

# Diabetes Mellitus and Increased Risk of Cancer: Focus on Metformin and the Insulin Analogs

*M. Shawn McFarland, Pharm.D.; Rebecca Cripps, Pharm.D.*

*From the Pharmacy Service, Tennessee Valley Healthcare System, Murfreesboro Campus, Tennessee (both authors).*

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## Abstract

Type 2 diabetes mellitus has been associated with an increased risk of hepatic, pancreatic, colon, endometrial, breast, and bladder cancer. Although a mechanism of action for the increased risk has been postulated, no definitive evidence has been completely elucidated in the medical literature. Results of recently released studies documented the use of specific antidiabetic drugs with increased rates of cancer. The insulin analog glargine was the focus of four observational studies published in 2009 that outlined an increase in the rates of cancer associated with its use. In contrast, the use of metformin has been shown to possibly decrease the rate of specific cancers when used in the treatment of type 2 diabetes. These data regarding cancer risk and antidiabetic drugs are contradictory and at this time are inconclusive. Until results of long-term randomized prospective studies are available to elucidate a correlation with cancer and insulin, we must continue treating diabetes in order to avert the long-term complications of the disease.

## Introduction

Type 2 diabetes mellitus has been linked with the possibility of an increased risk of cancer.<sup>[1]</sup> Specifically, higher rates of hepatic, pancreatic, colon, endometrial, bladder, and breast cancer have been reported in patients with diabetes.<sup>[2-7]</sup> A mechanism of action for the increased risk has been postulated but never completely elucidated in the medical literature. Obesity and insulin resistance have been linked to an increase in cancer of the colon, pancreas, and prostate.<sup>[8]</sup> Given that the pathophysiology of type 2 diabetes includes obesity and insulin resistance at its core, an increased risk of cancer seems to be logical in this patient population.

Recently, data have documented the use of specific antidiabetic drugs with increased rates of cancer. The insulin analog glargine was the focus of four observational studies published in 2009 that outlined an increase in the rates of cancer associated with its use.<sup>[9-12]</sup> In contrast, the use of metformin has been shown to possibly decrease the rate of specific cancers when used in the treatment of type 2 diabetes.<sup>[13-16]</sup>

To evaluate the relationship involving diabetes, cancer, metformin, and insulin analogs, we performed a literature search of the MEDLINE and OvidSP databases from January 1, 1960–June 15, 2010, using the following search terms: diabetes mellitus, type 2 diabetes, insulin, glargine, metformin, aspart, lispro, neutral protamine Hagedorn, cancer, breast cancer, colon cancer, and pancreatic cancer. Medical subject heading (MeSH) terms were insulin, insulin NPH, insulin aspart, Novolog Mix 70:30, neutral protamine lispro, insulin lispro, Humalog Mix 25, insulin detemir, and glargine. Additional references were evaluated, and resultant articles were obtained. A total of 1661 references were initially identified, of which 146 studies were evaluated after including only human and English-language studies.

# Diabetes and Cancer

## Risk of Cancer

Epidemiologic studies have linked diabetes to different types of cancer.<sup>[17–27]</sup> Dating back almost 20 years, meta-analyses have attempted to review the literature with regard to the incidence and mortality rates of specific cancers in patients with diabetes.<sup>[28]</sup> Specifically, higher rates of pancreatic and hepatic cancers have been identified.

**Pancreatic Cancer** In one meta-analysis, the risk of pancreatic cancer and type 2 diabetes was evaluated.<sup>[29]</sup> By searching multiple biomedical databases, the authors identified 36 studies from 1973–2005. Age- and sex-adjusted odds ratios (ORs) for pancreatic cancer associated with type 2 diabetes were extracted. Seventeen were case-control studies and 19 were cohort or nested case-control studies. Information was available on a total of 9220 patients. For the 17 case-control studies, a significant association was noted between type 2 diabetes and pancreatic cancer (OR 1.94, 95% confidence interval [CI] 1.43–2.46). Cohort studies yielded a similar finding, with an OR of 1.73 (95% CI 1.59–1.88). Combined OR for all studies was 1.82 (95% CI 1.66–1.99). The authors noted that there was some heterogeneity among both study designs ( $p=0.002$  for case-control studies,  $p=0.05$  for cohort studies) that was not explained by differences in sex, adjustment for smoking, or the method of diagnosing diabetes. The explanation given was the higher risk of pancreatic cancer reported in smaller studies and studies performed before the year 2000. Of the 36 studies, nine reported categories regarding disease duration. Evaluation of these studies revealed a 50% greater risk of developing pancreatic cancer in individuals with disease duration of less than 4 years versus individuals who had diabetes for more than 4 years (OR 2.1, 95% CI 1.9–2.3 vs OR 1.5, 95% CI 1.3–1.8). The authors concluded that along with cigarette smoking and obesity, type 2 diabetes may be a likely modifiable risk factor for pancreatic cancer.

**Hepatocellular Cancer** An evaluation of the literature regarding diabetes and hepatocellular carcinoma was conducted in 2006.<sup>[2]</sup> The authors performed a MEDLINE search for published articles from January 1966–February 2005 that pertained to diabetes and hepatocellular carcinoma. Twenty-six studies met the inclusion criteria (13 case-control studies and 13 cohort studies). Of the 13 case-control studies, eight found a statistically significant positive association between diabetes and hepatocellular carcinoma. The pooled OR for all case-control studies was 1.84 (95% CI 1.25–2.69). Confounders were adjusted for in eight of the 13 studies. Specifically, adjustment for alcohol use and viral hepatitis did not change the positive association between diabetes and hepatocellular carcinoma. In these 13 studies, diabetes was defined by face-to-face or mailed questionnaires in 10 studies and by medical record review or diagnostic codes in three studies.

Of the 13 cohort studies, seven evaluated patients with diabetes specifically, three studied a general population cohort, and three studied patients with underlying chronic liver disease. Diabetes was diagnosed based on glucose levels in five studies, use of a prescription drug for diabetes in two studies, diagnostic codes in three studies, and questionnaires in three studies. The pooled OR for all cohort studies was 2.5 (95% CI 1.93–3.24). Among the seven cohort studies of persons with diabetes, the pooled OR was 2.50 (95% CI 1.72–3.61). Three of the seven studies found a statistically significant positive association between hepatocellular cancer and diabetes. Only three of the seven studies adjusted for confounders, and although the risk was weakened, a risk still was associated with diabetes and hepatocellular carcinoma.

For both case-control and cohort study designs, heterogeneity did not exist among studies that used population-based controls ( $p=0.26$ ) but did exist among those with hospital-based controls ( $p<0.01$ ). Also noted was that heterogeneity existed among U.S. and European studies, but not

among Asian studies. The authors concluded that there was a 2.5-fold increase in the risk for hepatocellular carcinoma in patients with diabetes.

**Colorectal Cancer** A meta-analysis was conducted of published data on the association between diabetes and the incidence and mortality of colorectal cancer.<sup>[4]</sup> The authors searched MEDLINE for data published from 1966–2005 with specific MeSH terms for the subject of interest. They identified 15 studies overall (6 case-control and 9 cohort studies) that met their predefined inclusion and exclusion criteria. Eight of the 15 studies found a statistically significant positive association between diabetes and colorectal cancer (average relative risk (RR) for all studies 1.30, 95% CI 1.20–1.40); no heterogeneity was found among these studies ( $p=0.21$ ). Results did not differ depending on geographic location, as the results were significant whether the trial was conducted in Europe or the United States. The association did not differ with respect to sex. When restricted to studies controlling for physical activity and body mass index (BMI), two known confounders of the positive association of diabetes and cancer, a positive association still existed (summary RR 1.34, 95% CI 1.20–1.49).

Among the six cohort studies that evaluated mortality, a statistically significant positive association was noted between diabetes and colorectal cancer (summary RR 1.26, 95% CI 1.05–1.50), and significant heterogeneity existed among these studies ( $p=0.04$ ). Excluding the study contributing to heterogeneity identified by a sensitivity analysis,<sup>[18]</sup> the association between diabetes and mortality was not as strong (summary RR 1.9, 95% CI 1.10–1.28), with no statistically significant heterogeneity ( $p=0.40$ ). Once again, results did not differ based on sex. The authors concluded that published data trended toward a positive association between colorectal cancer and diabetes.

**Bladder Cancer** In 2006, a meta-analysis was conducted that evaluated the medical literature for the risk of bladder cancer in patients with diabetes.<sup>[6]</sup> The authors searched MEDLINE for data published from 1966–2006 with specific MeSH terms for the subject of interest. They identified 16 studies overall (seven case-control studies, three cohort studies, and six cohort studies of hospitalized patients with diabetes) that used external population comparisons and met their predefined inclusion and exclusion criteria. Evaluation of all studies revealed that diabetes was associated with a statistically significant increased risk of bladder cancer compared with patients without diabetes (RR 1.24, 95% CI 1.08–1.42). A strong indication of heterogeneity existed among the studies ( $p<0.0001$ ).

