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Shaya FT, **Lu Z**, Sohn K, Weir MR. Thiazolidinediones and Cardiovascular Events in High-Risk Patients with Type-2 Diabetes Mellitus: A Comparison with Other Oral Antidiabetic Agents. *Pharmacy and Therapeutics* 2009; 34(9): 490-501.

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Abstract

Title of Dissertation:

Use of Insulin and Risk of Cancer among Patients with Diabetes Mellitus:

A Nonconcurrent Prospective Study

Zhiqiang Lu, Doctor of Philosophy, 2011

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Objectives:

There have been a number of studies showing an association between diabetes and cancer risk and a growing concern that this risk maybe linked to insulin therapy. This study aimed to (1) to assess the effect of insulin exposure on the risk of developing solid cancer among patients with diabetes mellitus; and (2) to explore the role of HbA1c value in modifying the risk.

Methods:

The study used the General Practice Research Database (GPRD), a large UK-based research database of patient electronic health records from general practitioners, to explore the use of insulin on the risk of cancer. Cox's Proportional hazards models were used to estimate the hazard ratio of solid tumors, all sites and selected individual sites, by types of antidiabetic therapy. The potential modifying role of diabetes control as measured by hemoglobin A1c (HbA1c) was also explored.

Results:

The study cohort contained a total of 230,330 patients with claims for antidiabetic therapy. The study found that use of insulin alone or in combination with other oral agents was associated with an increased risk of cancer. Insulin use was strongly associated with pancreatic cancer risk (HR=1.875, 95% CI 1.261, 2.787 for insulin alone and HR=2.330, 95% CI 2.007, 2.705 for insulin with oral agents). Moreover, HbA1c appears to be a risk factor for pancreatic cancer (HR=1.385, 95% CI 1.324, 1.450). The risk of pancreatic cancer was similarly increased for premixed and intermediate-acting insulin when compared with short-acting insulins. Role of HbA1c value in modifying the risk of cancer among patients with diabetes varies across different cancer types.

Conclusion:

Use of insulin, alone or in combination with oral agents, may pose a strong risk for pancreatic cancer and overall cancer. Use of insulin alone was also associated with an

increased risk of colorectal cancer. These data suggest that there may be more than one mechanism by which insulin therapy impacts the risk of cancer among diabetics. Glucose control appears to impact the risk of pancreatic cancer, though it may be an independent factor for some common tumors. Caution should be used when prescribing insulin to patients for diabetes management.

Key words:

Insulin, Cancer, HbA1c, Risk

Use of Insulin and Risk of Cancer among Patients with Diabetes Mellitus: A Nonconcurrent Prospective Study

by
Zhiqiang Lu

Dissertation submitted to the faculty of the Graduate School
of the University of Maryland, Baltimore in partial fulfillment
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List of Abbreviations

DM	Diabetes Mellitus
NDDG	National Diabetes Data Group
WHO	World Health Organization
NDDG/WHO	National Diabetes Data Group/World Health Organization
ADA	American Diabetes Association
GDM	Gestational Diabetes Mellitus
IDDM	Insulin-Dependent Diabetes Mellitus
HLA	Human Leukocyte Antigen
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
CDC	Centers for Disease Control and Prevention
IGT	Impaired Glucose Tolerance
MN	Malignant neoplasm
ACS	American Cancer Society
IGF-I	Insulin-Like Growth Factor-I
IGF-IR	Insulin-Like Growth Factor-I Receptor
IGFBP1	Insulin-Like Growth Factor Binding Protein 1
IR	Insulin Receptor
GPRD	General Practice Research Database
GP	General Practitioner
UK	United Kingdom

UTS	Up to Standard
Medcode	Medical Code
EDA	Exploratory Data Analysis
CDA	Confirmatory Data Analysis

1 Background

1.1 Diabetes Mellitus Overview

Diabetes mellitus (DM)—often referred to simply as diabetes—is a group of metabolic diseases characterized by high glucose levels (hyperglycemia). In patients with diabetes mellitus, the body cannot produce enough, or does not properly respond to, insulin, a pancreas-produced hormone that has variety of effects on metabolism and other body functions. Diabetes mellitus is often associated with failure of various organs, such as eyes, kidneys, heart, nerves, and blood vessels.

1.1.1 Diagnosis

The first widely accepted classification criteria of diabetes mellitus was the National Diabetes Data Group /World Health Organization (NDDG/WHO) classification criteria released in 1977. In 2003, the American Diabetes Association (ADA) issued new classification criteria of diabetes mellitus based on newly emerged medical evidence since 1979, as well as recommendations from an international Expert Committee sponsored by the ADA. According to the most recent diagnosis and classification of the ADA, there are 4 types of diabetes:[1]

1) Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

2) Type 2 diabetes (may range from predominantly insulin resistance with some degree of insulin deficiency)

3) Other specific types (due to other causes, including genetic defects of β–cell function; genetic defects in insulin action; diseases of exocrine pancreas; endocrinopathies; drug-or chemical-induced diabetes; infections; uncommon forms of immune-mediated diabetes or other genetic syndromes associated with diabetes)

4) Gestational diabetes mellitus (GDM)

Because diabetics are predominantly with type 1 or type 2 diabetes, and other types of diabetes account for only 1% to 5% of all diagnosed cases, the present study will focus on type 1 and type 2 diabetes only.

1.1.2 Type 1 diabetes mellitus

Type 1 diabetes mellitus, which is also referred to as insulin-dependent diabetes mellitus (IDDM), or juvenile-onset diabetes, is far less common than type 2 diabetes. It typically affects younger individuals and usually begins before age 40, although there are exceptions. Type 1 diabetes mellitus can be further divided into two forms: immune-mediated diabetes and idiopathic diabetes. Immune-mediated diabetes is due to immune destruction of β–cell in the pancreas, with varying rate of destruction among different patients.[2,3] This form of diabetes is usually associated with human leukocyte antigen (HLA).[4,5]In contrast, idiopathic diabetes is characterized by unknown etiologies and is not HLA associated.[6] Only a very limited number of patients with type 1 diabetes fall in

this category. Patients with this form of diabetes usually do not present with obesity, although they are not incompatible. Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans. As a result, the body cannot produce sufficient insulin. If insufficient insulin is produced by the pancreatic islet cell in the body, the blood glucose rise can lead to hyperglycemia. The American Diabetes Association (ADA) states that approximately 1 in every 400 children and adolescents has type 1 diabetes, and about 15,600 youths are diagnosed with incident type 1 diabetes annually.[7]

1.1.3 Type 2 diabetes mellitus

Whereas type 1 diabetes mellitus is characterized by the onset in young persons (mean age at first diagnosis is 14), type 2 diabetes is usually seen in adults and is therefore previously referred to as non-insulin-dependent diabetes mellitus (NIDDM), or often referred to as "adult onset diabetes". Patients with type 2 diabetes mellitus are insulin resistant rather than the lack of insulin as seen in type 1 diabetes, and thus may suffer from a relative insulin deficiency. Some patients with type 2 diabetes may eventually require insulin treatment. Unlike type 1 diabetes, this type of diabetes does not result from autoimmune destruction of β–cells, although detailed etiologies are unknown.

