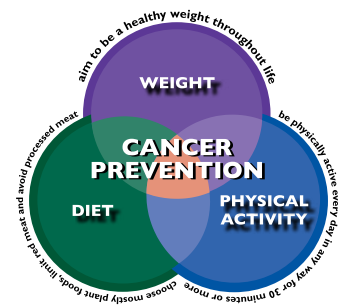


AICR InDepth



by Karen Collins, MS, RD, CDN

The Diabetes-Cancer Connection

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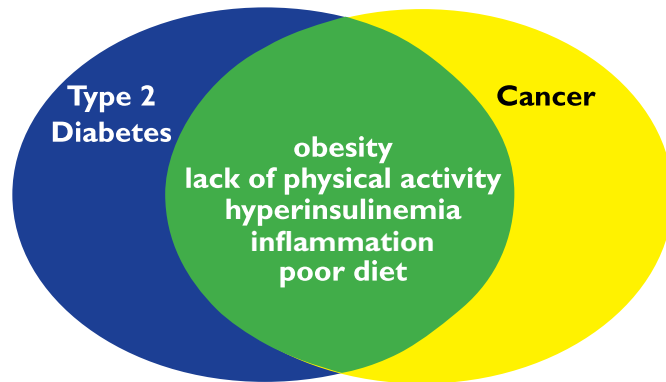
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The Diabetes-Cancer Connection



The Take-Home

Type 2 diabetes is associated with increased risk of several cancers.

- Risk is most clearly elevated for cancers of the liver, pancreas, colon and endometrium and is probably elevated for cancers of the breast (postmenopausal), bladder, kidney and non-Hodgkin lymphoma.
- Increase in cancer risk may occur with early metabolic changes that precede the development of full-blown diabetes.

The diabetes-cancer link seems connected to several highly inter-related factors:

- Obesity
- Inflammation
- Insulin resistance
- Chronic hyperglycemia

Lifestyle choices can influence risk of both diabetes and cancer. Many strategies that decrease risk of cancer also promote control of diabetes.

- **Weight:** Excess body fat is strongly related to risk of both diabetes and cancer.
For diabetes prevention and control: if overweight, 5 to 10 percent weight loss
For cancer prevention: maintain weight within normal range from age 21; avoid weight gain and increases in waist circumference throughout adulthood
- **Physical activity:** Lowers risk both directly and through promoting weight management benefit.
For diabetes prevention: at least 30 min/5x per week of moderate to vigorous intensity; working up to more to improve weight management
For cancer prevention: at least 30 min/day moderate intensity; as fitness improves aiming for at least 60 min/day moderate or at least 30 min/day vigorous intensity
- **Diet:** Emphasis on minimally processed, fiber-containing plant foods supports lower risk of diabetes and cancer through a variety of means.
For diabetes prevention: Reduce calories and dietary fat for weight loss as appropriate; dietary fiber intake of 14 g fiber/1,000 calories, including foods containing whole grains.
For cancer prevention: a mostly plant-based diet from a variety of vegetables, fruits, whole grains and legumes, limiting energy-dense foods and “fast foods,” and avoiding sugary drinks, while limiting red meat and avoiding processed meat. Alcohol, if consumed, should be kept in moderation.

Diabetes therapy may affect cancer risk, and some cancer therapies can worsen glycemic control.

Research Background

Research shows that diabetes is associated with an increased risk of several types of cancer. A consensus panel of experts convened by the American Diabetes Association and American Cancer Society issued a report (Giovannucci, 2010) on the association of diabetes with cancer incidence and prognosis, potential biologic links and risk factors that may connect them, and the impact of diabetes treatment on cancer.

Type 2 diabetes is associated with three of the five leading causes of cancer mortality in the United States

With the publication of this report and the clear evidence that lifestyle can change cancer risk (World Cancer Research Fund / American Institute for Cancer Research, 2007), it is time for diabetes care to include attention to cancer risk as well. To help health professionals understand and implement such steps, this paper will:

1. Review research of the risk of diabetes and cancer (including studies published since creation of the consensus report),
2. Discuss the intersection of steps to prevent both conditions, and
3. List specific strategies for guiding patients in lifestyle changes.

Type 1 and Type 2 Diabetes

One of every ten U.S. adults has diabetes. Type 2 is the more common and accounts for 90-95% of cases. (Centers for Disease Control and Prevention, 2008)

Type 1 diabetes is relatively uncommon and is characterized by absolute deficiency of insulin and requirement for exogenous insulin treatment. It also carries an excess cancer risk (Smith U, 2009), but involves somewhat different types of cancer (stomach, endometrium, cervix and pancreas) (Gerstein, 2010) and will not be the focus of this paper.

Type 2 diabetes initially includes hyperglycemia and hyperinsulinemia that usually coexist for years, because of insulin resistance in peripheral tissues. Eventually beta-cells in the pancreas tend to fail, and exogenous insulin therapy becomes necessary for many.

Type 2 diabetes is associated with three of the five leading causes of cancer mortality in the United States – cancers of the colon, breast (postmenopausal) and pancreas, as well as cancers of the liver, kidney, bladder and endometrium, and with non-Hodgkin lymphoma and possibly others (Vigneri P, 2009; Renehan A, 2010; Hjartaker A, 2008; Hemminki K, 2010; Chodick G, 2010; Coughlin S, 2004).

Mortality rates of cancer patients with pre-existing diabetes seem to be 40 to 50 percent higher than for those without diabetes (Barone B, 2010; Barone B, 2008) and are especially noted to increase for those with cancers of the colon, breast and endometrium (Larsson S, 2005; Meyerhardt J, 2003; Larsson S, 2007). It's unclear whether diabetes makes cancer more aggressive (perhaps through hyperglycemia or hyperinsulinemia), whether health problems that may accompany diabetes impair response to cancer therapy, or both.