When evaluated based on study design, there was a 40% increase in the risk of bladder cancer among cohort studies (summary RR 1.43, 95% CI 1.04–1.80) and case-control studies (summary RR 1.37, 95% CI, 1.04–1.80). However, there was no increased risk in cohort studies of patients with diabetes specifically (summary RR 1.01, 95% CI 0.90–1.12). Of interest, the summary estimates were significantly higher in studies conducted in North America than in Europe ( $p=0.07$ ), for studies published after 2000 ( $p=0.01$ ), and for studies that adjusted for smoking ( $p<0.0001$ ). Summary estimates were similar in studies that adjusted for BMI. The authors concluded that patients with diabetes mellitus may have an increased risk for bladder cancer.

**Breast Cancer** In another study, the risk of and mortality from breast cancer and diabetes mellitus were evaluated.<sup>[7]</sup> The MEDLINE database was searched for articles related to the topic from 1966–2007. Twenty studies met the authors' predefined inclusion and exclusion criteria (5 case-control and 15 cohort studies). Nine trials were conducted in the United States, seven in Europe, and four in Asia. An increased risk of breast cancer was found in 15 studies, with the risk reaching statistical significance in eight. The RR was 1.18 (95% CI 1.05–1.32) for case-control studies and 1.20 (95% CI 1.11–1.30) for cohort studies. Among all studies, the RR was 1.20 (95% CI 1.12–1.28) for women with diabetes versus women without diabetes, indicating a 20% increased risk of

breast cancer. Statistically significant heterogeneity existed among the studies ( $p=0.01$ ). Using a sensitivity analysis, the authors excluded three studies that contributed significantly to the summary estimate, due to a diagnosis of diabetes that was based on discharge data. The RR remained unchanged but the CI widened and heterogeneity among the studies was reduced (RR 1.20, 95% CI 1.09–1.33,  $p=0.10$ ).

Five of the studies reported mortality results on diabetes and breast cancer. Combined results of these studies provided a nonsignificant RR of 1.24 (95% CI 0.95–1.62). The authors concluded that diabetes, largely type 2, was associated with an increased risk of breast cancer but not an increase in mortality.

**Endometrial Cancer** Another group evaluated the risk of endometrial cancer and diabetes.<sup>[5]</sup> A MEDLINE database search was performed for articles related to the topic from 1966–2007. Twenty-five studies met the authors' predefined inclusion and exclusion criteria: 13 case-control studies and 12 cohort studies (5 reported incidence and/or mortality rate ratios as the measure of RR, and 7 reported standardized incidence or mortality rates as the measure of risk). Twelve trials were conducted in the United States, 11 in Europe, one in Asia, and one in South America. In this meta-analysis of endometrial cancer and diabetes (largely type 2), 16 of the 25 studies were used (3 cohort and 13 case-control). Twelve of the 16 studies found an increased risk of endometrial cancer and diabetes with a summary RR of 2.10 (95% CI 1.75–2.53). Heterogeneity existed among the studies ( $p=0.01$ ); however, when a sensitivity analysis was performed and individual studies were excluded one at a time, a significant positive association still remained (summary RR 1.98–2.18, with a 95% CI lower limit that never crossed 1.0). The association of endometrial cancer was somewhat stronger in studies conducted in Europe (summary RR 2.51, 95% CI 1.83–3.45) versus the United States (summary RR 1.70, 95% CI 1.47–1.98).

When the meta-analysis was restricted to the two studies that addressed the two confounders of physical activity and BMI, a positive association between endometrial cancer and diabetes still existed (summary RR 2.47, 95% CI 1.37–4.45). Of the two cohort studies that evaluated mortality, one reported a statistically significant increase and one did not. When the authors pooled the studies, a nonsignificant positive association existed between diabetes and mortality for endometrial cancer (summary RR 1.58, 95% CI 0.94–2.66). Unlike the previous meta-analyses, two cohorts provided standardized incidence ratios whereas one case-control study evaluated the association specifically in type 1 diabetes. When the three studies were combined, a positive association existed between type 1 diabetes and endometrial cancer (summary RR 3.15, 95% CI 1.07–9.29) with no evidence of heterogeneity ( $p=0.04$ ). The authors concluded that there was a positive association between diabetes and endometrial cancer.

**Non-Hodgkin's Lymphoma** The risk of non-Hodgkin's lymphoma was evaluated in two meta-analyses.<sup>[30, 31]</sup> The first analysis was published in September 2008.<sup>[30]</sup> The authors searched the MEDLINE and EMBASE databases for studies published before 2007 that reported an association between non-Hodgkin's lymphoma and diabetes. A total of 10 case-control and three cohort studies met inclusion criteria. Six were conducted in North America, four in Europe, and three in Asia. The meta-analysis for all studies combined showed a positive association between diabetes history and non-Hodgkin's lymphoma (RR 1.28, 95% CI 1.07–1.53). When analyzed individually by study design, a significant positive association was noted in hospital-based case-control and cohort studies (RR 1.36, 95% CI 1.00–1.86 and RR 1.79, 95% CI 1.30–2.47, respectively) and not in population-based case-control studies (RR 1.12, 95% CI 0.89–1.40). Significant heterogeneity existed in all included studies ( $p=0.05$ ). In the studies that evaluated sex, a positive association was seen in women specifically (RR 1.60, 95% CI 1.15–2.22) versus men (RR 1.15, 95% CI 0.84–1.59). A significant difference was noted based on location, with a significant association in studies

conducted in Europe (RR 1.23, 95% CI 0.99–1.52) and Asia (RR 1.74, 95% CI 1.31–2.33) versus North America (RR 1.11, 95% CI 0.82–1.50). When studies adjusting for the confounder of BMI were evaluated, there was still a statistically significant positive association (RR 1.56, 95% CI 1.23–2.00). The authors concluded that although a risk of non-Hodgkin's lymphoma seems to be present in patients with diabetes, their results were overall inconclusive.

Later in 2008, another group published results of their MEDLINE search for observation cohort and case-control studies from 1980–2008 that reported an association between non-Hodgkin's lymphoma and diabetes.<sup>[31]</sup> Fifteen studies met the authors' predefined inclusion and exclusion criteria: 10 case-control studies and 5 cohort studies (3 reported incidence and/or mortality rate ratios as the measure of RR, and 2 reported standardized incidence or mortality rates as the measure of risk). All studies combined provided an RR of 1.19 (95% CI 1.04–1.35) for non-Hodgkin's lymphoma in patients with diabetes. When specific study types were evaluated, a statistically significant risk was seen in prospective studies (RR 1.41, 95% CI 1.07–1.88) with no heterogeneity ( $p > 0.10$ ) but not seen among case-control studies (RR 1.12, 95% CI 0.95–1.31) with some heterogeneity ( $p = 0.09$ ). In studies that reported risk according to sex, a statistically significant increased risk was apparent in women (RR 1.38, 95% CI 1.06–1.80) but not men (RR 0.98, 95% CI 0.79–1.22).

As in previous analyses, several studies used age of onset or used a national registry to evaluate the type of diabetes.<sup>[31]</sup> The authors pooled the results of seven trials that used age of onset as a diagnosis of diabetes ( $> 30$  yrs for type 2 and  $< 30$  yrs for type 1). The pooled RR among patients with type 1 diabetes was 1.27 (95% CI 0.82–1.99) without evidence of heterogeneity ( $p > 0.10$ ), and the RR was 1.32 (95% CI 0.93–1.86) with heterogeneity ( $p = 0.04$ ) in patients with type 2 diabetes. The authors concluded that overall there seems to be a moderate risk for non-Hodgkin's lymphoma in patients with diabetes.

**Summary** Limitations exist among all meta-analyses. In most of the evaluated meta-analyses, individual studies did not distinguish between type 1 and type 2 diabetes, making it difficult to truly interpret the risk as a whole. In studies that defined diabetes, the diagnosis was made based on age, diabetes registry, or self-reported status. Evaluation of the risk of specific cancer with regard to diabetes can be confounded by multiple factors. Two of the most important would be obesity and physical inactivity. However, in the meta-analyses where adjustments for BMI and physical activity were made, a link still was present between diabetes and cancer. In all the evaluated meta-analysis publications, bias was possible. Finally, use of other drugs such as nonsteroidal inflammatory drugs or aspirin, which can modify overall cancer risk, may have been a confounder complicating interpretation of results from meta-analyses. Taking into consideration the published data, a link between diabetes and specific cancer types does seem to be probable. A review of the overall data is provided in Table 1.<sup>[2, 4–7, 28–31]</sup>

**Table 1. Meta-analyses of Diabetes Mellitus and Individual Site-Specific Cancers**

Cancer Type	Studies Included	End Point	Results
Pancreatic <sup>28</sup>	11 case-control 9 cohort or nested cohort	Risk of pancreatic cancer	Pooled RR: All studies: 2.1 (95% CI 1.6–2.8); cohort studies: 2.6 (95% CI 1.6–4.1); case-control studies: 1.8 (95% CI 1.1–2.7)
Pancreatic <sup>29</sup>	17 case-control 19 cohort or nested case-control	Incidence of pancreatic cancer	Summary OR: All studies: 1.82 (95% CI 1.66–1.99); case-control studies: 1.94 (95% CI 1.43–2.46) <sup>3</sup> ; cohort studies: 1.73 (95% CI 1.59–1.88) <sup>3</sup> Evaluation of studies quantifying duration of diabetes revealed a 50% greater risk of developing pancreatic cancer in patients with a disease duration of $< 4$ yrs vs those who had diabetes for $> 4$ yrs (OR 2.1, 95% CI 1.9–2.3 vs OR 1.5, 95% CI 1.3–1.8)