1.1.4 Epidemiology of diabetes

It is estimated that approximately 100 million people have diabetes mellitus worldwide, with forecasts suggesting that this number will triple by the year 2025.[1]Reports from the

Centers for Disease Control and Prevention (CDC) in 2011 estimate that diabetes affects 25.8 million people, or 8.3% of the U.S. population; about 7.0 million people are with undiagnosed diabetes.[8] Diabetes is responsible for 3.0% of the deaths, and ranks the 7thmost frequent cause of death in the U.S. in 2007. The economic burden of diabetes is unsurprisingly heavy. The estimated total (direct and indirect) cost of diabetes in 2007 was $174 billion, with $116 billion of direct medical costs, and $ 58 billion of indirect costs.

The prevalence of diabetes increases with age: about 215,000 people (7%) younger than 20 years had diabetes in the United States; this number increases to 25.6 million (11.3%) among people aged 20 years or older, and reached to 10.9 million (26.9%) for those aged 65 years and older in 2010.

The prevalence of diabetes also differs among races/ethnicities: when controlling for age differences, national survey data from 2007–2009 suggests the following race/ethnicity prevalence for people aged 20 years or older: 7.1% in non-Hispanic whites, 8.4% in Asian Americans, 11.8% in Hispanics, and 12.6% in non-Hispanic blacks for diagnosed diabetes. Among Hispanics, rates were 7.6%, 13.3%, and 13.8% for both Cubans and for Central and South Americans, for Mexican Americans and for Puerto Ricans, respectively.

1.1.5 Risk factors for diabetes

Type 1 diabetes is thought to be caused by a number of different etiologies which include autoimmune, genetic, and environmental exposure. There is no known way to prevent type 1 diabetes.[8] By contrast, there are many factors that may lead to type 2 diabetes. Major risk factors, according to the ADA and CDC, include obesity, unhealthy lifestyle (e.g., physical inactivity, smoking, and alcohol), family history/genetics, age, low HDL cholesterol, high triglycerides, high blood pressure, certain racial ethnic groups, and history of gestational diabetes.

Obesity

The estimated prevalence of obesity in the U.S. in 2010 was 35%, 36%, 33% and 55% in white males, white females, black males, and black females, respectively; This is a striking increase from the previous decade with 9.3 million more adults, aged between 20 and 74 years, classified as obese.[9] Obesity is reported to be associated with many conditions, the most devastating of which may be type 2 diabetes. A 2009 National Health Interview Survey showed that 28% of U. S. adults 20 years and older were obese, among whom, 9% had been diagnosed with diabetes.[10] In obese people, adipose tissue can produce increased level of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors, all of which are important in the development of insulin resistance.[11] Insulin resistance, combined with dysfunction of pancreatic islet – cells, may lead to increased blood glucose levels.[11]

Physical inactivity/Unhealthy eating habit

A number of studies have demonstrated that exercise and healthy eating habit can not only prevent the risk of high blood glucose, but may also improve HbA1c level among diabetics. Two randomized trials have showed that exercises such as150 min/week of physical activity can reduce the risk of development of type 2 diabetes among patients with impaired glucose tolerance (IGT) by 58%.[12,13] Another clustered randomized trial found that diet and exercise, alone or in combination, were equally effective in reducing this risk.[14]

Cigarette smoking and alcohol consumption

Cigarette smoking is the leading avoidable cause of mortality in the U.S., and is an important modifiable risk factor for type 2 diabetes. As concluded in the American Diabetes Association's technical review "Smoking and Diabetes", consistent results from epidemiological, observational studies provides convincing evidence that cigarette smoking is associated with increased risk of diabetes.[15] Alcohol abuse in Diabetics, can lead to hypoglycemia, which is a complication associated with diabetes, or antidiabetic use, although it is suggested that a moderate alcohol consumption may not affect blood glucose levels when diabetic is well controlled.[16]

Family history, genetics and race

It appears that people who have family members with diagnosed diabetes are at a higher risk for developing diabetes compared to those without family history record. In addition,

African Americans, Hispanic-Americans and Native Americans all have an elevated rate of type 2 diabetes. (Table 1.1)

Table 1.1 Prevalence of Diabetes by Race/Ethnicity[7]

Race/Ethnicity Group	Prevalence of Diabetes by Race/Ethnicity
non-Hispanic whites	7.10%
Asian Americans	8.40%
non-Hispanic blacks	12.60%
Hispanics	11.80%

Increased Age

People of different age have different risk of diabetes. It is proposed that the function of pancreas pumps insulin less efficiently and body cells become more resistant to insulin as people are getting older. (Table 1.2)

Table 1.2 Prevalence of Diabetes by Age[7]

Diabetes Type	Prevalence of Diabetes by Age	
	Age Group	Prevalence of Diabetes Mellitus
Type 1	Under 20 years of age	About 1 in every 400 children and adolescents
Type 2	Under 20 years of age	0.26%
	Age 20 years or older	11.30%
	Age 65 years or older	26.90%

High Blood Pressure and High Cholesterol Hypertension and hyperlipidemia are two key risk factors in metabolic syndrome, a cluster of syndromes that increases the risk of heart disease, stroke, and diabetes.[8]

1.1.6 Complications of Diabetes

Diabetes mellitus is a chronic illness that can affect many parts of the body and lead to serious complications, including heart disease and stroke, hypertension, blindness and eye problems, kidney disease, nervous system disease, amputations, dental disease and death.

1.2 Treatment of Diabetes Mellitus

The two goals of diabetes treatment are: (1) keeping blood glucose within normal range and; (2) preventing the development of diabetes-related complications, such as cardiovascular disease, diabetic neuropathy, or low blood glucose.

Keeping normal glycemic level in patients with diabetes mellitus is the key for minimizing the risk of complications. The approach to glycemic control, however, usually depends on the disease type and prescription needs may change over time. Patients with type 1 diabetes are insulin deficient and therefore, must be treated with exogenous insulin. On the other hand, patients with type 2 DM may be managed with one and/or more oral antidiabetic agents, insulin, or various combinations of oral agents and insulin.

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1.2.1 Insulin

In patients with type 1 or type 2 diabetes mellitus, insulin replacement therapy is administered to mimic physiologic insulin secretion. The clinical use of insulin began when it was first extracted from bovine and porcine pancreas in the 1920's.[17] Highly purified (monocomponent) insulins came to the market in the 1970s. The advent of recombinant DNA technology made it possible to produce human insulin commercially by the early 1980s.

Insulin is a naturally-occurring hormone secreted by the pancreas. Human insulin refers to a peptide hormone composed of 51 amino acids, whose structure varies slightly between species of animal. Within vertebrates, the similarity of insulin is extremely close. Bovine insulin differs from human by only three amino acid residues and porcine insulin by one. Insulin is required by the cells of the body to extract glucose from the blood and break it down to produce energy.