Diabetes and Prostate Cancer

Although Type 2 diabetes increases risk for many cancers, most studies link diabetes to decreased risk of prostate cancer (Vigneri P, 2009). In the prospective NIH-AARP Diet and Health Study, during five years of follow-up, men with diabetes showed nearly 30 percent lower risk of developing prostate cancer after adjusting for other risk factors (Calton B, 2007). Several other prospective studies show 25 to 35 percent lower risk (Rodríguez C, 2005; González-Pérez A, 2005; Zhu K, 2004; Giovannucci E, 1998), although two case-control studies do not show reduced risk (Pierce B, 2008). Most researchers attribute the decrease in risk to lower testosterone levels, and perhaps increased estrogen levels, in diabetic men; for a detailed review, see Giovannucci (2007a). In a study that analyzed data by tumor aggressiveness, the lower prostate cancer risk was only seen in non-aggressive prostate tumors, not in tumors of more advanced stage (Leitzmann M, 2008).

Some research suggests that although diabetes may be associated with reduced incidence of prostate cancer, it may have little or no effect on progression of the disease. Other studies link diabetes with increased long-term, overall mortality of men with prostate cancer, perhaps because insulin and elevated blood glucose may promote prostate tumor growth (Snyder C, 2010; Parekh N, 2009). However, this could also be due to cardiovascular and diabetes effects of androgen deprivation therapy commonly used in prostate cancer treatment (D'Amico A, 2009).

Understanding the Diabetes-Cancer Link: Shared Risk Factors

A major question concerning the influence of type 2 diabetes on cancer risk is whether diabetes independently increases risk for these cancers, or whether the two diseases occur together because of a shared link to obesity, lack of physical activity and tobacco smoking (Giovannucci E, 2010).

The diabetes-cancer connection is seen in many studies after adjusting for body mass index (BMI), and other studies link metabolic correlates of diabetes (such as hyperinsulinemia and inflammation) with increased cancer risk, so research generally concludes that type 2 diabetes and its metabolic abnormalities are plausible independent risk factors for cancer.

In addition, people often have pre-diabetes for years before being diagnosed with type 2 diabetes. Pre-diabetes, with its underlying insulin resistance, results in above normal insulin levels and elevated blood sugars (Zhou J, 2007). Cancer may also take years to develop, and it is likely that these early pre-diabetic metabolic changes also increase cancer risk (Grote V, 2010; Vigneri P, 2009; Giovannucci E, 2007).

Obesity

AICR's second expert report (World Cancer Research Fund/ American Institute for Cancer Research, 2007) reports high body fat as a convincing cause of several cancers. Obesity also increases risk of type 2 diabetes, but research suggests that insulin resistance and other metabolic changes associated with pre-diabetes do increase cancer risk independently of obesity (Grote V, 2010; Stocks T, 2009; Dankner R, 2007).

Adipose (or fat) tissue consists of adipocytes and infiltrating macrophage cells of the immune system. Fat tissue is now recognized as an endocrine organ (produces hormones), and changes in levels of these adipose-derived hormones may pro-

Type 2 Diabetes and the Link to Certain Cancers: Risk and Possible Mechanisms

Cancer Site	Risk Ratio* (95% CI) in meta-analysis of cohort studies	Potential mechanisms
Liver Cancer	2.51 (1.9-3.2) 7 cohort studies (El-Serag H, 2006)	<ul style="list-style-type: none"> • Insulin resistance leads to non-alcoholic fatty liver disease, which allows damage from free radicals and inflammatory cytokines. This may lead to cirrhosis and then cancer. • Possibly some effect of more hepatitis infections.
Pancreatic Cancer	1.73 (1.59-1.88) 19 cohort studies (Huxley R, 2005)	<ul style="list-style-type: none"> • Obesity • Elevated insulin • Oxidative stress from hyperglycemia • Association may reflect diabetes not only as risk but also as an early consequence of pancreatic cancer.
Endometrial Cancer	1.62 (1.21–2.16) 3 cohort studies (Friberg E, 2007)	<ul style="list-style-type: none"> • High levels of insulin and free IGF-1 • Increased bioavailable estrogen
Bladder	1.43 (1.18–1.74) 3 cohort studies (Larsson S, 2006)	<ul style="list-style-type: none"> • Hyperinsulinemia and increased IGF-1 • Possibly more urinary tract infections with diabetes
Non-Hodgkin Lymphoma	1.41 (1.07-1.88) 5 cohort studies (Mitri J, 2008)	<ul style="list-style-type: none"> • Abnormal immune function in diabetes
Colorectal Cancer	1.29 (1.16–1.43) 9 cohort studies (Larsson S, 2005) 1.23 (1.17-1.30) 15 cohort studies (Huxley R, 2009)	<ul style="list-style-type: none"> • Hyperinsulinemia • Inflammation • Slower bowel transit time • Elevated fecal bile acid concentrations
Breast Cancer (postmenopausal probably more affected than pre-menopausal)	1.20 (1.11–1.30) 15 cohort studies (Larsson S, 2007)	<ul style="list-style-type: none"> • High levels of insulin and IGF-1 • Increased bioavailable estradiol and testosterone resulting from inhibited sex-hormone binding globulin (SHBG) production

*Risk Ratios for various cancers comparing people with diabetes to people without diabetes.

Data are fully adjusted estimates. Studies differed in their inclusion criteria (e.g. Some studies included both type 1 and type 2 diabetes) and in covariates included. No meta-analysis of diabetes and renal cancer risk currently available.

mote development of both Type 2 diabetes and cancer. Two of these hormones are leptin and adiponectin.

Leptin is an appetite regulator in the feedback control system of body fat; in normal metabolism, high levels of leptin lead to decreased body fat. However, leptin resistance is often present in diabetes; leptin receptors function abnormally, and despite high levels of leptin, appetite remains high and adipose tissue continues to increase.

These elevated levels of leptin may increase cancer development indirectly, by promoting hyperinsulinemia, increasing inflammation and inducing aromatase enzymes that increase estrogen levels in postmenopausal women. They may also increase risk directly, as shown by *in vitro* studies in which leptin promotes cell proliferation and angiogenesis (development of blood supply that allows cancer cells to grow and metastasize) (Godsland I, 2009; Gnacińska M, 2009; Pais R, 2009).