Hepatocellular <sup>2</sup>	13 case-control 13 cohort (7 in patients with diabetes, 3 in general population, 3 in patients with chronic liver disease)	Risk between diabetes and hepatocellular-carcinoma	Pooled OR: All case-control studies: 1.84 (95% CI 1.25–2.69) <sup>b</sup> ; all cohort studies: 2.5 (95% CI 1.93–3.24) <sup>b</sup> ; cohort studies in patients with diabetes only: 2.50 (95% CI 1.72–3.61) <sup>b</sup>
Colorectal <sup>4</sup>	6 case-control 9 cohort	Incidence and mortality of colorectal cancer	Summary RR of incidence: All studies: 1.30 (95% CI 1.20–1.40); all cohort studies: 1.29 (95% CI 1.16–1.43); all case-control studies: 1.36 (95% CI 1.23–1.50) Summary RR of mortality: 6 cohort studies that evaluated mortality: 1.26 (95% CI 1.05–1.50) <sup>a</sup>
Bladder <sup>6</sup>	7 case-control 3 cohort 6 cohort studies of patients with diabetes	Association between bladder cancer and diabetes	Summary RR: All studies: 1.24 (95% CI 1.08–1.42) <sup>a</sup> ; cohort studies: 1.43 (95% CI 1.04–1.80); case-control studies: 1.37 (95% CI 1.04–1.80) <sup>a</sup> ; cohort studies of patients with diabetes: 1.01 (95% CI 0.90–1.12)
Breast <sup>7</sup>	5 case-control 15 cohort	Incidence and mortality of diabetes and breast cancer	Summary RR of incidence: All studies: 1.20 (95% CI 1.12–1.28) <sup>a</sup> ; all cohort studies: 1.20 (95% CI 1.11–1.30) <sup>a</sup> ; all case-control studies: 1.18 (95% CI 1.05–1.32) Summary RR of mortality: 5 cohort studies that evaluated mortality: 1.24 (95% CI 0.95–1.62)
Endometrial <sup>5</sup>	13 case-control 12 cohort	Risk and mortality between diabetes and endometrial cancer	Summary RR of incidence: All studies: 2.10 (95% CI 1.75–2.53); cohort studies: 1.62 (95% CI 1.21–2.16); case-control studies: 2.22 (95% CI 1.80–2.74) <sup>a</sup> Summary RR of type 1 diabetes specifically (2 cohort studies and 1 case-control study): 3.15 (95% CI 1.07–9.29) Summary RR of mortality: 2 cohort studies: 1.58 (95% CI 0.94–2.66)
Non-Hodgkin's lymphoma <sup>30</sup>	10 case-control 3 prospective cohort	Risk between diabetes and non-Hodgkin's lymphoma	Summary RR: All studies: 1.28 (95% CI 1.07–1.53) <sup>a</sup> ; case-control studies: .18 (95% CI .99–1.42) <sup>a</sup> ; prospective cohort studies: 1.79 (95% CI 1.30–2.47) <sup>a</sup>
Non-Hodgkin's lymphoma <sup>31</sup>	10 case-control 5 prospective cohort	Association between diabetes and non-Hodgkin's lymphoma	Summary RR: All studies: 1.19 (95% CI 1.04–1.35); case-control studies 1.12 (95% CI 0.95–1.31) <sup>a</sup> ; prospective cohort studies 1.41 (95% CI 1.07–1.88) Summary RR: Pooled results of 7 trials that used age of onset as a diagnosis of diabetes (> 30 yrs: type 2; < 30 yrs: type 1): Patients with type 1 diabetes 1.27 (95% CI 0.82–1.99); patients with type 2 diabetes 1.32 (95% CI 0.93–1.86)

RR = relative risk; CI = confidence interval; OR = odds ratio.

<sup>a</sup>Heterogeneity

existed.

<sup>b</sup>Heterogeneity did not exist among studies that used population-based controls (p=0.26) but did exist among those with hospital-based controls (p<0.01).

## Proposed Mechanism

Obesity, physical inactivity, and insulin resistance seem to play an important role in the risk of cancer and diabetes.<sup>[32]</sup> Obesity and physical inactivity are hallmarks of type 2 diabetes, leading to an initial hyperinsulinemic state. Insulin is known to have direct growth-promoting properties and promotes increased levels of insulin-like growth factor (IGF)-I.<sup>[33]</sup> Many of the growth-promoting factors of insulin are thought to occur through the IGF-I axis. When circulating insulin levels are low, growth hormone receptors in the hepatocyte are decreased and levels of IGF-I are suppressed.<sup>[34]</sup> Insulin also plays a role in reducing insulin-like growth factor binding protein (IGFBP)-I, IGFBP-II, and IGFBP-III. The IGFBP-I binds IGF and inhibits its action, leading to an increase in free or bioactive IGF-I levels. A study in nurses revealed an association between total IGF-I and IGF-I:IGFBP-III ratio and the risk of colon cancer.<sup>[35]</sup>

Therefore, insulin has an effect on the IGF axis by its direct effects on IGF-I levels, and it augments levels of bioactive IGF-I due to effects on IGFBP. These changes in the IGF axis due to hyperinsulinemia are thought to possibly promote survival and progression of early malignant cells by increasing tumor growth and decreasing cellular apoptosis.

# Metformin and Cancer

## Proposed Mechanism

Metformin is a biguanide commonly used for the treatment of type 2 diabetes mellitus. Metformin acts as an insulin sensitizer, which leads to inhibition of gluconeogenesis in the liver, and has been found to be beneficial especially in overweight patients with diabetes.<sup>[36]</sup> Metformin use has been postulated to contribute to a reduced risk of pancreatic, prostate, ovarian, and breast cancers.<sup>[13–16, 37–44]</sup> Many mechanisms for this risk reduction have been hypothesized, although none has been proven entirely. Researchers have focused on metformin's mechanism of action for diabetes and considered that similar mechanisms could inhibit cell growth in cancer cells. This pathway was examined recently and determined to be initiated by metformin's role as an adenosine 5'-monophosphate-activated protein kinase (AMPK) activator through a tumor suppressor protein kinase known as LKB-1, which regulates AMPK levels.<sup>[39, 43–45]</sup> Activation of AMPK has been shown to suppress the mammalian target of the rapamycin (mTOR) signaling pathway, leading to antiproliferative and antiangiogenic effects.<sup>[39]</sup> The LKB-1 is also found within epithelial tissue and has beneficial antiproliferative and antiangiogenic effects.<sup>[43]</sup> In addition, metformin plays a role by activating 5-amino-imidazol-4-carboxamide-1- $\beta$ -D-ribofuranoside, which has been shown to mimic AMPK.<sup>[46]</sup>

Metformin has an effect on the  $G_0$ – $G_1$  phase of the cell cycle. This cell cycle is known to promote growth of cancerous cells. Metformin affects the expression and phosphorylation of the cancerous cell's key proteins and blocks the cell cycle in the  $G_0$ – $G_1$  phase of prostate cancer cells, inhibiting cell growth and the process of cell division. This effect of the drug occurred with a downregulation of the mTOR pathway but was independent of AMPK.<sup>[45]</sup> Inhibiting this cycle could be another crucial component in metformin's mechanism as an antitumor drug.

Insulin and IGF have been shown to increase crosstalk with G protein-coupled receptor (GPCR) signaling systems in pancreatic cancer cells. Research has demonstrated that metformin disrupts this crosstalk between insulin receptors and GPCR by preventing insulin-induced calcium signaling, DNA synthesis, and proliferation in response to GPCR agonists in pancreatic cancer cells. Metformin's role in AMPK stimulation is the initial mechanism that leads to inhibition of GPCR crosstalk and, subsequently, inhibits growth of pancreatic tumors.<sup>[38]</sup>

## Specific Trials

Most of the discussed data has been in vitro in origin. Population-based studies have been performed in order to determine metformin's benefit in reducing cancer in humans. A retrospective cohort study evaluated the data of 923 patients with diabetes who had metformin exposure and received a diagnosis of malignant cancer from 1993–2001.<sup>[14]</sup> Mean age was 73 years, and 53% of the patients with cancer were men. Approximately 36.4% of patients had received a prescription for metformin the year before diagnosis. The unadjusted OR for developing cancer in patients who received metformin during the year before their index date (date of their first hospital admission for cancer) was 0.86 (95% CI 0.73–1.02). The unadjusted OR for patients who had any exposure to metformin since January 1993 was 0.79 (95% CI 0.67–0.93). Results showed that metformin may be beneficial in reducing cancer risk. Benefit was directly correlated with a higher cumulative total dose (> 964,000 mg) and extended total duration of metformin use (> 1806 days), with patients in these groups having an OR of 0.63 (95% CI 0.49–0.82) and 0.62 (95% CI 0.47–0.8), respectively. The authors did comment that additional evidence is necessary to determine if a true dose-response relationship occurs with metformin's reduction in cancer risk.