1.2.2 Biosynthesis of Insulin

Insulin is synthesized largely only in the islets of Langerhans, which are dendritic cells of the epidermis in the exocrine pancreas.[18,19] Insulin biosynthesis begins when mRNA is translated as a single chain precursor often referred to as proinsulin; proinsulin is then generated by removal of its signal peptide during insertion into the endoplasmic reticulum. Proinsulin consists of three parts: a carboxy-terminal (A chain), an amino-

terminal (B chain), and the C peptide which connects A chain and B chain in the middle. (Figure 1.1)

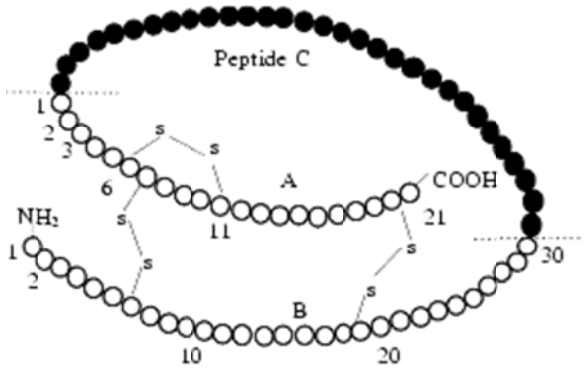

Figure 1.1 Amino acid sequence of human proinsulin[20]

Two types of proteolytic activity are involved when proinsulin is exposed to several specific endopeptidases which then process it to insulin.[21] First, the C-terminal sides of the basic dipeptides at either end of the C-chain are cleaved by a trypsin-like endoprotease activity; second, the arginine dipeptide of the carboxyl end of the B-chain is removed by a carboxypeptidase B-like activity. As a result, the mature form of insulin and free C peptide are secreted from the cell by exocytosis and diffuses into islet capillary blood, with C peptide having unknown biological activity.

Insulin analogues were developed mainly for their pharmacokinetic properties. Therefore, insulins can be subdivided by not only by source, but also by time of onset, peak, and concentration strength. When choosing among insulin, the time of onset and peak are the most clinically important factors. Time of onset is the length of time before insulin

reaches the bloodstream and begins to lower blood sugar; the peak is after injection/administration when insulin is most effective in lowering blood sugar, and duration measures that how long insulin continues to lower blood sugar. Insulin can be classified into five types by time of onset and peak. (Table 1.3)

Table 1.3 Insulin Types by Time of Onset/Peak[22]

Type of Insulin Brand Names (Generic Name)	Onset	Peak	Duration	Role in Blood Sugar Management
Rapid-Acting				
Humalog (lispro)	15-30 min.	30-90 min	3-5 hours	Rapid-acting insulin covers insulin needs for meals eaten at the same time as the injection. This type of insulin is used with longer-acting insulin.
Novolog/Adderal l (aspartate)	10-20 min.	40-50 min.	3-5 hours	
Apidra(glulisine)	20-30 min.	30-90 min.	1-2½ hours	
Short-Acting				
humulin R or novolin R (insulin regular)	30 min.-1 hour	2-5 hours	5-8 hours	Short-acting insulin covers insulin needs for meals eaten within 30-60 minutes
Velosulin (Human)	30 min.-1 hour	2-3 hours	2-3 hours	
Intermediate-Acting				
NPH (N) (currently no generic)	1-2 hours	4-12 hours	18-24 hours	Intermediate-acting insulin covers insulin needs for about half the day or overnight. This type of insulin is often combined with rapid- or short-acting insulin.
Lente (insulin zinc)	1-2½ hours	3-10 hours	18-24 hours	
Long-Acting				
Humulin® U (Ultralente U)	30 min.-3 hours	10-20 hours	20-36 hours	Long-acting insulin covers insulin needs for

Lantus® (insulin glargine)	1-1½ hour	No peak time; insulin is delivered at a steady level	20-24 hours	about 1 full day. This type of insulin is often combined, when needed, with rapid- or short-acting insulin.
Levemir(insulin detemir), FDA approved June 2005	1-2 hours	6-8 hours	Up to 24 hours	
Pre-Mixed*				
Humulin 70/30	30 min.	2-4 hours	14-24 hours	
Novolin 70/30	30 min.	2-12 hours	Up to 24 hours	
Novolog 70/30	10-20 min.	1-4 hours	Up to 24 hours	These products are generally taken twice a day before mealtime.
Humulin 50/50	30 min.	2-5 hours	18-24 hours	
Humalog mix 75/25	15 min.	30 min.-2½ hours	16-20 hours	

*Premixed insulin(s) are a combination of specific proportions of intermediate-acting and short-acting insulin in one bottle or insulin pen (the numbers following the brand name indicate the percentage of each type of insulin).

Rapid acting insulin includes Humalog, Novolog and Apidra. These insulins can generally be absorbed in less than 30 minutes, and have their peak action between 30-90 minutes of injection in most individuals. Their duration of action is approximately 3 to 5 hours, which allows meals eaten at the same time as the injection.

Short-Acting insulin includes Regular (R) Humulin (HR), and Velosulin. These insulins start to be absorbed in 30-60 minutes, and have their peak action within 2 to 5 hours of injection in most individuals. Their duration of action is approximately 2 to 8 hours. Short-acting insulins are often used before eating to control the large rise of blood

glucose that often occurs after a meal. Both rapid-acting and short-acting insulin are classified as short-acting insulin in the U.K.

Intermediate-Acting insulin includes NPH (N) and Lente (L). Such insulins start being absorbed 1-2 hours after injection, and have their peak action after 3-10 hours. One of the best uses of Intermediate-Acting insulins is to administer an injection at bedtime to control the morning glucose of the next day.

Long-Acting insulins include Ultralente (U), Lantus and Levemir. Their onset time is between 1-3 hours, with the peak time between 10-20 hours, or delivered at a steady level with no obvious peak (e.g., Lantus). Long-acting insulin may cover insulin needs for about 1 full day.

Premixed insulins are a combination of specific proportions of intermediate-acting and short-acting insulin in one bottle or insulin pen. The numbers following the brand name indicate the percentage of each type of insulin. Therefore, premixed insulins contain two kinds of insulin; the intermediate-acting insulin helps the body control blood sugar (blood glucose) all through the day. The short-acting insulin helps the body control blood sugar at meal times.

1.2.3 Pharmacologic Treatments for Type 2 Diabetes

Unlike type 1 diabetes which requires administration of insulin, not all type 2 diabetics require insulin. Treatment of type 2 diabetes usually begins with oral agents. There are 9 distinct classes of oral agents currently approved treatments for type 2 diabetes in the U.S. (Table 1.4)

Table 1.4 Classes of Oral Agents Approved for the Treatment of Type 2 Diabetes[23]

Drug Class With Examples	Presumed Primary Mechanism of Action
Sulfonylureas	
- Glipizide	Stimulate insulin release by inhibiting the ATP-dependent potassium channel on pancreatic beta-cells
- Glyburide	
Biguanides	
- Metformin	Decrease hepatic glucose production
Alpha-glucosidase inhibitors	
- Acarbose	Delay glucose absorption from the gastrointestinal tract by inhibiting enzymes that convert carbohydrates into monosaccharides
- Miglitol	
Thiazolidinediones	
- Pioglitazone	Insulin sensitizers Modulate the transcription of genes involved in glucose metabolism
- Rosiglitazone	
Meglitinides	
- Nateglinide	Stimulate insulin release by inhibiting ATP-dependent potassium channels on pancreatic beta-cells
- Repaglinide	
GLP-1 analogues	
- Exenatide	Stimulate glucose-dependent insulin secretion