Adiponectin is a hormone with anti-inflammatory effects, and obesity is linked with decreased levels of this hormone, unlike other adipose-derived hormones. Reduced adiponectin may promote cancer development in the following ways:

- ◆ Increase insulin resistance
- ◆ Increase inflammation

- ◆ Increase in tumor necrosis factor- α (TNF- α) and nuclear factor- κ B (NF- κ B) which seem to increase cell proliferation and angiogenesis (Becker S, 2009; Pais R, 2009).

Insulin Resistance

Insulin resistance (IR) is a state of reduced sensitivity to insulin. In IR, insulin has impaired ability to 1) inhibit liver production of glucose and 2) stimulate glucose uptake by muscle and adipose cells. As a result, more insulin is required and the pancreas tries to keep up by producing more. Normal or near-normal blood sugar levels may occur in IR as long as pancreatic beta-cells are able to continually increase insulin secretion (Godsland I, 2009). IR may exist for many years before a diabetes diagnosis.

Higher blood levels of insulin and a biomarker of insulin secretion (C-peptide) are associated with some cancers, including a two- to three-fold increase in colon cancer risk in men (with mixed results in women) and a two- to four-fold increase in pancreatic cancer (Becker S, 2009; Pais R, 2009).

How Hyperinsulinemia May Increase Cancer Risk

Hyperinsulinemia and insulin resistance may cause pre-malignant lesions to grow into invasive cancer (Godsland I, 2009).

When insulin binds to its receptor, it promotes proliferation of cells, both normal and cancerous (Pais R, 2009; Xue F, 2007). Many cancer cells reportedly have increased concentrations of insulin receptors, so cancer cells may be especially responsive to growth signals from elevated insulin (Xue F, 2007, Becker S, 2009).

Furthermore, increased insulin levels decrease liver synthesis of insulin-like growth factor binding proteins, leading to an increase in bioavailable insulin-like growth factor-1 (IGF-1). Like insulin, IGF-1 promotes cell proliferation and inhibits apoptosis in many tissues (Becker S, 2009).

The impact of insulin resistance on estrogen is complex. Hyperinsulinemia generally inhibits aromatase activity, which can decrease estrogen production in postmenopausal women. However, there is an increased bioavailability of estrogen and testosterone because insulin resistance decreases circulating levels of sex-hormone-binding globulin (SHBG). Some evidence also suggests that the IGF-1 signaling system and estrogen may synergistically promote cell proliferation (Xue F, 2007). The net effect is still unclear, but is likely promotion of estrogen-related cancers (Hjartaker A, 2008).

Many researchers consider chronic, subclinical inflammation a key factor leading to insulin resistance and to cancer development and progression

Inflammation

Many researchers consider chronic, subclinical inflammation a key factor leading to insulin resistance and to cancer development and progression (Godsland I, 2009).

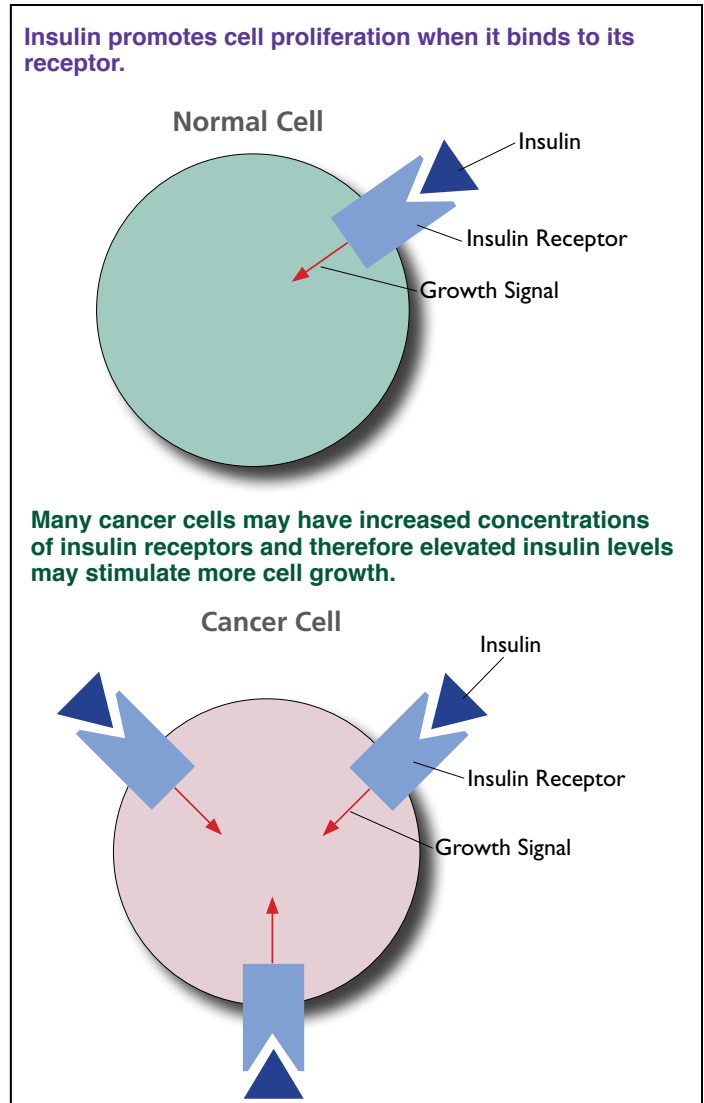
- ◆ Chronic inflammation leads to high concentrations of free radicals that can damage cell DNA and disrupt insulin signaling. Genetic mutations that ensue can lead to tumor formation (Godsland I, 2009; Vigneri P, 2009).
- ◆ Several studies link signs of inflammation, such as increased C-reactive protein (CRP, a circulating biomarker of inflammation) and inflammatory cytokines (cell-to-cell signaling proteins), with colorectal carcinogenesis and possibly with larger tumor size (Pais R, 2009). Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), seem to promote cancer development and progression through several pathways.