An observational cohort study was conducted by analyzing medical record databases in Scotland to determine if metformin reduced the risk of cancer.<sup>[15]</sup> The databases were used to identify

patients with a diagnosis of type 2 diabetes who were initially treated with metformin at any time between January 1, 1994, and December 31, 2003. Patients who had not been treated with metformin were identified and matched to metformin users by year of diabetes diagnosis. The year of diagnosis was chosen as the matching variable because of the inability to control treatment patterns in patients. Baseline data were obtained and compared, including age at index date, age at diagnosis of diabetes, sex, smoking status, mean BMI, mean hemoglobin A<sub>1c</sub> (A1C) value during the study period, and use of sulfonylureas or insulin within 3 months or 1 year of the index date. Cancer was diagnosed in 7.3% of the 4085 metformin users compared with 11.6% of 4085 comparators who had not been treated with metformin. When metformin users were compared with patients who did not use metformin, median times to cancer were 3.5 years (interquartile range [IQR] 2.1–5.8 yrs) and 2.6 years (IQR 1.2–4.1 yrs), respectively. Significant reductions in cancer risk were noted with metformin use when patients treated with metformin were compared with those who were not treated with metformin (hazard ratio [HR] 0.46, 95% CI 0.4–0.53). Significant reductions in cancer risk continued to be associated with metformin even after adjusting for sex, age, BMI, A1C, material deprivation (based on variables from the U.S. National Census), smoking, and other drug use (HR 0.63, 95% CI 0.53–0.75). Based on these data, the authors concluded that metformin use may be associated with a reduced risk of cancer.

A case-control analysis of 22,621 women was completed in order to evaluate whether oral hypoglycemic agents were associated with an increased risk of breast cancer.<sup>[16]</sup> With use of the United Kingdom–based General Practice Research Database (UKGPRD), patients who had diabetes and/or who received at least one prescription for an oral hypoglycemic drug, including sulfonylureas, metformin, thiazolidinediones,  $\alpha$ -glucosidase inhibitors, or prandial glucose regulators with or without concomitant insulin therapy were evaluated between 1994 and 2005. Of the 22,621 women included in the study population, 305 (1.4%) had a diagnosis of breast cancer. The OR for any versus no metformin use was 1.03 (95% CI 0.76–1.39) when adjusted for use of insulin, sulfonylureas, thiazolidinediones, prandial glucose regulators,  $\alpha$ -glucosidase inhibitors, smoking, BMI, use of postmenopausal estrogens, diabetes duration, and A1C level. Long-term use of metformin, as defined by 30 or more prescriptions, resulted in an adjusted OR of 0.63 (95% CI 0.39–1.00) for developing breast cancer. When long-term use of metformin was defined as 40 or more prescriptions, the adjusted OR was 0.44 (95% CI 0.24–0.82,  $p=0.01$ ). When patients with long-term metformin use ( $\geq 40$  prescriptions) were compared with those not taking metformin, the adjusted OR was significant at 0.42 (95% CI 0.21–0.87,  $p=0.02$ ). The results of this study showed a reduced risk of breast cancer in women with type 2 diabetes who were treated with metformin for several years ( $\geq 40$  prescriptions). No reduced risk was found for patients who received short-term treatment with metformin. Limitations of this study were noted, including the possibility of misclassification of cancer diagnoses in the medical records, the lack of differentiation of cancer staging or histology, unknown glycemic control of the patients included, pertinent health information that may cause patients to be at higher risk for breast cancer (age of menarche, age at first delivery and parity, and family history of breast cancer), and the reliance of a small subgroup of 17 long-term metformin users and 120 controls. The authors concluded that long-term use of metformin may reduce the risk of breast cancer.

Another group conducted a population-based cohort study by using databases to evaluate cancer-related mortality among cohorts of patients who were new users of metformin and users of sulfonylurea monotherapy.<sup>[13]</sup> New users of metformin or a sulfonylurea who were at least 30 years of age and who had continuous drug coverage for 1 year were identified during a 5-year window from 1991–1996. A total of 10,309 patients met inclusion criteria and were evaluated. Mean age in the cohort was 63.4 years, and 55% were men. Of the 10,309 patients, 6969 were taking metformin and 3340 were taking a sulfonylurea. Some of the patients in the metformin group (5740 patients) took a combination that included a sulfonylurea. Baseline characteristic in both groups were similar,

although the sulfonylurea group was older (66 vs 61 yrs) and contained more men. Patients in the metformin group were more likely to have been receiving insulin (16.3% vs 9.2%). After adjustment for multiple variables, the sulfonylurea group had a cancer-related mortality rate higher than that of the metformin group (HR 1.3, 95% CI 1.1–1.6,  $p=0.012$ ). The authors also noted that insulin use, irrespective of oral treatment, was associated with a higher rate of cancer mortality (HR 1.9, 95% CI 1.5–2.4,  $p<0.001$ ). The authors concluded that patients exposed to a sulfonylurea or insulin had a higher overall risk of cancer-related mortality compared with those receiving metformin. However, they did document limitations regarding the lack of data on overall diabetes control, insulin dosage, weight, or smoking status, all variables that could lead to misinterpretation of the data.

In a recent retrospective cohort study, the risk of cancer associated with different antidiabetic drugs was evaluated.<sup>[10]</sup> This study included 62,809 patients from the United Kingdom who received a diagnosis of diabetes at later than 40 years of age and who started new treatment with oral agents or insulin. Four cohorts were identified. Cohorts 1 and 2 were patients who were newly treated with metformin or sulfonylurea monotherapy. Cohort 3 was treated with both metformin and sulfonylurea, and cohort 4 consisted of patients who had previously been treated with oral drugs and were newly switched to insulin. The primary outcome of the study was progression to the first record of any solid tumor cancer. The secondary outcome evaluated was progression to a specific solid tumor cancer (breast, pancreatic, colorectal, or prostate). Of the total cohort, 50% of patients were treated with metformin monotherapy, 12% with sulfonylurea monotherapy, 22% with combination metformin and sulfonylurea, and 16% with an insulin-based regimen. As commonly seen in practice, patients receiving monotherapy with metformin were younger and required more intensive therapy as age and duration of disease increased.

Although not significant, results showed metformin had the lowest risk of cancer (HR 0.90, 95% CI 0.79–1.03) compared with treatment with metformin and sulfonylurea in combination (HR 1.08, 95% CI 0.96–1.21), sulfonylurea monotherapy (HR 1.36 95% CI 1.19–1.54), and insulin-based regimens (HR 1.42, 95% CI 1.27–1.6).<sup>[10]</sup> When metformin was added to insulin, cancer incidence was also reduced (HR 0.54, 95% CI 0.43–0.66). Individual cancer incidence was similar to that of the entire cohort. No significant differences were seen for breast or prostate cancer alone. Large differences were seen for colorectal and pancreatic cancer among the four groups, with the sulfonylurea monotherapy group having the highest risk compared with metformin monotherapy (colorectal cancer HR 1.80, 95% CI 1.29–2.53, and pancreatic cancer HR 4.95, 95% CI 2.74–8.96).

Additional studies have shown metformin's effects with specific cancers. A retrospective review was conducted of the data of 2529 patients receiving neoadjuvant chemotherapy for early-stage breast cancer to determine if metformin use was associated with a significant change in pathologically confirmed complete response (pCR) rates.<sup>[37]</sup> Although definitions of pCR vary, broadly, it is considered to be an absence of viable tumor cells in resected specimens. Patients were compared by groups, with one group composed of 68 patients with diabetes taking metformin, a second group of 87 patients with diabetes not taking metformin, and a third group of 2374 patients without diabetes. The rate of pCR was higher in the metformin group (24%, 95% CI 13–34%) than in the non-metformin group (8%, 95% CI 2.3–14%) and the nondiabetic group (16%, 95% CI 15–18%,  $p=0.02$ ). A statistically significant difference was seen in pCR rates when the metformin group was compared with patients with diabetes not taking metformin, with the metformin group having higher rates of pCR ( $p=0.007$ ). Nonsignificant increases in pCR rates were seen when the metformin group was compared with the nondiabetic group ( $p=0.1$ ). Therefore, this study showed that patients with diabetes with concurrent breast cancer who are receiving metformin and neoadjuvant chemotherapy have significantly higher pCR rates than patients with diabetes with breast cancer who are not treated with metformin. The authors stated that additional

data are necessary to determine if metformin use in nondiabetic patients can increase pCR rates, as results of this study did trend in a positive direction but did not reach statistical significance.

## Insulin Analogs and Cancer

### Proposed Mechanism

The introduction of insulin analogs into the drugs available for the treatment of type 2 diabetes has allowed providers to mimic physiologic insulin replacement compared with the traditional use of human insulin. Insulin analogs are made by recombinant DNA technology with modification of amino acid strains on the sequence molecule to allow for a change in the dissolution rate from hexameric complexes to dimer and monomer complexes in the blood stream. These changes alter the pharmacokinetic characteristics of the insulin to improve the ability to mimic a true physiologic insulin replacement. The changes to the amino acid structure of the original insulin molecule are minor and do not alter the biologic properties with regard to binding of the insulin receptor.<sup>[47, 48]</sup> However, change of the structure can change the affinity for binding to the IGF-I receptor and could stimulate growth of human mammary epithelial cells.<sup>[49]</sup> In addition, prolonged binding of insulin to the insulin receptor has been implicated in increased rates of cancer.<sup>[50]</sup>

In one study, a comparison was performed of the insulin- and IGF-I receptor-binding properties and metabolic and mitogenic potencies of human insulin, insulin aspart,<sup>[51]</sup> insulin lispro,<sup>[52]</sup> insulin glargine,<sup>[53]</sup> insulin detemir,<sup>[54]</sup> and the reference insulin analog B10Asp (which was chosen as the reference insulin because it was the first insulin analog ever developed).<sup>[55]</sup> The insulin analog B10Asp was observed to have a 10-fold increase in mitogenicity compared with human insulin and was withdrawn when mammary tumors appeared in rats.<sup>[56]</sup> Multiple techniques were used to measure mitogenicity including the use of human osteosarcoma cells. Both insulin aspart and lispro were found to have similar insulin receptor binding, metabolic potency, mitogenic potency, and IGF-I receptor binding. Insulin lispro was found to have an increase in IGF-I receptor binding affinity. Insulin detemir had reduced metabolic and mitogenic properties compared with human insulin. Insulin glargine, in contrast, was found to have a 6–8-fold increase in receptor affinity and mitogenic potency when compared with human insulin.