Amylin analogues - Pramlintide acetate	Slow gastric emptying and suppresses the postprandial rise in plasma glucagon
DPP-4 inhibitors - Sitagliptin phosphate	Slow inactivation of incretion hormones (e.g., GLP-1), which stimulate glucose-dependent insulin secretion
Bile acid sequestrants - Colesevelam hydrochloride	Unknown
Insulins - Insulin Aspart - Insulin Glulisine - Insulin Lispro	Stimulate peripheral glucose uptake by skeletal muscle and fat and inhibit hepatic glucose production

GLP-1 = glucagon-like peptide 1

DPP-4 = dipeptidyl peptidase 4

1.3 Diabetes Mellitus and Cancer Risk

Malignant neoplasm (MN), or cancer, is a group of diseases characterized by uncontrolled growth (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues, and metastasis (spread to other locations in the body via lymph or blood) of the body cells. Most solid cancers form a tumor. The malignant tumors are different from benign tumors. Benign tumors are self-limited, and do not invade or metastasize in the body.

Cancer has remained a major public health concern in the U.S. According to statistics from the American Cancer Society (ACS) in 2010, cancer is responsible for about 25% of all deaths in the U.S., and ranks the 2nd leading cause of death in the U.S.[24] In the U.S.,

lung cancer causes about 30% of cancer deaths though just 15% of new incident cancers are in this area. The most commonly occurring cancer in men is prostate cancer (about 25% of new cases) and in women, it is breast cancer (also about 25%).[25]

A number of epidemiologic studies have found associations between diabetes mellitus and cancer.[26-30] Among these studies, pancreatic and liver cancers have been most consistently associated with diabetes mellitus. In addition, type 2 diabetes mellitus is also reported to be associated with an increased risk of mortality from colon, breast and pancreatic cancers. The literature documents that having type 2 diabetes carries an increased risk of 50% risk for pancreatic cancer, 30% for colon cancer, and 20% risk for breast cancer.[31-33]

Type 1 diabetes also carries a modest increased cancer risk by 20% overall. Specifically, it increases the risk of stomach cancer (SIR = 2.3, 95% CI = 1.1 to 4.1), cervix cancer (SIR = 1.6, 95% CI = 1.1 to 2.2), and endometrium cancer (SIR = 2.7, 95% CI = 1.4 to 4.7).[34]

Obesity (defined as a body mass index (BMI) of 30 or greater) is a major risk factor for both type 2 diabetes and cancer. Adverse metabolic effects resulted from obesity have negative impacts on blood pressure, lipid levels and insulin resistance, and thus is a major risk for type 2 diabetes. Moreover, it is concluded that obesity-related cancers include breast cancer[35-53], colon[35,54-58], endometrium (the lining of the uterus[35,54-59], colorectal

cancer [35,60,61], kidney[35,62-69], and esophagus [70-74], prostate cancer [75-86], gallbladder [87-89], ovaries[90-95], and pancreas [35,96-100].

One of the common adverse effects of insulin use is weight gain, which is common among patients with either type 1 or type 2 diabetes. Excessive weight gain worsens glycemic control and is a major risk factor for many diseases.

Several mechanisms may contribute to insulin-related obesity. Insulin can decrease blood glucose levels below the renal threshold for glucose excretion, and accumulated excessive glucose can lead to conservation of ingested calories. Another widely accepted mechanism is compensation for hypoglycemia or 'defensive snacking'.[101] Deranged pharmacodynamic and metabolic profile of exogenous insulin do not have exact physiological secretion profiles as endogenous insulin, and thus considerable day-to-day variations could result in episodes of hypoglycemia, which promotes weight gain through 'defensive snacking'.[101-103]

1.4 Insulin Use and Cancer Risk

There is a growing concern that the risk of cancer among diabetics maybe linked to antidiabetic therapy. There have been five published studies which report a positive association between Lantus® (insulin glargine) and breast, colon or pancreatic cancers. These studies are described in Table 1.5 and results are summarized in Table 1.6 below.

Hemkens and colleagues used the German statutory health insurance data to investigate the risk of any malignant neoplasms and mortality among patients with diabetes who had been treated with insulin.[104] The adjusted HR for all cancers was 1.09 (95% CI 1.00–1.19) for glargine (a long-acting basal insulin analogue marketed by Sanofi-Aventis under the name Lantus) relative to human insulin for a daily dose of 10 IU, 1.19 (95% CI 1.10 – 1.30) for a daily dose of 30 IU, and 1.31 (95% CI 1.20–1.42) for a daily dose of 50 IU. The study demonstrates an increased risk of cancer associated with insulin glargine and thus raised the question of safety concerns of using glargine in diabetic patients. Limitations of this study include a short mean period follow-up to insulins (mean follow-up time was 1.63 years) and inability to control for important confounders such as BMI and cigarette smoking. They were not able to determine hazards for specific tumor sites due to small numbers. This is important because of the low probability that any one agent can increase the risk of all cancer types.

Jonasson et al. linked data from a number of registries in Sweden to explore the possible risk of cancer due to insulin glargine use among diabetics.[105] Poisson regression analyses were implemented to explore the association between different insulin use and the risk of cancer. The study shows that insulin glargine alone had a RR of 1.97 (95% CI 1.29–3.00) for breast cancer compared with insulin other than insulin glargine. Despite the significant finding, the authors concluded that the elevated risk of breast cancer among glargine users compared with users of other types of insulin was only due to a random fluctuation. Limitations of the Swedish study includes small number of cases of breast

cancers (25 cases for insulin glargine alone) and short follow-up period (mean was 2 years). Additionally, the unbalanced proportion of young patients in certain groups suggests a strong possibility of confounding by indication (type 1 vs. type 2), and/or severity of diabetes.

Cohounet al. examined the difference in cancer risks among diabetics in three exposure groups (non-glargine insulin, non-glargine plus glargine insulin, and insulin glargine alone) using Cox proportional hazards models for survival analyses.[106] The study did not find an increased risk of all cancers for insulin glargine users (n=3,959) relative to non-insulin glargine users (HR 1.02, 95% CI 0.77–1.36, p=0.9 in the fixed cohort). However, the study shows that using insulin glargine alone (n=447) was associated with a significantly higher incidence of all cancers than using other insulin (n=32,295) (HR 1.55, 95% CI 1.01–2.37, p=0.045). The authors concluded that insulin glargine use did not elevate the risk of all cancers or site-specific cancers in Scotland, and that the excess risk of cancer in the subgroups was a result of confounding by indication. Limitations of this study include small number of site-specific cancers, no dosage information and short follow-up time.

Curries and colleagues used The Health Information Network (THIN) data for the UK to explore the risk of solid tumors in relation to anti-diabetic prescriptions among type 2 diabetics.[107] Cox proportional hazards models were used in a cohort abstracted from the UK general practices. The study found that insulin therapy elevated the risk of colorectal (HR 1.69, 95% CI 1.23–2.33) or pancreatic cancer (HR 4.63, 95%CI 2.64–8.10) relative

to metformin. However, they concluded that insulin analogues were not associated with increased cancer risk as metformin is documented to have protective effect on the risk of cancer. Limitations include no detailed comparison of different insulin use (e.g., long acting vs. short) on the risk of cancer, unavailability of treatment duration, no control for disease severity, lack of dosage-based comparisons, low number of tumor events, or no control for important covariates, such as BMI.

