the AICR/WCRF continuous update project shows a 17% increased risk of colorectal cancer per 100 g of red meat eaten daily.76 Its higher heme iron content may increase risk by promoting nitrosamine formation within the gut as well as through the generation of DNA-damaging free radicals.
Processed meats—those preserved by smoking, curing, salting, or preservatives—are linked to increased colorectal cancer risk, showing an 18% higher risk for each 50 g consumed per day. Most processed meats are high in sodium, so limiting them already is a boon for heart health. A meta-analysis links about 2 oz of daily processed meat consumption with a 42% rise in CHD and also a 19% increase in diabetes risk.

Clients can reduce their meat consumption through several different approaches, all of which fit well with other prevention-focused goals, such as the following:

- The AICR recommends individuals eat no more than 18 oz (cooked weight) of red meat per week, which includes beef, lamb, and pork.

- Substitute vegetables and beans for some or all of the red and processed meat in dishes, which supports the goals of increasing plant foods and decreasing calorie density.

- The American Heart Association (AHA) recommends eating at least 8 oz, or two servings, of fish each week.

**Curb High-Sodium Foods**

Sodium intake is another concern. The 2010 Dietary Guidelines call for keeping daily sodium consumption below 2,300 mg. However, about one-half of the US population falls into groups whose blood pressure tends to be especially sodium sensitive and are therefore advised to reduce sodium to 1,500 mg per day. This includes people aged 51 and older, and those of any age who are African American or have hypertension, diabetes, or chronic kidney disease.

Although sodium targets for cardiovascular health are lower than needed to decrease cancer risk, consumption of salt and salt-preserved foods is linked to an increased risk of stomach cancer.

Limiting sodium may make dietary strategies seem more complex, but it can support a healthful eating pattern if the medical community does the following:

- Pairs messages about limiting salt with suggestions for using herbs, spices, garlic, and other flavorings. People will be able to enjoy flavorful food and get health-protective phytochemicals into their diets.

- Teaches people how to replace high-sodium convenience foods with whole foods, which often are lower in saturated and trans fats and added sugar.

**Alcohol Consumption**

Alcohol in moderation is strongly linked to a decreased risk of CHD, possibly related to increased HDL cholesterol, reduced inflammation, and lower fibrinogen, a protein essential for blood clotting that when too high is a marker of increased CVD risk. In moderation, alcohol decreases insulin resistance and type 2 diabetes risk. However, alcohol in excess can raise triglycerides and boost the risk of developing hypertension and diabetes.
Many people are unaware that alcohol is linked to an increased risk of colon cancer in men, pre- and postmenopausal breast cancer, and mouth and throat cancers.

According to the AHA, "Consumption of alcohol cannot be recommended solely for CVD risk reduction."\(^{46}\)

For people who choose to drink alcohol, the unified recommendation from the AICR, the ACS, the AHA, and the ADA is to limit alcoholic drinks to two per day for men and one per day for women. Women need to consume fewer than one drink per day to reduce their breast cancer risk to that of nondrinkers, so they will need help making choices based on their individual health risks and lifestyle preferences.

Due to the trends in increased portion sizes, the healthcare community must clearly define what’s meant by one drink: 5 oz of wine, 12 oz of beer, or 1 1/2 oz of 80-proof liquor.

**Weaving Recommendations Into Healthful Eating Patterns**

Research increasingly is looking beyond the health impact of individual food choices to how combined choices as part of overall eating patterns impact diabetes, heart disease, and cancer. Sometimes individual studies compare a particular eating pattern to the Western diet and show a reduced risk of one or more of these conditions. Such comparisons don’t show that the particular alternative-eating pattern tested is “the best” choice for everyone.

Research is exploring how genetic polymorphisms may affect response to dietary fat, carbohydrate, and protein intake and certain cancer-protective phytochemicals. Meanwhile, the challenge is to help people follow healthful eating patterns that satisfy their unique food preferences, calorie needs, health issues, and lifestyles.

Healthful food choices can be combined into different predominantly plant-based eating patterns, including a vegetarian diet, Dietary Approaches to Stop Hypertension (DASH), and the Mediterranean diet.