Studies have further tested the impact of insulin analogs on cancer in vitro and have yielded varied results.<sup>[57–60]</sup> Unfortunately, the use of in vitro data makes it difficult to extrapolate data from bench to bedside in the care of patients. In addition, due to the relative short duration of the preclinical testing required by the United States Food and Drug Administration, these trials cannot fully quantify the risk of cancer with the use of insulin analogs. For this reason, evaluation of the risk of cancer with the use of insulin analogs in practice still needed to be clarified.

### Specific Trials

Recently, four observational studies in humans were published that evaluated insulin analogs with regard to risk of cancerous tumors.<sup>[9–12]</sup>

**German Database** The initial report was a retrospective review of Germany's largest insurance database in patients who had used either human insulin, insulin glargine, insulin lispro, or insulin aspart for the first time between January 1, 2001, and June 30, 2005.<sup>[9]</sup> Patients were older than 18 years with no history of malignant disease. The distinction of type 1 or type 2 diabetes was not made in the database; however, the authors made the assumption of type 2 diabetes if a patient was receiving insulin and oral drugs for diabetes concomitantly. Patients were excluded if they were receiving a combination of insulin products. The primary outcome of the trial was the diagnosis of a malignant neoplasm defined by *International Classification of Diseases, Ninth*

*Revision* (ICD-9) or *Tenth Revision* (ICD-10) codes, with a secondary outcome of overall mortality. Variables of interest included age, sex, year insulin was started, and the cumulative dose of insulin over the time at risk.

A total of 322,732 patients were identified in the database, and 127,031 patients met inclusion for evaluation. Of the patients meeting inclusion, 75.4% were receiving human insulin, 3.2% aspart, 2.6% lispro, and 18.8% glargine. The mean age for each group for the human insulin, aspart, lispro, and glargine was 69.6, 66.2, 66.8, and 69.5 years, respectively. The authors found an increase in cancer risk and insulin dose regardless of the insulin used. When adjusted for dose, however, the rate of cancer compared with that for human insulin was significantly higher with glargine ( $p < 0.0001$ ) and not with the other insulin analogs. Patients receiving insulin glargine were prescribed a median of 22 units/day (21.1, 56.2, and 100 units for lower quartile, upper quartile, and 95% quantile, respectively) compared with a median of 37 units/day (20.0, 49.3, and 98.4 units, respectively) of human insulin. When the insulin dose was not adjusted, glargine was not significantly linked with an increased cancer risk (HR 0.85, 95% CI 0.79–0.93). The adjusted HR for patients receiving 50 units/day of glargine was 1.31 (95% CI 1.20–1.42) compared with human insulin. Unfortunately, the mean follow-up for observation of malignant neoplasms was 1.31 years in the glargine group compared with 1.70 years the human insulin group, which could have confounded the results. None of the insulin analogs significantly increased all-cause mortality when compared with human insulin. Specifically, an HR of 0.68 (95% CI 0.65–0.72) was seen with glargine compared with human insulin when the insulin dose was not adjusted. When the insulin dose was adjusted, patients receiving 50 units/day of glargine were noted to have a statistically significant difference in all-cause mortality, with an HR of 1.20 (95% CI 1.11–1.30).

There were many limitations to the study. Patients were not randomized to a treatment group based on the dose of insulin, rather a cumulative dose of insulin was calculated over the time of exposure. This has been suggested to invalidate the comparison of events-per-dose relationship.<sup>[40]</sup> Also, data were not adjusted for confounding factors such as BMI, smoking, and duration of diabetes, all of which have implications for cancer risk. Patients were discontinued from the study if they switched insulin, leading to a large number of exclusions (71,784). Because of the multiple methodologic flaws and the need to replicate the potential finding of an increase in cancer risk with insulin glargine, three other studies<sup>[10–12]</sup> were initiated in an effort to corroborate the findings before publication of the original article in 2009.<sup>[9]</sup>

**Swedish Database** Residents in Sweden are assigned a unique personal identity number in order to link with certain Swedish Registries.<sup>[61]</sup> Of these, the Prescribed Drug Register, the Cancer Register, the Swedish National Diabetes Register, and the Cause of Death Register were evaluated in an effort to quantify the short-term incidence of malignancies with insulin glargine.<sup>[41]</sup> Residents were included if they were aged 35–84 years at the end of 2005, had at least one prescription of insulin between July 1 and December 31, 2005, and were alive at the start of follow-up on January 1, 2006. Sex, age, educational status, and diabetes duration were documented for each resident. Diabetes duration was obtained from age at onset documented in the National Diabetes Register or was estimated from the time of first admission for hospital care for diabetes. Type 1 diabetes was defined as onset at age younger than 30 years, and type 2 diabetes was defined as onset at age older than 30 years. Information on BMI, smoking status, estrogen use, and metformin use was also obtained. Residents were placed in the following categories of insulin use: insulin glargine monotherapy (glargine only group), insulin glargine combined with any other insulin (combination group), or use of any insulin other than insulin glargine (other insulin group). Residents were evaluated for five malignancy outcomes (all malignant tumors, all malignant tumors and in situ tumors, breast cancer in women, prostate cancer, and gastrointestinal cancer), death from any cause, and acute myocardial infarction. Residents with a diagnosis of any malignancy

before December 31, 2005, were excluded. Residents were followed from January 1, 2006–December 31, 2007.

A total of 114,841 residents were deemed to meet the inclusion criteria, including 5.2% of the glargine only group, 17.7% of the combination group, and 77.1% of the other insulin group. Age by classifications was similar in all groups with the exception of residents in the combination group being younger (45.3% aged 35–54 yrs vs 23.4% in the glargine only group and 19.4% in the other insulin group). In the glargine only group, most residents were deemed to have type 2 diabetes (62.8%) or their diabetes status missing (27.7%). This was similar among all groups with the only exception being an increase in type 1 diabetes status in the combination group compared with the other groups (38.9% in combination group vs 9.4% in glargine only and 10.2% in other insulin groups). Record of BMI was missing in 52.9% and 51.2% of the glargine only and other insulin groups, respectively. Smoking status was also missing in 52.2% of the glargine only group and 50.1% of the other insulin group. More patients in the combination group were nonsmokers (57.6%) compared with the glargine only group (38.3%) and other insulin group (41.7%). Rates of former smokers were similar among groups.

Overall, no increase for prostate cancer, gastrointestinal cancer, or any type of malignancy was noted in the glargine only group compared with the other insulin group, with a reported RR of 1.07 (95% CI 0.91–1.27). Of interest, the RR for breast cancer in women who used insulin glargine alone compared with insulin other than glargine was 1.91 (95% CI 1.25–2.89). When adjusted for age, the result still showed an increased risk with an RR of 1.99 (95% CI 1.31–3.03). The authors also further adjusted for age, BMI, smoking, age at onset of diabetes, cardiovascular disease, age at birth of first child, and metformin use, and a RR of 1.97 (95% CI 1.30–3.00) was still reported. In residents who used insulin glargine in combination with another insulin, there was no increased risk of breast cancer (RR 1.10, 95% CI 0.77–1.56). When evaluating mortality among the women with breast cancer, a 17% decrease was noted, with a RR of 0.83 (95% CI 0.71–0.96) in residents who used insulin glargine alone. This was also seen in women who used insulin glargine in combination with another insulin (RR 0.87, 95% CI 0.77–0.97).

The study did have limitations with regard to the breast cancer analysis. For one, there was a low number of cases of breast cancer overall (25 cases in the glargine group vs 183 in the other insulin group). Also, as stated above, the age in the combination group was much lower than that in the other groups, possibly leading to a lower overall risk of breast cancer in general. The authors stated that the increased rate of breast cancer among those using insulin glargine only could have been due to random fluctuation, as the group who used insulin glargine with other insulins did not have an increased rate of breast cancer. They further stated that any explanation they provided was pure speculation.

## **Scottish Database**

The third analysis was done from the Scottish Care Information–Diabetes Collaboration (SCIDC).<sup>[12]</sup> This database covered Scottish residents with diabetes during the period of observation. Investigators examined patients who had been exposed to any insulin between January 1, 2002, and December 31, 2005. All data related to prescribed diabetes-related drugs, age, sex, BMI, age at diagnosis of diabetes, type of diabetes as designated by the clinician, and smoking history were extracted from the database. For the purpose of the study, type 1 diabetes was defined as age of onset or first insulin use before age 30 years. Type 2 diabetes was defined as first drug use for treatment after age 35 years. Ages between 30 and 35 years were given an indeterminate status. The Scottish Index of Multiple Deprivation, an item looking at income, employment, education, housing, skills, and training, was also retrieved. Data from the SCIDC were extracted, then linked

to cancer registry data for evaluation of the incidence of cancer or cancer at any site. Patients were followed until one of the following occurred: date of first cancer registration or cancer death, date of death from any cause, or December 31, 2005.