Dejgaardet al. conducted a meta-analysis design of Novo Nordisk-sponsored, randomized clinical trials to evaluate the impact of insulin detemir on cancer risks.[108] Conditional odds ratios were estimated using both the Mantel–Haenzel and Peto methods to ensure robustness of results. The study found that odds ratio for cancer is greater than 1 when comparing NPH insulin with insulin detemir. The authors concluded that patients treated with insulin detemir had a lower or similar occurrence of cancer diagnosis compared with patients treated with NPH insulin or insulin glargine, respectively. Limitation of the study includes small number of events (8 events for insulin detemir, 13 events for NPH insulin, and 8 events for insulin glargine) which limited the study power, short follow-up period (follow-up time equal or greater than 3 months were included) due to the nature of clinical trials, while cancers usually develop over a much longer period of time.

Table 1.5 Published Studies of Insulin use and Cancer Risks among Diabetics: Study Design and Methods

Studies	Data Set	Study Population	Sample Size	Study Period	Analysis	Insulin Studied	Covariates	Outcomes
Hemkens[104]	German AllgemeineOrtskrankendasse (AOK) Health Insurance Dataset	Adults 18 years or older	127,031 type 1 and type 2 patients	2001-2005	Cox regression model	Aspart, lispro, glargine	Age, sex	ICD-10, All types of cancer, no breakdown
Jonasson[105]	Prescribed Drug Register, the Cancer Register and the Causes of Death Register Dataset	35-84 y/o	114,841 insulin users	2005-2007	Incidence rate ratio (RR) incidence rate of having cancer among glargine alone users and compared with the incidence rate among users of other types of insulin	Glargine vs. glargine in combination with other types of insulin	Age, BMI, Cardiovascular disease	ICD-10, breast cancer, prostate cancer, gastrointestinal cancer
Colhoun[106]	The Scottish Care Information-Diabetes Collaboration (SCI-DC) Dataset	No detailed info	12,845 antidiabetics	2002-2005	Cox proportional hazard model	Glargine only, non-glargine insulin, non-glargine+glargine	Smoking, BMI, Diabetes duration, blood pressure, baseline HbA1c	All cancers and cancers at specific sites (breast, colon, prostate, pancreas, lung)

Currie[107]	The Health Information Network (THIN) Dataset	40 years or older	62,809 type 2 patients	Not specified	Cox proportional hazard model	Human basal insulin, biphasic insulin, analogue biphasic insulin	Age, sex, smoking status, prior solid tumor(yes/no)	Breast cancer, pancreatic cancer, colorectal cancer and prostate cancer
Dejgaard[108]	Novo Nordisk-sponsored, randomised and controlled diabetes trials	Children were excluded	8,693 patients with type 1 or type 2 diabetes	at least 12 weeks in duration	Meta-analysis. Conditional ORs were estimated applying both the Mantel–Haenzel and Peto methods to ensure robustness of results	Insulin detemir, NPH insulin, Insulin glargine	N/A	Suspected treatment-emergent malignant tumors

Table 1.6 Published Studies of Insulin use and Cancer Risks among Diabetics: Study Results

Studies	Comparator	Reference	Results	Conclusion
Hemkens[104]	Glargine	Human insulin	Adjusted HR was 1.09 (95% CI 1.00 to 1.19) for a daily dose of 10 IU, 1.19 (95% CI 1.10 to 1.30) for a daily dose of 30 IU, and 1.31 (95% CI 1.20 to 1.42) for a daily dose of 50 IU	Data support safety concerns of insulin glargine
Jonasson[105]	Insulin glargine alone	Other types of insulin	RR for breast cancer was 1.97 (95% CI 1.29–3.00)	This result may be due to a random fluctuation
Colhoun[106]	Insulin glargine alone	Other insulins	HR was 1.55 (95% CI 1.01–2.37), p=0.045	Confounding by indication. Overall, insulin glargine use was not associated with an increased risk of cancers
Currie[107]	Insulin therapy	Metformin	Colorectal cancer (HR 1.69, 95% CI 1.23–2.33);pancreatic cancer (HR 4.63, 95%CI 2.64–8.10)	Metformin use was associated with lower risk of cancer of the colon or pancreas, however, metformin is documented to have protective effect on cancer risk; insulin analogues use was not associated with increased cancer risk as compared with human insulin
Dejgaard[108]	NPH insulin	Insulin detemir	OR>1	it is not possible to definitively draw conclusions on the risk of cancer by insulin therapy

1.5 Possible Mechanism for Tumor Promotion

Given the short follow up periods of studies which found an association between insulin glargine with solid tumors, it is likely that if there is a true causal association, it is more likely to tumor promotion and not induction (tumor genesis). Insulin-like growth factor-I (IGF-I) is a known tumor growth factor. The role of IGF- I in promoting cancer has been investigated for many years.[109] Lopez and colleagues designed a mouse model providing proof that growth and progression of established tumors were driven and enhanced by active IGF-I signaling facilitate malignant transformation.[110] Pollak et.al also confirmed that IGF-I plays an important role in the progression and development of human cancers.[111] Indeed, low IGF-I levels are reported to be associated with reduced growth and metastasis of tumors and xenografts and vice versa.[112-114]

With the advent of recombinant DNA technology, insulin analogues which are specifically destroyed to manipulate absorption time are frequently used for diabetes treatment. The preferred site for structural modification of recombinant DNA insulin is the B26-B30 region because it effectively modifies the pharmacokinetics of the insulin particles without impacting insulin receptor recognition. However, such modifications may enhance their affinity for the related IGF-I receptor (IGF-IR), and display atypical activities, such as inhibition of apoptosis.

Therefore, it is proposed that mitogenic effect of certain insulin analogues are caused mainly by higher affinity to the IGF-I receptor.[115,116] For instance, insulin glargine has an

affinity to the IGF-I receptor 6.5-times higher than that of human insulin.[117] In contrast, the two short-acting insulin analogues (insulin regular and velosulin) were documented to be similar to human insulin in most respects.[118]

Figure 1.2 below summarizes the mechanism in detail. The increased levels of insulin can reduce not only blood levels of insulin-like growth factor binding protein 1 (IGFBP1), but also IGFBP2 in the blood, which leads to increased levels of bioavailable IGF-I. Also, certain recombinant DNA insulins have greater affinity towards IGF-I receptors. Insulin and IGF-I signal through the insulin receptors (IRs) and IGF-I receptor (IGF1R), respectively, to promote cellular proliferation and inhibit apoptosis in many tissue types. Any of these effects might contribute to tumor genesis.