Very low-fat vegetarian eating patterns include the lacto-ovo vegetarian approach Dean Ornish, MD, originally took to help reverse atherosclerotic heart disease.\(^{79}\) He has since shown decreases in inflammation markers and endothelial dysfunction with this approach in a small group of men with CAD or CAD risk factors\(^{80}\) and protective changes in prostate cancer gene expression and decreased prostate-specific antigen among men with low-risk prostate cancer with a very low-fat vegan diet.\(^{81,82}\)

These eating patterns keep fat and carbohydrate intake to 10% and 75% of total calories, respectively. Total fat intake is very low, avoiding even fats in nuts and oils often considered healthful. Despite the high carbohydrate content, hemoglobin A1c levels have been reduced.\(^{83}\) However, these diets’ effects as reported in these studies can’t be separated from other components that promote health, such as three hours per week of moderate physical activity, smoking cessation, one hour of stress management daily, and active group support.
The 2010 Dietary Guidelines support following the DASH diet, which was originally developed to prevent or control hypertension. It decreases LDL cholesterol and blood pressure, and some research suggests it can decrease inflammation and hemoglobin A1c levels in people with type 2 diabetes. Limited research links scores showing how closely the DASH diet was followed with reduced risk of colorectal and estrogen receptor-negative breast cancer and type 2 diabetes.

An eating pattern such as the DASH diet is low in total and saturated fat but does include limited amounts of oil. It’s high in vegetables, fruits, and grains (with at least three servings of whole grains per day) and includes low- or nonfat dairy daily, beans and nuts often, and substantially limited sweets and sodium. (Details of how the proportions of different food groups are combined in the DASH diet are provided in Appendix 10 of the 2010 Dietary Guidelines report.) The DASH diet emphasizes vegetables and fruits, so it generally increases an individual’s intake of potassium and dietary fiber, and reduces sodium intake.

Moreover, the DASH diet is relatively high in carbohydrate. Results of the OmniHeart intervention trial suggest that, at least for some people and in the short-term, replacing some carbohydrate with plant proteins or unsaturated fat may produce even greater improvements in blood pressure and atherogenic lipoproteins, molecules that transport cholesterol in the bloodstream that can cause blood vessel blockages and lead to heart attacks and strokes.

The 2010 Dietary Guidelines advisory panel also highlights the Mediterranean eating pattern as a healthful choice. It’s a plant-based diet that includes an abundance of vegetables, fruits, grains, and beans. The Mediterranean eating pattern isn’t necessarily low in total fat, but most of the fat comes from olive oil and nuts, so saturated fat is below 10% of total calories. Research links this eating pattern with decreases in metabolic syndrome and in cardiovascular and cancer mortality. Glucose control and insulin resistance also may improve.

Because many people think of low-fat eating as a key to health, clinical trials comparing the Mediterranean diet with a low-fat diet are of particular interest. In the PREDIMED dietary intervention trial, people assigned to a Mediterranean-type eating pattern were less likely to develop diabetes or metabolic syndrome than those eating a low-fat diet, and showed lower levels of the oxidized form of LDL now considered an essential influence in atherosclerosis. A meta-analysis that compared the Mediterranean diet with low-fat eating in overweight adults linked this eating pattern with lower levels of metabolic syndrome components, including blood pressure and fasting glucose, and reduced levels of high-sensitivity C-reactive protein, a marker of inflammation.

Weight management is a major goal for lowering the risk of and controlling type 2 diabetes, heart disease, and cancer. The Mediterranean diet shows how a diet containing plenty of vegetables and a higher percentage of calories from fat still can have moderately low calorie density and support weight goals.

Paradigm Shift
Research increasingly shows that the risk of and damage from type 2 diabetes, CVD, and cancer is associated with a constellation of insulin resistance, inflammation, cell signaling and epigenetic changes, and hormones. As health professionals specialize and become more problem focused, it
can be easy to concentrate on single measures, such as hemoglobin A1c or LDL levels, and miss the big picture. This big picture extends beyond an intersection of heart disease and diabetes, and includes cancer as well.