The authors evaluated three different cohorts. First, a fixed cohort analysis was performed in which any patient who used insulin during a 4-month period between July 1 and October 31, 2003, was evaluated. Patients were grouped with regard to whether they had used insulin glargine or not, and were then followed without regard to subsequent change in exposure to insulin glargine. This setup was supposed to mimic a true intent-to-treat analysis. The second cohort was an incident insulin cohort where only patients with type 2 diabetes who started insulin for the first time during follow-up from January 1, 2002, to the end of 2005 were evaluated. The third cohort analysis was based on exposure classification across the follow-up period and evaluated patients who used insulin glargine only, patients who used an insulin other than insulin glargine, and patients who used insulin glargine combined with another insulin; this analysis was performed because the fixed cohort analysis allowed switching among groups.

A total of 36,254 people were using any type of insulin during the 4-month evaluation period between July 1 and October 31, 2003. Most patients (89.1%) were using an insulin other than insulin glargine. Of the 10.9% of patients who were using insulin glargine, 9.7% were using insulin glargine in combination with another insulin. Only 447 patients were using insulin glargine as monotherapy. Baseline characteristics among the three groups were significantly different, with more patients having type 1 diabetes in the combination insulin glargine and another insulin group. In accordance, age at diagnosis was 25 years in this group compared with 41 years in the nonglargine insulin group and 57 years in the insulin glargine monotherapy group. In addition, patients in the glargine monotherapy group had diabetes longer, had poorer control of their glucose, and had been using insulin for a shorter time than the other two groups. A total of 19,899 insulin users had a definite diagnosis of type 2 diabetes. Again, compared with users of a nonglargine insulin alone, patients in the glargine insulin plus another insulin combination group were younger, had a higher incidence of diabetes, lower BMI, less cardiovascular disease, and worse glucose control overall.

In the fixed cohort analysis, there was no significant difference in risk of all cancers among patients receiving insulin glargine versus those not receiving insulin glargine (HR 1.02, 95% CI 0.77–1.36). For breast cancer, no significant difference was noted between patients receiving insulin glargine versus a regimen that did not include insulin glargine (HR 1.49, 95% CI 0.79–2.83). Patients receiving another insulin plus glargine insulin had a nonsignificant lower rate of cancer compared with patients using a nonglargine insulin regimen alone. Of interest, patients using insulin glargine alone had a higher rate of cancer that reached borderline statistical significance (HR 1.55, 95% CI 1.01–2.37,  $p=0.045$ ). Also, the rate of breast cancer was noted to be higher in those receiving insulin glargine alone compared with those receiving other insulins (HR 3.39, 95% CI 1.46–7.85), although only six events of breast cancer were documented in the insulin glargine only group. When the authors restricted the analysis only to patients who had type 2 diabetes, no significant difference was found in cancer rates between insulin glargine users and users of nonglargine insulin (HR 1.08, 95% CI 0.78–1.49)—regardless of whether insulin glargine was used as monotherapy or in combination with another insulin, and after adjusting for baseline exposure of other oral antidiabetic drugs. The same trend was seen when the analysis was restricted to patients with type 1 diabetes (HR 1.02, 95% CI 0.50–2.09).

In the incident cohort analysis, among the 12,852 patients with type 2 diabetes who used insulin for the first time, the overall incidence of cancer was not significantly different between the insulin glargine and nonglargine insulin groups (HR 0.93, 95% CI 0.70–1.25). In contrast to the fixed

cohort analysis, patients in the insulin glargine only group did not have a higher incidence of cancer versus those in the nonglargine insulin group (HR 0.87, 95% CI 0.63–1.21). Breast cancer rates were not higher for insulin glargine versus nonglargine insulin users in this analysis (HR 1.47, 95% CI 0.59–3.64).

In the analysis summarizing exposure across the entire follow-up, 41,197 patients received a prescription for insulin between January 1, 2002, and December 31, 2005. Overall, any insulin glargine use was noted to have a significantly lower rate of total cancer when adjustments were made for age, sex, previous cancer, and type of diabetes (HR 0.66, 95% CI, 0.57–0.76). For breast cancer, there was a nonsignificant increase in the incidence among those receiving insulin glargine alone compared with those receiving a nonglargine insulin regimen (HR 1.33, 95% CI 0.69–2.56).

Limitations also existed in this analysis. For one, the sample size for insulin glargine users was low, as only 3512 patients in Scotland used the insulin during the time frame of interest, with only 447 using glargine as monotherapy. The overall increased risk for breast cancer in the fixed cohort group could reflect chance, as there were only six cases of breast cancer, and the result was not mimicked in the incident cohort analysis. It was also noted that generally older, more sick patients were prescribed insulin glargine monotherapy, increasing the possibility of allocation bias. Doses for insulin were not available in this analysis. Finally, cancer registry data were only available through 2005, with first insulin glargine exposure being 2002. This short time frame limits overall risk extrapolation. The authors finally concluded that the overall data do not prove a lack of risk with glargine and cancer but does not point to definite evidence of harm.

**United Kingdom Cohort** As mentioned previously, a retrospective cohort study was recently completed of patients treated in the United Kingdom to evaluate the risk of cancer associated with different antidiabetic drugs.<sup>[10]</sup> Four cohorts were identified. Cohorts 1, 2, and 3 have already been discussed. Cohort 4 included patients who had previously been treated with oral drugs and had been newly switched to insulin. The insulin cohort was then divided into patients receiving insulin glargine, human long-acting insulin, human biphasic insulin, or analog biphasic insulin. Again, the primary outcome of the study was progression to the first record of any solid tumor cancer. The secondary outcome evaluated was progression to a specific solid tumor cancer (breast, pancreatic, colorectal, or prostate).

A total of 10,067 patients were identified as being treated with an insulin-based regimen with 8034 having used insulins in the four cohorts of interest. Patients in the insulin treatment group as a whole had a mean age of 64 years, had diabetes for a longer period of time, had worse glucose control, and were more likely to smoke compared with patients in the other cohorts. Individual differences were also noted among the individual cohorts. Specifically, patients who began analog biphasic insulin were overall younger (62 yrs) and more likely to be female.

In the overall insulin group, patients were more likely to progress to have a solid tumor cancer (HR 1.42, 95% CI 1.27–1.60). The different insulin regimens did not significantly differ in their risk to progression to a solid tumor cancer. Specifically, patients receiving insulin glargine alone versus human basal insulin showed no significant difference in progression to solid tumor cancer (HR 1.24, 95% CI 0.90–1.70). However, as stated previously, patients who were exposed to metformin in combination with insulin had the lowest risk of cancer among insulin-treated patients (HR 0.54, 95% CI 0.43–0.66). In evaluation of the combined risk for individual cancers (breast, colorectal, or prostate), patients receiving insulin-based therapies had a higher risk (HR 1.55, 95% CI 1.27–1.89). No significant differences were noted among the therapies for individual breast or prostate cancer. Patients in the insulin treatment group did have a higher rate of colorectal cancer (HR 1.69, 95% CI 1.23–2.33) and pancreatic cancer (HR 4.63, 95% CI 2.64–8.10). When looking at the

insulin groups individually for a combined end point of breast, colorectal, and pancreatic cancer, no significant differences were seen. Evaluation of glargine specifically compared to other insulins showed no difference with progression to breast cancer (HR 0.86, 95% CI 0.42–1.75).

The authors noted that their observational study had many limitations. Other than the traditional problem with a retrospective observation trial, the number of overall tumor events among cohorts was relatively low, prohibiting a separate analysis for individual insulin-based therapies for each cancer. In addition, evaluation of the individual dose of insulin was not possible. The authors concluded by stating that insulin glargine and insulin premixed analogs were not associated with a greater risk of cancer. However, insulin therapy in general may be associated with an increased risk of cancer.

**Other Trials** After publication of the above-mentioned four trials,<sup>[9–12]</sup> a letter to the editor reported findings from a 5-year, randomized, open-label study with insulin glargine and neutral protamine Hagedorn (NPH) insulin in 1017 patients with type 2 diabetes.<sup>[62]</sup> The study was designed to detect a difference in ocular complications of diabetes in patients treated with these two types of insulin. However, the long duration of the study allowed a comparative assessment to be possible. More than 70% of the patients included in the study had been treated with insulin glargine or NPH insulin for more than 4 years (76% and 71%, respectively). The baseline demographics were comparable between the two groups with respect to diabetes duration, BMI, oral hypoglycemic agent duration, previous insulin use, A1C, and fasting plasma glucose level. No major differences were noted in the other demographic characteristics of the two groups.