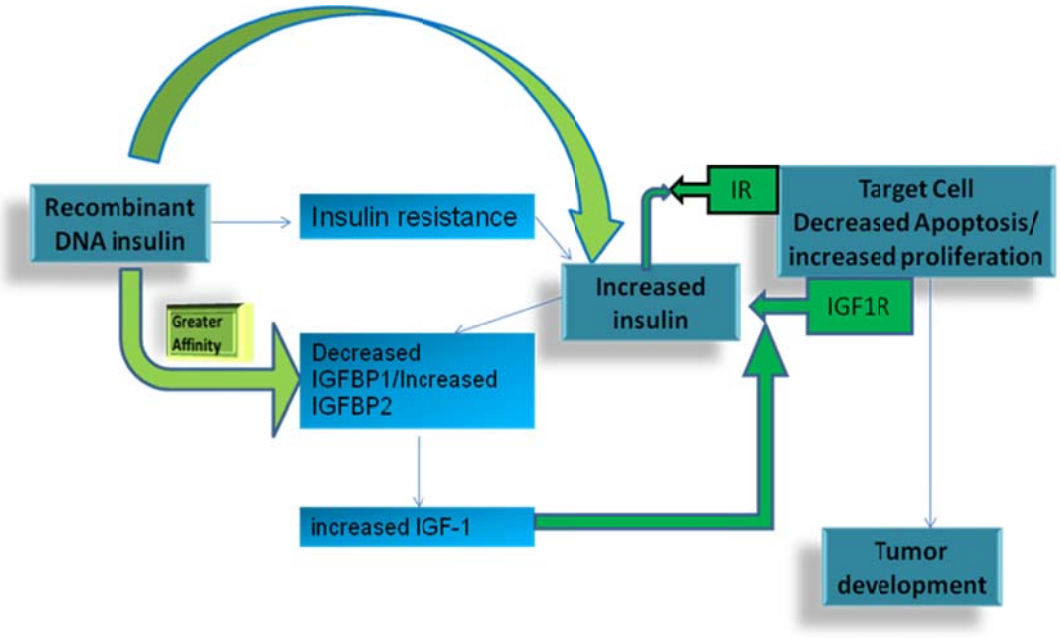

Figure 1.2 Mechanism of Recombinant DNA insulin and increased risk of cancer[119]

1.6 Study Significance

The Centers for Disease Control and Prevention (CDC) estimates that diabetes affects 25.8 million (8.3%) of the U.S. population in 2011, and another 7.0 million people with undiagnosed diabetes.[8] Insulin use is critical for diabetes mellitus treatment: type 1 diabetes must be treated with insulin, and type 2 diabetes will eventually need insulin although it has other oral regimens. Therefore, whether insulin therapy is associated with an additional increased risk of cancer has raised particular concern. Most recently, the FDA became aware of the published observational studies on use insulin glargine and possible risk for cancer in diabetics.[120] It is now reviewing safety data for Lantus from a variety of sources, including both completed and on-going randomized controlled clinical trials, to understand the potential risk of cancer, if any, due to insulin use. In December, 2009, a consensus development conference was convened by the American Cancer Society and the American Diabetes Association. A consensus report was immediately released following the conference to high-light the controversial findings and possible mechanisms of the link between insulin use and cancer.[121] The European Medicines Agency is also calling for studies on the link between insulin exposure and the risk of cancer, and has listed this research area as its 2011 Priorities for Drug Safety Research.[122]

Published studies generally have limited power to detect modest associations between insulin therapy and site-specific cancers, have short follow-up time for incident cancers, and do not fully adjust for confounding that are important when exploring cancer risks.

More importantly, it remains unclear if the increased risk of tumor, if any, is specific to a single agent (Lantus), other similar drugs (e.g., long acting agents), or common to all insulins. None of the published studies investigated the link between insulin treatment and cancer by looking at insulin as a drug class. This study used the General Practice Research Database (GPRD), a large UK-based research database of patient electronic health records from general practitioners, to explore the use of insulin on the risk of cancer. Furthermore, it evaluated the role of HbA1c between all cancers and selected site-specific cancers. The study results would inform regulatory agencies, policy makers of the potential risk of insulin, and inform the health care providers so that they can apply this message to determine the best use of anti-diabetic drugs.

2 Study Purposes and Research Methods

2.1 Study Purpose

The purpose of this proposed study is (1) to assess the effect of insulin exposure (alone or in combination with oral agents for hypotheses 1 and 3; insulin subtypes of short-acting, intermediate-acting, long-acting and pre-mixed insulin for hypothesis 2) on the risk of developing solid cancer among patients with diabetes mellitus; and (2) to explore the role of HbA1c value in modifying the risk.

2.2 Specific Aims and Hypotheses

Aim 1: Determine the impact of human recombinant DNA insulin exposure on the risk of cancer;

Hypothesis 1: Diabetics who use human recombinant DNA insulin have a greater cancer incidence than those with oral regimens.

Aim 2: Determine if the risk of solid tumor differs by insulin subtypes;

Hypothesis 2: Diabetics who use long-acting insulins, or intermediate-acting insulins, or pre-mixed insulins have a greater cancer incidence than those using short-acting insulins.

Aim 3: Determine the role of HbA1c value in modifying the risk of cancer.

Hypothesis 3: Level of HbA1c is directly associated with cancer risk, independent of insulin use.

2.3 Data Source

The study used the General Practice Research Database (GPRD), a large computerized database of patient level data. The GPRD data collection began in the late 1980's as the VAMP Health. A commercial company, VAMP Health, installed computers in general practitioners (GPs)' offices so that they could use their practice management software throughout the United Kingdom (UK) for administrative and research purposes. The database got its current name of GPRD in 1994 and has been considered by many researchers to be the 'gold standard' of longitudinal anonymised research databases of primary care. In 1995, GRPD physicians began using a new medical record and patient management system called the vision clinical system software. The vision system has many advantages for the physician as well as the researcher. For example, the vision system creates a unique consultation identifier that links all entries recorded at the same consultation, greatly improving the validity of links between services, such as indications for therapies. Additionally, quantitative as well as qualitative (normal/abnormal) laboratory test results are recorded alongside the laboratory-specific normal range. Wood and Martinez describe the GPRD research databases and data collection methods in an article published in *Pharmacoepidemiology and Drug Safety* (2004).[123] More details are also available on the GPRD website (www.gprd.com).

Currently, the GPRD research databases are maintained by the Secretary of State for Health, UK. The Medicine Control Agency manages the GRPD and has initiated a program to enable broader research use of the data both within the UK and worldwide. GPRD contains over 9 million active patient records drawn from approximately 400

primary care practices in the UK. The database has clinical and prescription data and can provide information to support pharmacovigilance (indication, utilization, and risk/benefit profiles of drugs) and formal pharmacoepidemiologic studies, including information on demographics, medical symptoms, therapy (medicines, vaccines, devices), and treatment outcomes. The GPRD can provide data for both clinical and academic researchers. It is used extensively in pharmacoepidemiology research with over 400 articles published in peer-reviewed journals which have used GPRD data.