Hyperglycemia

Elevated blood glucose levels and impaired glucose tolerance without diabetes are both associated with increased cancer risk. Cancer cells use glucose for proliferation, and some laboratory studies suggest that higher circulating glucose may especially support malignant cell growth (Xue F, 2007). Potential mechanisms include decreased immune function and increased free radical formation associated with elevated glucose (Vigneri P, 2009). Hyperglycemia may also lead to formation of advanced glycation end products (AGEs), which could increase inflammation (Becker S, 2009).

Two reviews (Pais, R 2009, Becker, S 2009) link measures of hyperglycemia such as A1C with increased risk of colorectal, pancreatic, endometrial and other cancers.

Because chronically elevated glucose levels are associated with insulin resistance, and often with excess body fat and its metabolic effects, research is not yet clear about the direct impact of hyperglycemia per se on cancer risk (Vigneri P, 2009; Bowker S, 2007).



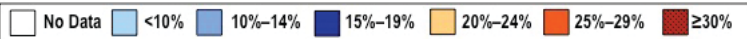
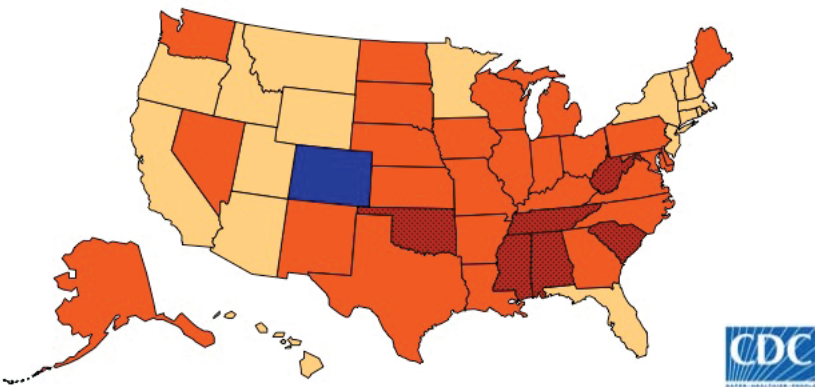
Recommendations for Practice: The Intersection of Diabetes & Cancer Prevention

Lifestyle and Diabetes Prevention

Two landmark intervention studies—The Finnish Diabetes Prevention Study (Tuomilehto J, 2001) and the Diabetes Prevention Program (Knowler W, 2002) – demonstrated that lifestyle changes could decrease incidence of diabetes by 58 percent. Ten-year follow-up data on the Diabetes Prevention Program showed that intensive lifestyle change remained more effective for preventing diabetes than metformin medication (Diabetes Prevention Program Research Group,

Obesity Trends* Among U.S. Adults BRFSS, 2008

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



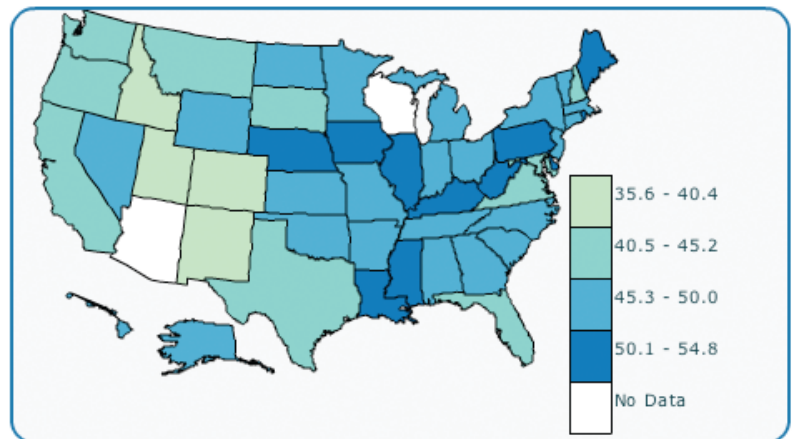
Source: Behavioral Risk Factor Surveillance System, CDC.

Overlap of Obesity Rates, Diabetes Rates and Incidence of Colorectal Cancer by State

Age-Adjusted Incidence Rate of Cancers of the Colon and Rectum 2006

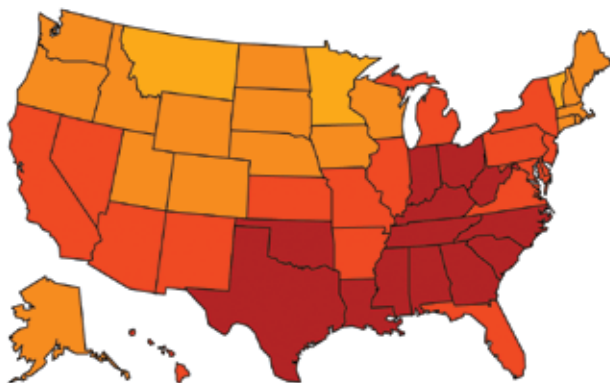
Age-Adjusted Incidence Rate – Colon and Rectum***

■ 2006** ■ All Races ■ Male and Female



*Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population.
Centers for Disease Control. <http://www.cdc.gov/cancer/colorectal/statistics/state.htm>

Age-adjusted Percentage of U.S. Adults Who Had Diagnosed Diabetes 2008



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>



2009). Other trials summarized by Paulweber et al. (2010) also demonstrate that lifestyle can decrease diabetes incidence, and several smaller intervention studies, such as the one by Matvienko and Hoehns (2009), show that the methods from these large trials can be successful in community settings. A systematic review recently concluded that these interventions can be cost-saving or very cost effective (Li R, 2010)

The American Diabetes Association recommends dietary and lifestyle changes aimed at reducing insulin resistance for those who have or are at risk of diabetes (American Diabetes Association, 2008). Research increasingly emphasizes the need to target more than glucose control, since that alone is not sufficient to decrease the chronic inflammation that seems to promote the negative health consequences of diabetes and of insulin resistance itself (Pradhan A, 2009; de Ferranti S, 2008).