The overall number of patients with a diagnosis of neoplasm during the trial was similar between the two groups: 57 patients (11.1%) in the insulin glargine group (RR 0.9, 95% CI 0.64–1.26) and 62 patients (12.3%) in the NPH insulin group. The rate of malignant neoplasms reported as treatment-emergent events was also similar between the two groups: 20 patients with 23 events in the insulin glargine group (RR 0.63, 95% CI 0.36–1.09) and 31 patients with 32 events in the NPH insulin group. No safety issues with respect to neoplasms were noted in this long-term study.

A meta-analysis was performed to evaluate 21 randomized, controlled, open-label trials in order to determine cancer risk with insulin detemir compared with NPH insulin or insulin glargine.<sup>[63]</sup> These trials included 8693 patients with type 1 or type 2 diabetes who were included in Novo Nordisk-sponsored trials with a duration of at least 12 weeks. Sixteen of the 21 trials compared insulin detemir with NPH insulin, whereas the other five trials used insulin glargine as the comparator treatment. Nine trials included patients with type 1 diabetes, 11 trials included patients with type 2 diabetes, and the remaining trial included patients with types 1 and 2 diabetes. Patient demographics were comparable among all trials included in the meta-analysis, with a few differences. Duration of treatment was longer in trials that compared insulin detemir with insulin glargine. Patients with type 1 diabetes were more commonly associated with the trials that compared NPH insulin with insulin detemir. Malignant neoplasms of the breast, bladder, lymph nodes, skin, colon, lung, lung metastasis, prostate, pharynx, and pancreas were noted.

In the NPH insulin trials, eight patients with malignant neoplasms were treated with insulin detemir compared with 13 patients treated with NPH insulin. In the insulin glargine trials, eight patients with malignant neoplasms were in both the insulin glargine and insulin detemir groups. When the trials were compared, estimated ORs implied that patients treated with NPH insulin had higher odds of receiving a diagnosis of cancer than patients treated with insulin detemir (OR 2.44, 95% CI 1.01–5.89,  $p=0.048$ ). No statistically significant differences in the occurrence of cancer were noted when insulin detemir and insulin glargine were compared (OR 1.47, 95% CI 0.55–3.94,  $p=0.44$ ). Results did not reveal a clear pattern in distribution of malignant neoplasms across four insulin doses of 0–

25 units, 25–38 units, 38–57 units, and greater than 57 units or between patients with type 1 or type 2 diabetes. This meta-analysis concluded that no increased cancer risk exists with insulin detemir compared with insulin glargine and NPH insulin. The incidence of cancer was small for all insulin treatment groups. A limitation of this analysis was that these trials were not conducted to assess cancer risk. Therefore, no follow-up data were available for review.

Recently, an evaluation of insulin use and the risk of cancer was undertaken in Hong Kong.<sup>[64]</sup> The authors evaluated patients by using a new-user cohort study design with the hopes of eliminating the possibility of prevalent user bias that existed in the previous analysis. Each patient who was a new insulin user was matched to two subjects who did not use insulin, based on age, smoking status, and the likelihood of starting insulin. Follow-up in the new insulin user cohort and the nonuser cohort began as soon as insulin was started in the insulin user cohort to ensure comparability. Patients in both groups were then evaluated for the first incident cancer or death during follow-up. A total of 973 insulin users were compared with 1935 nonusers. Median age of the overall cohort was 57 years (IQR 47–67 yrs), and median duration of diabetes was 5 years (IQR 1–10 yrs). The median time to the primary end point was 5.11 years (IQR 2.86–7.15 yrs). Almost all patients (971) in the new insulin user group had a matched nonuser. Despite best efforts for comparability, new insulin users were older, had a higher baseline A1C, higher baseline lipid profile, and were more likely to have renal dysfunction. Patients who used insulin also were more likely to be taking modulators of the renin-angiotensinaldosterone system and were more likely to be taking oral antidiabetic drugs.

Overall, in the new insulin user cohort, A1C was not statistically significant for an increased risk of cancer (HR 1.16, 95% CI 0.99–1.36,  $p=0.0747$ ). When adjusted for high-density lipoprotein cholesterol, triglycerides, glomerular filtration rate, and metformin use (covariates with a  $p<0.3$ ), the A1C was associated with an increased risk of cancer (HR 1.24, 95% CI 1.03–1.49,  $p=0.0267$ ). The overall use of insulin in the new insulin user cohort compared with the nonuser cohort was associated with a decreased risk of cancer after adjusting for age, smoking status, A1C, and overall likelihood of insulin use (HR 0.18, 95% CI 0.10–0.33,  $p<0.0001$ ). After adjusting for the same covariates as in the A1C evaluation, the HR was 0.17 (95% CI 0.09–0.32,  $p<0.0001$ ). Use of insulin was associated with a lower risk of cancer of the digestive system (HR 0.19, 95% CI 0.08–0.46) and cancers of the nondigestive system (HR 0.20, 95% CI 0.10–0.41). Limitations of this study were the short follow-up time, the observational nature of the study, and the inability to differentiate between specific insulin types.

In an Italian case-control study, the overall risk of cancer with insulin glargine was evaluated.<sup>[65]</sup> Patients with type 2 diabetes treated with insulin who were free of previous malignancy were identified between January 1, 1998, and December 31, 2007. Patients with incident cancer were deemed to be cases and compared for treatments with matched controls. Cancer cases were identified as a hospital admission or death based on ICD-9 codes. The exposure to drugs for diabetes was evaluated from baseline to the first documentation of cancer in the cases or from the same corresponding time in the controls. The mean daily dose was calculated for each individual insulin. Demographic information, including smoking history, alcohol history, prescription drugs, A1C, lipid profile, and serum creatinine concentration, was also evaluated.

A total of 1340 patients with a mean  $\pm$  SD age of  $63 \pm 14.9$  years and a median duration of diabetes of 7.5 years (IQR 0.5–19.2 yrs) were identified. Baseline A1C in the cohort was  $8.7\% \pm 1.9\%$ . Overall, 112 patients had a new diagnosis of cancer during the median follow-up time of 75.9 months (IQR 27.4–133.7 mo). Overall, cases had more comorbidities, assessed by the Charleston Comorbidity Score, and a trend toward less exposure to metformin during the 10-year period. This

trend was not statistically significant overall, with the case group having had metformin for 40 months and the control group 27.5 months ( $p=0.08$ ).

After adjusting for Charleston Comorbidity Score and mean daily dose, time of exposure to metformin and metformin doses were both inversely associated with cancer (OR 0.993, 95% CI 0.986–0.999,  $p=0.046$ , and OR 0.943, 95% CI 0.915–0.971,  $p\leq 0.01$ , respectively). Overall exposure to individual insulins did not significantly differ among the case and control groups. Mean duration of glargine treatment was similar in both groups. Of interest, among the cases, a significantly higher mean daily dose of insulin glargine was noticed compared with controls (0.24 unit/kg, IQR 0.10–0.039 unit/kg vs 0.16 unit/kg, IQR 0.12–0.24 unit/kg,  $p=0.036$ ). In addition, the proportion of patients who used 0.3 or more unit/kg/day of glargine was higher in cases than controls (11.6% vs 3.8%,  $p=0.002$ ), whereas no significant difference existed among the other insulins. After adjusting for metformin use, Charleston Comorbidity Score, and mean daily dose, exposure to a mean daily dose of insulin of 0.3 unit/kg or more was not significantly associated with incident cancer (OR 0.75, 95% CI 0.50–1.17,  $p=0.21$ ). However, when evaluated individually, basal insulin alone at doses of 0.3 unit/kg/day or more was associated with incident cancer (OR 1.90, 95% CI 1.10–3.28,  $p=0.021$ ).

The increased risk with basal insulin could be explained by an association of cancer with high-dose glargine (OR 5.43, 95% CI 2.18–13.53,  $p<0.001$ ) that was not observed with NPH insulin (OR 0.75, 95% CI 0.41–1.37,  $p=0.35$ ). The risk of cancer with glargine was still present when cases of cancer that developed in the first 12 months were excluded (OR 3.71, 95% CI 1.32–10.36,  $p=0.013$ ). Other models adjusting for prandial insulin use and use of basal insulin before glargine yielded similar results. Insulin doses were also treated as a continuous variable, and no increased risk was noted with any insulin preparation. However, again when the authors adjusted for exposure to metformin, Charleston Comorbidity Score, and total insulin dose, glargine was associated with an increased risk of incident cancer for each 1 unit/kg/day (OR 1.33, 95% CI 1.07–1.65,  $p=0.011$ ) compared with human basal insulin (OR 1.06, 95% CI 0.91–1.24,  $p=0.11$ ). When adding smoking, similar risk was still noted with glargine (OR 1.35, 95% CI 1.04–1.76,  $p=0.020$ ). Again when cases of cancer that developed in the first 12 months were excluded, a positive association with incident cancer and glargine still existed for each 1 unit/kg/day (OR 1.34, 95% CI 1.04–1.73,  $p=0.024$ ).

Limitations did exist in this study. Although longer in duration than previous studies, the follow-up could have been insufficient to detect differences in the incidence of cancer. Also, the use of hospital admission and death according to ICD-9 codes could have underestimated the overall incidence of cancer in either group.