There are several strengths for using GPRD data for this study. First, GPRD is population-based observatory data with large sample size that is representative of the UK population. The GPRD research database covers about 6% of the total UK population, a population large enough to study rare diseases and uncommon exposure. Because no intervention was applied when collecting GPRD data during the routine practice of the GPs, the data are nationally representative of the UK population at the patient level. For instance, demographic information from GPRD is similar to the distribution result from the National Population Census, and therefore, the geographical distribution of the practices in the GPRD is representative of the UK population. Second, GPRD collects extensive information. The following information is collected in the United Kingdom: Demographics (including age, sex and location); Medical symptoms, signs and diagnoses; Therapy (medicines, vaccines, devices); Treatment outcomes; Detailed information on hospital admissions, discharge diagnoses and medications; Events leading to withdrawal of a drug or treatment; Referrals to hospitals or specialists; Laboratory tests, pathology results; Lifestyle factors (height, weight for BMI, smoking and alcohol consumption);

Socioeconomic status; Patient registration, practice and consultation details. For this proposed study, for instance, we used laboratory tests such as HbA1c, life style information on smoking status, alcohol consumption, and BMI. This information usually does not exist in many of the other commercial insurance database.

Third, GPRD has information on disease severity/control and duration. Patient information and drug information are continuously updated with new diagnosis, referral consultation and other medical events, so that it is possible for studies that need disease severity/control or disease duration identifications. In addition, patients tend to stay with their GPs in a long period of time, allowing for longer follow-ups than most commercial insurance databases.

Finally, GPRD is a high quality and validated database. All health related information from patient level is maintained by the GP, minimizing gaps in the collection of the medical information. Validity and quality of the entries have been documented and confirmed. Studies show that concordance for clinically relevant outcomes is between 90%-95%.[124]

The above features make the GPRD an ideal dataset for drug safety studies: The GPRD has been the most widely utilized dataset for pharmacoepidemiological research world-wide.[124]

2.4 Population/Cohort

A nonconcurrent prospective cohort study design was utilized. The study cohort was defined as patients with at least one prescription for an antidiabetic drug, and registered with a medical practice within the GPRD. The study was limited to those with "up to standard practice" (Once the GP is deemed competent at entering data, then the subsequent data are determined to be of high quality, valid and competent based on an established quality standards and is labeled as 'up to standard").[124] The inclusion and exclusion criteria of the study were as follows:

Inclusion Criteria

- Patients on antidiabetic therapy
- Patients contributed "up-to-standard" data

Exclusion criteria

- Patients less than 2 years of age at the time of receiving the first antidiabetic medication were excluded
- For research question 3, those patients without any HbA1c values during follow-up were excluded, because this laboratory measure was the key variable for this research question
- Patients with any existing cancer prior to diagnosis of diabetes were excluded
- Patients with any anti-diabetic medication one year prior to Jan1, 1988 were excluded, so we have incident medication users. We also use this one year period to exclude any pre-existing cancers before diabetes.

Study Period was between January 1, 1987 and December 31, 2009. A patient was entered into a cohort at the earliest date of receiving therapy or the date when the practice began submitting 'up to standard' (UTS) data, whichever came last within study period. A patient's follow-up ended at the date of a diagnosis of cancer, death, transfer out of the medical practice, loss to follow-up or the end covered data. The follow-up length is the subject's end of study period subtracted from the subject's start of study period.

2.5 Exposure

GPRD prescription data precisely reflect what was prescribed by the GPs (e.g., in order for a GP to write a medication to their prescription, they must enter it in the GPRD database electronically). These prescriptions were used as a proxy for drug exposure. The drug exposure of interest is insulins or oral agents. For research question 1 and 3, drug exposure is categorized as exposed to oral agent, exposed to insulin only, and exposed to a combination of both insulin and oral agents. For research question 2, insulin is categorized as long-acting, short-acting, intermediate-acting and premixed acting insulin.). (Table 1.3)

2.6 Outcomes

The primary outcome for this study is an incident diagnosis of a cancer. The secondary outcome measure was an incident diagnosis of cancers at the following sites: breast,

colon and/or rectum, prostate, pancreas, bladder, lung, endometrium, esophagus, and kidney. This secondary outcome is a total of nine specific solid tumor cancers (Table 2.1). Among them, six cancers (breast cancer, colorectal cancer, prostate cancer, pancreatic cancer, bladder cancer or lung cancer) are associated with diabetes mellitus alone or with both diabetes and obesity. The other 3 cancers (endometrial cancer, esophageal cancer, kidney cancer) are associated with obesity, an important risk factor for both diabetes and cancer.[104-108] Cancers were identified using Medical Codes (Medcode) in the Medical dictionary and Medical_to_ffgprd dictionary, a diagnostic coding in the GPRD database with the first diagnosis date of the studied cancer. A systematic review of the literature demonstrates good accuracy and completeness of diagnostic coding in the GPRD for chronic diseases.[125] Furthermore, a study published in Lancet in 1997 used questionnaires to GPs verifying the validity of cancer diagnosis for all computer-identified cancer cases showed a ninety-five percent agreement in incident cancer cases.[126]

Table 2.1 Secondary Outcomes

Conditions	**Associated Cancers**
Diabetes & Obesity	breast cancer, colon cancer, prostate cancer
Diabetes Only	pancreatic cancer, bladder cancer, lung cancer
Obesity Only	endometrial cancer, esophageal cancer, kidney cancer

2.7 Covariates

Demographic variables included in the study were age, gender and location. The age variable was categorized into 5 groups: less than 18-30, 31-40, 41-65, 66-79, and 80 or over (Appendix 1); Location was categorized into four regions: England, Northern Ireland, Scotland and Wales (Appendix 1) as cancer prevalence often differ by living environment; Lifestyle risk factors included smoking status, alcohol consumption and BMI. Smoking status was categorized as nonsmoker, former smoker, current smoker or unknown; Alcohol intake was categorized as 0 unit/week, 1-15 units/week, 16-42 units/week, and 42 units/week or more Wales (Appendix 1). BMI was derived from patients' median weight and height during the follow-up time using the formula BMI=mass (lb)*4.88/height^2(ft^2), which was then categorized into the following groups: 0-18.4, 18.5-24.9, 25.0-29.9, 30.0-34.9(Obese Class I), 35.0-39.9(Obese Class II), and 40.0 or over (Obese Class III) Wales (Appendix 1). Co-morbidities were hypertension and hyperlipidemia, defined as at least one recorded diagnosis by their GP (Appendix 2); Oral antidiabetic agents were included as a covariate in the model for adjustment purposes. This variable was an indication whether the patient received any oral medication (Table 1.4 for definition).

Because HbA1c is a good measure for mid- to long-term diabetes control, the extended length of follow-ups to study cancer risk allows for various measures of HbA1c over time, the following measure of HbA1c was explored:

1) HbA1c level at baseline (the latest time of HbA1c measure before an antidiabetic medication was used)

2) Median HbA1c over the follow-up period
3) Mean HbA1c over the follow-up period
4) Median/mean HbA1c in the year prior to an event or end of the study
5) Median/mean HbA1c within the first year of follow up

For hypothesis 3, models was run with HbA1c coded as both a continuous variable and as a categorical variable to determine the impact of HbA1c on modifying the insulin-cancer association, and to determine if the effect is continuous or a threshold effect. (Appendix 3)

2.8 Statistical Analysis

SAS version 9.1 (SAS Institute, Inc., Cary, NC) was used for data analysis. Cox proportional hazards models for survival data was implemented for research questions.