Lifestyle and Cancer Prevention

With relationships to obesity, insulin resistance and inflammation in common, it may be no surprise that recommendations to prevent diabetes (American Diabetes Association, 2008; Paulweber B, 2010) overlap considerably with recommendations to prevent cancer (World Cancer Research Fund / American Institute for Cancer Research, 2007). Research suggests that implementation of the latter recommendations could prevent about one-third of our most common cancers (World Cancer Research Fund/American Institute for Cancer Research, 2009).

Weight Management

1. Help patients set initial goal of 5-7% weight loss

Excess body fat, as noted above, is strongly related to risk of both diabetes and cancer, and weight loss if overweight is one of the primary recommendations for reducing risk of Type 2 diabetes.

Diabetes: The Diabetes Prevention Program for people with pre-diabetes targeted a 7 percent weight loss (14 pounds for someone who weighs 200 pounds). Weight loss was one of the strongest predictors of diabetes risk; each kilogram decreased incidence of type 2 diabetes by 16 percent (Paulweber B, 2010). Weight loss was also even more strongly related to reducing a marker of inflammation than change in physical activity or blood sugar control in one study. CRP, a marker of inflammation, decreased about 30 percent in the intervention group compared to a decrease less than 15% in the metformin group and an increase of less than 5% in the placebo group (Haffner S, 2005).

Cancer: As body fatness increases (measured by body mass index), risk for many cancers increases (World Cancer Research Fund / American Institute for Cancer Research, 2007). More research is needed on how weight loss changes cancer risk, but a few prospective cohort studies do show significant impact (Parker E, 2003; Eliassen A, 2006; Harvie M, 2005).

2. Work with patients to identify strategies to decrease calorie consumption by at least 500 calories a day

Position papers from the American Dietetic Association (Seagle H, 2009) and American Diabetes Association (American Diabetes Association, 2008) recommend decreasing calorie consumption by 500 to 1000 kcal/day from levels that maintain current weight to achieve a five to ten percent weight loss. Maintenance of a lower weight is critical, so

treatment should identify dietary changes that make ongoing reduced calorie consumption realistic and include cognitive and behavioral interventions (Seagle H, 2009).

Review of research on diet's relationship to weight control led to these recommendations from the American Institute for Cancer Research expert report (2007): limit consumption of energy-dense foods and avoid sugary drinks. A previous AICR *InDepth* paper reviews the evidence and recommendations for implementing a low energy density diet. One prospective cohort from the EPIC study suggests that diets lower in energy density might even reduce risk of diabetes independently of its effects on weight and weight gain (Wang J, 2008). Avoiding sugar-sweetened soft drinks may pay off in decreasing risk of diabetes beyond their impact on weight: in the Nurses' Health Study II, compared with women consuming less than one sugar-sweetened soft drink per month, women consuming more than one daily soft drink showed more than an 80 percent increase in risk of diabetes, and after adjustment for BMI and calorie consumption, risk remained a significant 32 percent higher (Schulze M, 2004).

Excess body fat is strongly related to risk of both diabetes and cancer, and weight loss if overweight is one of the primary recommendations for reducing risk of Type 2 diabetes.

Regular Physical Activity

1. Set goals with patients to increase physical activity above their current levels

Diabetes: A second vital step in diabetes prevention programs is establishing a pattern of regular physical activity, because sedentary lifestyles seem to contribute to risk of type 2 diabetes independently (Paulweber B, 2010) as well as through impact on obesity. Physical activity leads to an increase in insulin sensitivity that lasts 24 to 72 hours (Hayes C, 2008). Most of the large-scale diabetes prevention programs aim for at least 150 minutes a week, equal to about 30 minutes of moderate exercise such as walking five days a week. People who already have diabetes should work with their health-care providers to adapt physical activity level so that it is appropriate for their condition, being careful to monitor their blood glucose. Regular moderate exercise improves metabolic control in Type 2 diabetes (USDHHS, 2008).

Cancer: Regular physical activity convincingly lowers incidence of colorectal cancer, probably reduces endometrial and postmenopausal breast cancers, and may reduce risk of other cancers as well (World Cancer Research Fund/American Institute for Cancer Research, 2007). Proposed mechanisms for physical activity's role in lowering cancer risk include its effects on obesity, insulin resistance, inflammation and reproductive hormones. The AICR expert report recommends at least 30 minutes daily of moderate physical activity to reduce cancer risk, noting that reaching 60 minutes of moderate, or 30 minutes of vigorous, daily activity is even more beneficial

for cancer prevention. This is compatible with the latest recommendations for overall health from the American College of Sports Medicine (ACSM 2007) and the U.S. Department of Health and Human Services (USDHHS, 2008). Cancer survivors, like others with chronic conditions, should consult their health-care providers to see if physical activity plans need adjustment to match their health needs.

2. Help patients identify support and strategies for maintaining regular physical activity

Clinicians and educators can emphasize that the 30- or 60-minute goals need not be accomplished all at once and help people find blocks of 10 or 15 minutes during the day that could be spent in walking or other moderate physical activity. By keeping a log of time spent in sedentary activities such as television viewing, which is linked with greater waist, body fat and BMI, people might identify opportunities to take a portion of that time for physical activity that they could find relaxing and enjoyable (Cleland V, 2008; Jakes W, 2003; World Cancer Research Fund/American Institute for Cancer Research, 2007). Planning for and setting aside specific blocks of time for physical activity and tracking physical activity seem to support this behavior change.

Clinicians and educators can emphasize that the 30- or 60-minute goals need not be accomplished all at once, and help people find blocks of 10 or 15 minutes during the day. . .(for) physical activity.

Diet

1. Teach patients how to follow a mostly plant-based diet:

Diabetes: Low-fiber diets have been linked with increased risk of Type 2 diabetes in several population studies, and increased fiber consumption has been part of diabetes prevention interventions (Paulweber B, 2010).