Avoiding tobacco is vital to reducing the risk of all three diseases and promoting overall health. However, lifestyle matters to nonsmokers, too. Among almost 112,000 nonsmoking men and women in the Cancer Prevention Study-II Nutrition Cohort, all-cause mortality—reflecting fewer deaths because of both heart disease and cancer—was 42% lower with weight control, regular physical activity, limited use of alcohol, and a healthful diet limited in red and processed meats, and focused around whole plant foods.100

The Nutrition Professional’s Role
What does this mean for nutrition care? Dietitians have more reason than ever to encourage nutrition interventions focused on preventive health and act early in response to undesirable metabolic changes in their clients and patients. When these individuals are faced with prediabetes or prehypertension, they may think trouble doesn’t start until later, but that’s not the case. By reframing this as a metabolic environment conducive to heart disease and cancer development, nutrition professionals will be better able to help clients and patients make changes sooner rather than later.

Strong evidence shows that one of the most effective steps to reducing cancer risk and addressing the metabolic abnormalities of the diabetes-CVD-cancer connection is to reach and maintain a healthful level of body fat. Since research doesn’t clearly show more protection from one type of healthful eating pattern than another, dietitians need to help people shift their focus from what diet is best to identify changes they can make to alter the balance of calories expended and consumed.

The health impact of eating patterns requires more than calculating percentages of fat grams, protein, or carbohydrate; it involves the specific food choices behind those numbers. For example, the type of grain products and animal proteins chosen, and both the amount and variety of vegetables and fruits are all pieces in this puzzle.

As the word spreads about how heart disease, diabetes, and cancer risk are interrelated, it will be imperative for nutrition professionals to learn the steps necessary to help clients and patients lower risk. These steps are both evidence based and compatible with overall nutrition strategies. By showing people eating patterns with multiple health benefits and referring them to reliable sources of information, dietitians can provide important support for their clients’ and patients’ overall health.

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References


Examination

1. Type 2 diabetes is not associated with an increased risk of which of the following cancers?
   A. Liver
   B. Colorectal
   C. Prostate
   D. Endometrial

2. Which of the following statements explains the interrelationships involving type 2 diabetes, cardiovascular disease, and cancer risk?
   A. Insulin resistance leads to both increased small-dense LDL and increased cell proliferation.
   B. Increased adipose hormones lead to inflammation and insulin resistance.
   C. Insulin resistance leads to decreased HDL and increased bioavailable estrogen.
   D. All of the above

3. Which of the following statements describes the effect of hyperinsulinemia on increased cancer risk?
   A. It's linked to increased LDL cholesterol.
   B. It probably does not begin until after a diagnosis of type 2 diabetes.
   C. It's linked with elevated levels of testosterone.
   D. It occurs through the activation of mitogenic cell-signaling pathways.

4. Which of these statements correctly reflects recommendations about excess body fat and waist size in this triad of health conditions?
   A. Large waist size is linked to an increased risk of colorectal cancer.
   B. Health risks associated with increased waist size seem related to elevated adiponectin.
   C. Health risks linked to excess waistline fat begin at 40 inches in men and 35 inches in women.
   D. a and c

5. The most recent standards from the American Diabetes Association recommend that individuals who are overweight or obese lose what percentage of their body weight to reduce the risk of developing type 2 diabetes?
   A. 3
   B. 5
   C. 7
   D. 9

6. In addition to obesity, which of the following are the proposed metabolic mechanisms that explain the common associations of type 2 diabetes, heart disease, and cancer?
   A. Hyperinsulinemia and insulin resistance
   B. Inflammation
   C. Hypoglycemia
   D. a and b
7. The role of plant foods to reduce cancer risk seems to involve which of the following?
A. Antioxidants, including beta-carotene and vitamins C and E
B. Phytochemicals that influence carcinogen metabolism
C. Low calorie density
D. All of the above

8. Which of the following is true regarding red meat's link to colorectal cancer risk?
A. Cancer risk is not related to lean red meat.
B. Red meat’s link to cancer risk is similar to that of processed meat.
C. Colorectal cancer risk is the reason for the recommended limit of 18 oz of red meat weekly.
D. In this context, red meat refers mainly to beef.

9. Optimizing the health impact of eating patterns requires which of the following steps?
A. Calculating percentages of fat grams, protein, and carbohydrates
B. Choosing types of grain products and animal proteins
C. Selecting the amount and variety of fruits and vegetables
D. b and c

10. Which dietary pattern can decrease both hemoglobin A1c and biomarkers of inflammation?
A. Very low-fat vegetarian diet
B. Dietary Approaches to Stop Hypertension (DASH)
C. Mediterranean diet
D. All of the above