Table 2 summarizes the trials with metformin and the insulin analogs and cancer.<sup>[9–16, 37, 62–65]</sup>

**Table 2. Summary of Studies of Specific Diabetes Mellitus Therapies and Cancer**

Study Design	Population	Intervention	End Point	Results
Retrospective cohort <sup>14</sup>	923 patients with diabetes who were receiving metformin and were included in Scottish databases (DARTS/MEMO) and received a diagnosis of malignant cancer from 1993–2001	Metformin	Incidence of cancer	Summary OR: For developing cancer in patients who received metformin within 1 yr of first hospital admission for cancer: 0.86 (95% CI 0.73–1.02) For any exposure to metformin since January 1993: 0.79 (95% CI 0.67–0.93)

Cohort <sup>15</sup>	4944 patients with type 2 diabetes who were new users of metformin during 1994–2003 and 5883 comparators who matched metformin users by year of diabetes diagnosis who had never used metformin	Metformin	Risk of cancer	Median time to cancer: 3.5 yrs (IQR 2.1–5.8 yrs) for metformin users vs 2.6 yrs (IQR 1.2–4.1 yrs) for nonusers Summary HR for new metformin users: 0.46 (95% CI 0.4–0.53)
Case-control <sup>16</sup>	22,621 females with type 2 diabetes who were taking oral antidiabetic drugs	Metformin Sulfonylureas Thiazolidinediones $\alpha$ -Glucosidase inhibitors Prandial glucose regulators with or without insulin	Incidence of breast cancer	Summary OR: Metformin vs no metformin: 1.03 (95% CI 0.76–1.39) Long-term ( $\geq 40$ prescriptions) metformin: 0.44 (95% CI 0.24–0.82, $p=0.01$ ) Long-term ( $\geq 40$ prescriptions) sulfonylurea: 1.03 (95% CI 0.62–1.70)
Population-based cohort <sup>13</sup>	10,309 patients aged $\geq 30$ yrs who had continuous drug coverage for 1 yr with metformin or sulfonylurea monotherapy identified during a 5-yr window from 1991–1996	Metformin Sulfonylureas	Cancer-related mortality	Summary HR: Sulfonylurea vs metformin: 1.3 (95% CI 1.1–1.6, $p=0.012$ ) Insulin use, irrespective of oral treatment 1.9 (95% CI 1.5–2.4, $p<0.001$ )
Retrospective cohort <sup>10</sup>	62,809 patients treated in United Kingdom general practices who developed diabetes at age $> 40$ yrs and started treatment with oral antidiabetic agents or insulin after 2000	Metformin Sulfonylureas Basal human insulin Insulin glargine	Progression to any solid tumor or cancer of the breast, colon, pancreas, or prostate	Summary HR of cancer risk: Metformin: 0.90 (95% CI 0.79–1.03) Metformin vs metformin-sulfonylurea combination therapy: 1.08 (95% CI 0.96–1.21) Metformin vs sulfonylurea monotherapy: 1.36 (95% CI 1.19–1.54) Metformin vs insulin-based regimens: 1.42 (95% CI 1.27–1.6)
Retrospective review <sup>37</sup>	2529 patients receiving neoadjuvant chemotherapy for early-stage breast cancer	Metformin	Association between metformin use and a	Summary HR of cancer incidence: When metformin added to insulin: 0.54 (95% CI 0.43–0.66) For colorectal cancer, sulfonylurea monotherapy vs metformin monotherapy: 1.80 (95% CI 1.29–2.53) For pancreatic cancer, sulfonylurea monotherapy vs metformin monotherapy: 4.95 (95% CI 2.74–8.96)
Retrospective review <sup>9</sup>	127,031 patients included in Germany's largest insurance database who had taken any treatment intervention for the first time from January 1, 2001–June 30, 2005, were aged $> 18$ yrs, and had no history of malignant disease; patients receiving a combination of insulin products were excluded	Human insulin Insulin glargine Insulin lispro Insulin aspart	Diagnosis of a malignant neoplasm with a secondary outcome of overall mortality	Pathologic complete response rates: 24% for metformin group vs 8% for nonmetformin group ( $p=0.007$ ) 8% for nonmetformin group vs 16% for nondiabetic group ( $p=0.04$ ) 24% for metformin group vs 16% for nondiabetic group ( $p=0.1$ ) A dose-dependent increase in cancer risk

				was found for treatment with insulin glargine vs human insulin (p<0.0001): 10 units/day: HR 1.09 (95% CI 1.0–1.19) 30 units/day: HR 1.19 (95% CI 1.1–1.3) 50 units/day: HR 1.31 (95% CI 1.2–1.42) No significant difference in cancer risk: aspart vs human insulin (p=0.3), lispro vs human insulin (p=0.96)
Population-based follow-up study <sup>11</sup>	114,841 patients aged 35–84 yrs at the end of 2005 who had at least one prescription for insulin dispensed between July 1, 2005, and December 31, 2005, and who were alive at the start of the study on January 1, 2006	Insulin glargine monotherapy Insulin glargine + any other insulin Insulin other than insulin glargine	Five malignancy outcomes (all malignant tumors, all malignant tumors + in situ tumors, breast cancer in women, prostate cancer, and gastrointestinal cancer)	For users of insulin glargine alone compared with users of insulin other than glargine (after adjustment for age and sex): Breast cancer: RR 1.99 (95% CI 1.31–3.03) Gastrointestinal cancer: RR 0.93 (95% CI 0.61–1.40) Prostate cancer: RR 1.27 (95% CI 0.89–1.82) Any type of malignancy: RR 1.07 (95% CI 0.91–1.27) For users of insulin glargine + other types of insulin: 95% CIs crossed 1.0 for the RR calculated in all analyses
Prospective cohort <sup>12</sup>	36,254 patients from the Scottish Care Information– Diabetes Collaboration who had been exposed to any insulin between January 1, 2002, and December 31, 2005	Insulin glargine	Incidence of cancer	Summary HR for risk of all cancers: Insulin glargine vs no insulin glargine: 1.02 (95% CI 0.77–1.36) Summary HR for risk of breast cancer: Insulin glargine vs no insulin glargine: 1.49 (95% CI 0.79–2.83)
Randomized, open-label <sup>62</sup>	1017 patients with type 2 diabetes	Insulin glargine NPH insulin	Incidence of cancer	Summary OR: NPH insulin vs insulin detemir: 2.44 (95% CI 1.01–5.89)
Meta-analysis <sup>63</sup>	21 randomized, controlled, open-label trials that included 8693 patients with type 1 or type 2 diabetes who were included in Novo Nordisk–sponsored trials with durations ≥ 12 wks in which insulin detemir was compared with NPH insulin or insulin glargine	Insulin detemir Insulin glargine Insulin NPH	Risk of cancer	Risk of cancer with increased A1C: HR 1.16 (95% CI 0.99–1.36)
New insulin user cohort <sup>64</sup>	Patients from the Hong Kong diabetes registry; each new insulin user (n=973) was matched to two nonusers (n=1935) based on age, smoking status, and likelihood of starting insulin	Insulin (vs no insulin)	Patients in both groups were evaluated for first incident cancer or death during follow-up with regard to increased A1C and insulin use	Risk of cancer with insulin use: HR 0.18 (95% CI 0.10–0.33)
Italian case-control <sup>65</sup>	1340 patients with type 2 diabetes treated with insulin who were free of previous malignancy; patients with incident cancer were deemed to be cases and compared for treatments with matched controls, evaluating individual drugs and insulin	Basal insulin Prandial insulin Human insulin Aspart insulin Lispro insulin Glargine insulin	Cancer cases were identified as a hospital admission or death based on ICD-9 codes; exposure to drugs for diabetes was evaluated from baseline to first documentation of cancer in cases or from the same corresponding time in controls	Incidence of cancer with exposure to metformin: OR 0.993 (95% CI 0.986–0.999)

DARTS/MEMO = Diabetes Audit and Research in Tayside Scotland/Medicines Monitoring Unit Collaboration; OR = odds ratio; CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NPH = neutral protamine Hagedorn; RR = relative risk; A1C = hemoglobin A<sub>1c</sub>; GFR = glomerular filtration rate; ICD-9 = *International Classification of Diseases, Ninth Revision*.

## Conclusion

Diabetes does seem to be linked to a variety of cancers including breast, hepatic, colorectal, and pancreatic cancer. The proposed mechanism of action includes hyperinsulinemia and the effects that insulin has on the IGF axis to promote survival and progression of early malignant cells by increasing tumor growth and decreasing cellular apoptosis. The data regarding cancer risk and antidiabetic drugs are contradictory and at this time inconclusive. There does seem to be a decreased risk of cancer in patients treated with metformin. The mechanism of action for a decreased risk of cancer with metformin includes AMPK activation, an effect on the G<sub>0</sub>–G<sub>1</sub> phase of the cell cycle, and increased crosstalk with GPCR signaling systems in pancreatic cancer cells.

Use of insulin analogs overall does not seem to increase cancer risk any more than the use of human insulin. Although an increased risk of cancer was seen with insulin glargine in one trial, multiple flaws prevent the extrapolation of the data to a large population. Furthermore, none of the other studies reported provide data that insulin glargine is more carcinogenic than the other insulins studied. The observational design of previous studies also limits the overall interpretation of the data due to the multiple opportunities for bias to exist. Data regarding individual cancers are also difficult to interpret given the low number of cases in each group.

Until long-term, randomized, prospective studies are available to elucidate a correlation with cancer and insulin, it is important to continue treating diabetes with insulin analogs in order to avert the long-term complications of the disease.

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