The American Diabetes Association recommends the general health target of 14 g total dietary fiber per 1,000 kcal for people at increased risk of diabetes (American Diabetes Association, 2008). The Finnish Diabetes Prevention Study targeted fiber intake of at least 15 g per 1,000 kcal.

High fiber foods tend to have a low glycemic index (raise blood sugars to a limited degree), which may contribute to the reduction in diabetes risk. However, not all foods with a low glycemic index are high in fiber or nutrients. Research does not consistently demonstrate that diets low in glycemic index or load reduce risk of diabetes, though they may help to manage existing diabetes (American Diabetes Association, 2008; Paulweber B, 2010).

Cancer: Dietary recommendations to reduce cancer risk focus on predominantly plant-based diets emphasizing a wide variety of vegetables, fruits, whole grains and legumes. Foods high in dietary fiber probably protect against colorectal cancer and also provide a wide range of nutrients and phytochemicals that may act in a variety of pathways, possibly synergistically, to reduce the development of many cancers

(World Cancer Research Fund/American Institute for Cancer Research, 2007).

The simple concept of AICR's New American Plate, that at least two-thirds of our plate should be composed of plant foods – vegetables, fruits, whole grains and beans – can be an easy way to share this message. We can help people identify ways to include vegetables and/or fruits in every meal and in snacks.

2. Educate patients about appropriate consumption of dietary fat

Diabetes: Most of the diabetes prevention trials have included a moderately low-fat diet (<30 percent of calories), but the importance of fat consumption to diabetes risk beyond its concentrated calories is unclear (Tinker L, 2008; Paulweber B, 2010). Trans fat is consistently linked to diabetes risk (Paulweber B, 2010) and the American Diabetes Association recommends that saturated fat intake be limited to <10 percent of calories. Replacing saturated fat with monounsaturated fat, with less focus on reducing total fat, may improve insulin sensitivity and glucose control (Coppell K, 2010; Esposito K, 2010; Esposito K, 2009), though other researchers recommend reducing consumption of virtually all fats (Barnard N, 2009).

Cancer: The AICR expert report found that foods high in energy density are a probable cause of weight gain, overweight and obesity. Many high fat foods are high in energy density, but otherwise the expert report did not find dietary fat consumption as a significant risk factor for cancer (World Cancer Research Fund / American Institute for Cancer Research, 2007).

Helping a patient move toward a diet lower in energy density and with more healthful fats might begin with working together to identify frequent high calorie, high fat and low nutrient choices. First steps could be decreasing deep-fried foods; fat-laden snack foods, baked goods or desserts; high-fat meats and full-fat dairy products. It's important to show people who are used to getting much of the flavor in their food from added fat how they can make food delicious in other ways, such as herbs, spices and fruits. Simply decreasing portions or frequency of consuming higher-fat foods without giving them up completely can also be a successful strategy.

It's important to show people who are used to getting much of the flavor in their food from added fat how they can make food delicious in other ways, such as herbs, spices and fruits

3. Demonstrate appropriate serving sizes and total recommended amounts for red and processed meat consumption

Diabetes: Traditionally, only meat's saturated fat content has been a diabetes-related focus. Some research suggests that highest consumers of red and processed meat may be at increased risk of diabetes, but the nature of such a relationship is not clear at this time (Aune D, 2009).

Cancer: To reduce risk of colorectal cancer, recommendations call for consuming no more than 18 ounces per week of red meat and avoiding processed meat (World Cancer Research Fund / American Institute for Cancer Research, 2007).

4. Explain recommendations for alcohol consumption

Diabetes: Observational studies suggest that moderate alcohol consumption may reduce insulin resistance and risk of diabetes. However, the American Diabetes Association concludes that research does not support recommending alcohol consumption to decrease risk of diabetes, and consumption of more than three standard alcoholic drinks (45 g ethanol) per day may be linked with increased risk of diabetes (American Diabetes Association, 2008). Alcohol's concentrated calories represent a concern for both diabetes and cancer risk, since both are strongly linked to overweight.

Cancer: If alcohol is consumed at all, recommendations from the American Diabetes Association and AICR are to limit alcohol to no more than one drink per day for women and no more than two drinks per day for men. Alcohol is a convincing cause of colorectal cancer in men (a probable cause in women), pre- and post-menopausal breast cancer, and cancers of the mouth, pharynx, larynx and esophagus (World Cancer Research Fund / American Institute for Cancer Research, 2007).

cancer risk (Giovannucci E, 2010; Vigneri P, 2009; Becker S, 2009; Godsland I, 2009). Clinical trials are currently underway to evaluate potential anti-cancer benefit of metformin (Becker S, 2009; Godsland I, 2009).

Sulfonylureas, a separate family of oral agents, stimulate endogenous insulin secretion, which may increase hyperinsulinemia, potentially increasing cancer risk (Vigneri P, 2009). Different sulfonylureas may have different effects, and direct impact on cancer (positive or negative) is not yet known (Giovannucci E, 2010).

Clinical trials are still needed to clarify the impact on cancer from other oral agents, thiazolidinediones and glinides (Giovannucci E, 2010).

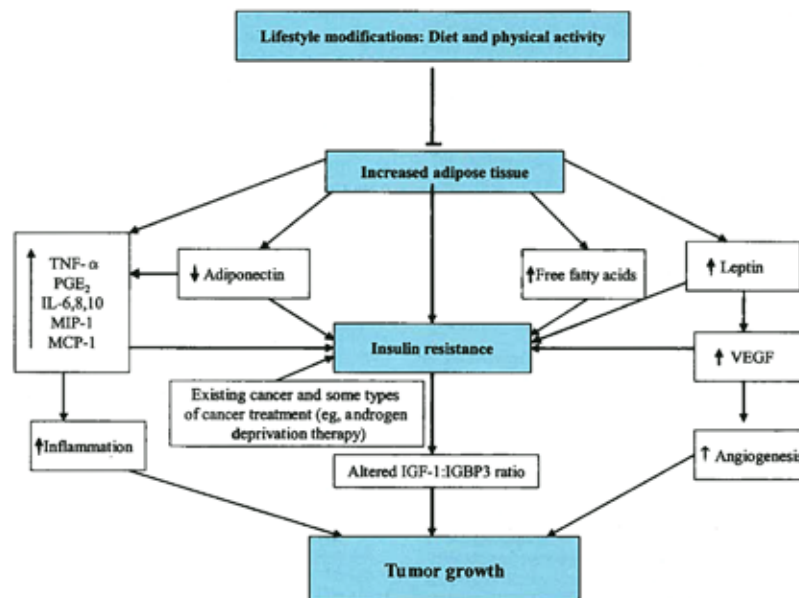
In response to tighter blood sugar control goals, more than a quarter of patients with diabetes reportedly now use some form of exogenous insulin therapy (Call R, 2010). Several studies suggest an association between insulin therapy and increased cancer risk, possibly with time- and dose-dependent effects (Yang X, 2010; Bowker S, 2006). Yet it's difficult to separate risks related to exogenous insulin from risks related to poor glucose control. Clinicians are urged to be diligent in screening for cancer and growth of existing cancer in patients receiving insulin (Call R, 2010).

Special Consideration: Treatment Issues

Impact of Diabetes Treatment on Cancer

Metformin, an oral agent used in controlling type 2 diabetes, increases insulin sensitivity. *In vitro*, animal and limited epidemiological studies suggest that metformin could reduce

Clinicians are urged to be diligent
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receiving insulin.



Potential mechanisms of obesity, insulin resistance, and related biomarkers in cancer progression. This figure illustrates how adipocyte-derived cytokines (adipokines), inflammatory factors, insulin, and the insulin-like growth factor-1 (IGF-1) axis, might work in concert to promote tumor growth. Insulin resistance seems central to the pathway promoting tumor growth. Management of insulin resistance and obesity through lifestyle modification, specifically consumption of healthier diets and increased physical activity, may prevent or delay cancer progression. TNF- α =tumor necrosis factor α ; PGE2=prostaglandin E-2; IL-6, -8, -10=interleukin-6, -8, -10; MIP-1=macrophage inflammatory protein 1; MCP-1=monocyte chemoattractant protein 1; VEGF=vascular endothelial growth factor; IGF-1:IGBP3=insulin-like growth factor 1:insulin-like growth factor binding protein 3.

Source: Parekh, N et. al. Journal of the American Dietetic Association 2009; 109:1346-1353
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Impact of Cancer Treatment on Diabetes

Some drugs used to treat cancer or side effects of cancer therapy may either cause diabetes or stimulate transformation of existing pre-diabetes or metabolic syndrome to full-blown diabetes.

- ◆ High dose glucocorticoids are well known to aggravate blood sugar control.
- ◆ Androgen deprivation therapy for prostate cancer increases insulin resistance and also leads to a “sarcopenic obesity” (rapid loss of muscle tissue and increased body fat)
- ◆ Newer therapies that target IGF-1 because of its role in promoting cancer may also lead to hyperglycemia (Vigneri P, 2009).

Finally, adult survivors of childhood cancer are at increased risk of developing diabetes or metabolic syndrome. Risk seems especially related to a history of radiation therapy (Meacham L, 2009), but may also relate to some types of chemotherapy, becoming overweight or a sedentary lifestyle.

Clinicians are urged to be mindful of the increased risks in this population, both in being diligent in screening for diabetes and in promoting healthful lifestyle habits.

Questions That Need More Research

Is the relationship between diabetes and cancer risk most affected by excess body fat, hyperinsulinemia, inflammation or other factors?

These influences are so interwoven that it is difficult to identify the impact of each individually. Many lifestyle strategies, as noted above, that benefit one factor benefit others as well. Research in many areas of health seems to be moving away from “reductionist” approaches, supporting instead the importance of overall healthful lifestyle patterns. However, it is possible that more focused lifestyle changes or medical therapies could be developed if a key target is identified.

To reduce cancer risk, how tight should glycemic control be and does it matter how glucose control is achieved?

In order to reduce eye, kidney and cardiovascular complications of diabetes, clinicians are setting lower and lower blood sugar targets. This may either lower cancer risk through reduced glucose levels or earlier resolution of hyperinsulinemia, or increase cancer risk due to elevated levels of insulin or other side effects of some treatments.

How much do diabetes and pre-diabetes influence progression and mortality rates of cancer that has developed?

Diabetes does seem linked with increased mortality rates of at least some cancers. It’s not clear how diabetes, and various approaches to controlling diabetes, might impact progression of cancer once it develops.

How should clinicians manage hyperglycemia that occurs during cancer treatment?

People undergoing cancer treatment sometimes have trouble eating enough, so they use foods and supplements designed to boost calories. These foods often contain high loads of sugar and low-fiber carbohydrate that may increase hyperglycemia. In other cases, the treatment causes hyperglycemia. It would be helpful to have evidence-based guidance on the

best way to respond: 1) Reduce blood glucose through oral medications or exogenous insulin therapy, 2) reduce blood glucose by changing carbohydrate intake or 3) simply allowing the somewhat elevated glucose levels.

Clinicians are urged to be mindful of the increased risks in this population, both in being diligent in screening for diabetes and in promoting healthful lifestyle habits.

Talking with Patients about the Diabetes-Cancer Connection

I. There is a connection between type 2 diabetes and increased risk for certain types of cancer.

- ◆ These include cancers of the liver, pancreas, colon, endometrium, breast (postmenopausal), kidney and bladder, and non-Hodgkin lymphoma.
- ◆ Changes in the body that occur with type 2 diabetes can promote cancer development.
 - Even before diabetes fully develops, inflammation and increased levels of insulin seem to create an environment in the body that encourages development of cancer.

II. Lifestyle changes are more effective than diabetes medications in reducing risk for type 2 diabetes and for diabetes-related cancer.

- ◆ Blood sugar control alone is not enough to decrease chronic inflammation.
- ◆ Studies show lifestyle changes to be more effective than metformin in preventing diabetes.

III. Weight management will lower risk for type 2 diabetes and some cancers.

- ◆ Excess body fat is a cause of type 2 diabetes and of some cancers.
 - Insulin may become less effective. The body responds by secreting more insulin, and these high loads of insulin can promote cancer development.
 - Fat tissue produces hormones that affect development of both diseases.
- ◆ Evidence is strong that overweight people who reduce their weight by 5 to 10 percent (10 to 20 pounds for someone who weighs 200 pounds) can reduce their risk of diabetes or improve its control.
- ◆ Maintaining weight within a normal range, and avoiding weight gain and increases in waist size throughout adulthood reduce cancer risk.
- ◆ Successful weight loss efforts include reducing intake by 500 to 1000 calories/day.
 - Decrease portion sizes overall, particularly of more calorie-dense foods.
 - Substitute foods less concentrated in calories for low-nutrient foods and drinks high in fat or sugar.

IV. You can reduce risk of both type 2 diabetes and cancer with moderate activity daily.

- ◆ Regular physical activity helps control blood sugar and reduces hormones that promote cancer.
- ◆ If not already physically active, aim for at least 30 minutes a day of moderate activity like walking. You can do it all at once or accumulate it in blocks of 10 or 15 minutes.
- ◆ Work up to at least 60 min/day moderate or 30 min/day vigorous activity to reach and maintain a healthy weight, for lower risk of diabetes, cancer and other health problems.
- ◆ Physical activity can mean “exercise,” but also includes moderate to strenuous activities in your workday, errands and hobbies such as gardening and dancing.

V. Choose a healthy diet with a variety of vegetables, fruits, whole grains and beans.

- ◆ Nutrients and natural plant compounds help prevent diabetes and cancer in many different ways. For example, these foods provide fiber that can help control blood sugar and reduce risk of colon cancer. Choose mostly minimally processed plant foods that retain their healthful compounds.
- ◆ Limit high-fat dairy products and meats to avoid too much saturated fat. But even if meat is lean, keep total red meat to no more than 18 ounces a week and avoid processed meat for lower colon cancer risk.
- ◆ If you drink alcohol, include no more than one drink per day for women or two per day for men. One drink is 12 ounces of beer, 5 ounces of wine or 1½ ounces of 80-proof liquor.

For more information:

Check out AICR’s New American Plate for healthy meals that promote lower risk of cancer and help with weight control.

Visit www.aicr.org/reduceyourcancerrisk_home.

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Glossary

Beta Cell: a cell that makes insulin. Beta cells are located in the islets of the pancreas.

Nuclear Factor- κ B: a transcription factor that controls the gene expression of several pro-inflammatory proteins.

Cohort Study: A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes later), followed up for a period of time during which outcomes of interest are noted. Differences in the frequency of outcomes (such as disease) within the cohort are calculated in relation to different levels of exposure to factors of interest, for example smoking, alcohol consumption, diet and exercise. Differences in the likelihood of a particular outcome are presented as the relative risk comparing one level of exposure to another.

Insulin, exogenous: a type that comes from a source external to a diabetic patient's body, taken to offset the patient's natural deficiency of insulin.

Hyperglycemia: Higher than normal amount of glucose (a type of sugar) in the blood. Hyperglycemia can be a sign of diabetes or other conditions. Also called high blood sugar.

Hyperinsulinemia: medical term for high levels of insulin in the blood.

IGF (Insulin Like Growth Factor): A protein made by the body that stimulates the growth of many types of cells. IGF is similar to insulin (a hormone made in the pancreas). There are two forms of IGF called IGF-1 and IGF-2. Higher than normal levels of IGF-1 may increase the risk of several types of cancer. IGF is a type of growth factor and a type of cytokine. Also called somatomedin.

IL-6 (Interleukin-6): One of a group of related proteins made by leukocytes (white blood cells) and other cells in the body. It causes B lymphocytes to make more antibodies and also causes fever by affecting areas of the brain that control body temperature. IL-6 is a type of cytokine that stimulates cell growth and inhibits apoptosis (self-destruction of abnormal cells).

Insulin resistance: the body's inability to respond to and use the insulin it produces. Insulin resistance may be linked to obesity, hypertension and high levels of fat in the blood.

Inflammation: The immunologic response of tissues to injury or infection. Inflammation is characterized by accumulation of white blood cells that produce several bioactive chemicals, causing redness, pain and swelling.

Macrophage: A type of white blood cell that surrounds and kills microorganisms, removes dead cells and stimulates the action of other immune system cells. (NCI Dictionary of Cancer Terms)

Meta-analysis: The process of using statistical methods to combine the results of different studies.

Processed Meat (usually red meat) preserved by smoking, curing, or salting, or by the addition of preservatives. Definitions vary between countries and studies as to what precisely is included.

Risk Ratio: A measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group. In cancer research, risk ratios are used in prospective (forward looking) studies, such as cohort studies and clinical trials. A risk ratio of one means there is no difference between two groups in terms of their risk of cancer, based on whether or not they were exposed to a certain substance or factor or how they responded to two treatments being compared. A risk ratio of greater than one or of less than one usually means that being exposed to a certain substance or factor either increases (risk ratio greater than one) or decreases (risk ratio less than one) the risk of cancer, or that the treatments being compared do not have the same effects.

TNF (tumor necrosis factor): A protein made by white blood cells in response to an antigen (substance that causes the immune system to make a specific immune response) or infection. TNF can also be made in the laboratory. It may boost a person's immune response, and also may cause necrosis (cell death) of some types of tumor cells. TNF is being studied in the treatment of some types of cancer. It is a type of cytokine.

<http://www.cancer.gov/dictionary>

<http://diabetes.niddk.nih.gov/dm/pubs/dictionary/>

<http://www.dietandcancerreport.org/>