Step 1 Descriptive Analyses

To assess the statistical properties (distribution and spread) of each study variable of the GPRD data, exploratory data analysis (EDA) was conducted in the full cohort. These were as follows:

1) Univariate analyses

For categorical variables, frequencies and percentages were generated to determine their distributions and extent of missing values. For continuous variables, the distribution, outliers/skewness, measures of central tendency and spread were assessed. These strategies were necessary to locate outliers and nonsense codes, and will guide decisions to exclude outliers or to categorize them. For example, to comply with IRB requirement, some oldest aged patients may need to be grouped into one category if the number of persons is less than five in one age group.

2) Bivariate analyses

Bivariate analyses were also conducted to determine the number of cases and the significance level of our demographic, co-morbidities, or behavioral variables in relation to the study exposure and outcome variables. T-test and Chi-square test were applied to continuous and categorical variables between groups, respectively. In addition, correlation coefficients among continuous covariates were calculated.

Step 2 Handling missing data

Not controlling for behavioral risk factors, such as smoking status and alcohol consumption, may be a concern for studies exploring the risk of cancer as these two behavioral variables are critical for cancer development. The availability of this information in the GPRD database is one of the advantages of the proposed study over the others. Patients with missing information on behavioral risk factors such as smoking status and alcohol consumption, however, were categorized as “unknown” in the analysis.

There are three possible mechanisms for data missing: missingness completely at random (MCAR), missing at random (MAR) and not missing at random (NMAR). MCAR refers to data in which a variable is missing completely at random if the probability of missingness is the same for all units. MAR refers to data, in which most missingness is not completely at random, as can be seen from the data themselves. NMAR refers to data that have missingness either depends on unobserved predictors or on the missing value itself. It is usually difficult to handle missing data because of NMAR. There are several different approaches to handling missing data, including pairwise deletion, replace missing data with imputed values using propensity score method, regression method and Markov chain Monte Carlo (MCMC) method. These approaches either require a strong assumption of data missing at random, or the imputed values can be any real value rather than being restricted to 0 and 1. Based on the fact that the behavioral risk factors such as smoking status and alcohol consumption were dummy variables and thus coded as 0 (No) and 1(Yes), and we do not have information if the assumption holds, we categorized missing data as "unknown'.

Step 3 Confirmatory data analysis (CDA)

Estimation of Hazard Ratio

The models and analyses used in this study only looked at the first cancer event in relation to antidiabetic therapies. The analysis for the interval between insulin exposure and the first cancer event was estimated using Cox's regression model. This semiparametric regression model can estimate time to cancer event, measured in days.

The hazard for an individual *i* at time *t* can be written as

$$\mathbf{h_i(t)=\lambda_0(t)\ exp\ (\beta_1 x_{i1}+\ldots\ldots\ldots\ldots+\beta_k x_{ik})}.$$

Where the baseline hazard function $\lambda_0(t)$ is nonnegative. The model can be rewritten as

$$\mathbf{\log h_i(t)= \alpha(t) + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots\ldots\ldots\ldots + \beta_k x_{ik}}.$$

Where $\alpha(t)= \log\lambda_0(t)$.

The ratio of the hazard for the exposure group to the hazard of the non-exposure group can be calculated as follows:

$$\underline{\mathbf{h_{RT}(t)}}\mathbf{=exp\ \{\beta_1(x_{exposure1}-x_{non\text{-}exposure1})+\ldots\ldots\ldots\ldots+\beta_k(x_{exposurek}-x_{non\text{-}exposurek})\}}$$

$$\mathbf{h_{NRT}(t)}$$

where $\mathbf{x}_{exposure1}$ is the x variable in the treatment group for L at time t, and $\mathbf{x}_{non\text{-}exposure1}$ is the x variable in the reference group for L at time t.

Partial likelihood function is used for to estimate the β coefficients of the proportional hazards model.

Analysis plan for hypothesis 1

Diabetics who use human recombinant DNA insulin have a greater cancer incidence than those on oral regimens.

Study sample was patients on antidiabetic therapy without prior diagnosis of cancer. Diabetes type, controlled as a covariate, was also assessed for those patients with available information on diabetes types.

The algorithm for identifying patients with type 1 and type 2 diabetes was as follows:

1) If the diabetes diagnosis code was specific to the type of diabetes (type 1, type 2) then the person was classified into type based on that diagnosis.
2) If the diabetes diagnosis code was not specific to type of diabetes (e.g. unknown or missing in the chart), then patients were classified as follows:
    a) If a patient received any oral agents during the first 3 months of treatment, then the patient was classified as type 2 diabetes;
    b) If a patients received any insulin during the first 3 months of treatment, and no any oral agents during the first 6 months of treatment, then the patient was classified as type 1 diabetes;
    c) The rest of the patients would be classified as unknown types.

Model 1

Log Hazard of (time to cancer event) = **α(t)**+ â1 (drug exposure) + â2 (demographic variables) + â3 (comorbidities) + â4 (behavioral factors) + â4 (diabetes types)

Where time to cancer[1] was the length of time from first exposure to an antidiabetic product to the date that an incident cancer is diagnosed, measured in days; drug exposure

[1] Cancer will be a) all cancers for primary outcome and b) specific cancers as secondary outcome (see Exposure, Outcomes and Covariates section)

was categorized as oral agent therapy only, insulin only therapy, and a combination therapy of both insulin and oral agents, with oral therapy as the reference group. Demographic variables, co-morbidities, behavioral factors and other covariates are described in Appendix 1 and 2.

Analysis plan for hypothesis 2

Diabetics who use long-acting insulins, or intermediate-acting insulins, or premised insulins have a higher cancer incidence than those on short-acting insulins. Study sample was patients on insulin therapy without prior diagnosis of cancer, a subset of our study cohort. Diabetes type, controlled as a covariate, was also assessed for those patients with available information on diabetes types.

Model 2

Log Hazard of (time to cancer event) = $\alpha(t)$+ â1 (types of insulin) +â2 (demographic variables) + â3 (comorbidities) + â4 (behavioral factors) + â5 (diabetes types)

Where time to cancer[2]was the length of time from first exposure of medication to the date that an incident cancer was diagnosed, measured in days; Types of insulin include long-acting insulin, Inter-mediate acting insulin, premixed insulin, with short-acting insulin as the reference group. Measure of different types of insulin was based on dominant use of that insulin type. Demographic variables, co-morbidities, behavioral factors and other covariates are described in Appendix 1 and 2.

[2] Cancer will be a) all cancers for primary outcome and b) specific cancers as secondary outcome (see Exposure, Outcomes and Covariates section)

Analysis plan for hypothesis 3

The level of HbA1c is associated with the increase of cancer risk, independent of insulin choice.

The study sample was diabetics on insulin medication or oral treatment and with HbA1c value available. Diabetes type, controlled as a covariate, was also assessed for those patients with available information on diabetes types.

Model 3

Log Hazard of (time to cancer event) = $\alpha(t)$ + â1 (drug exposure) + â2 (HbA1c level) +â3 (demographics) + â4 (comorbidities) + â5 (behavioral factors) + â6 (diabetes types)

Where time to cancer[3] was the length of time from first exposure of medication to the date that an incident cancer was diagnosed, measured in days; Oral medication was controlled as a covariate.

Demographic variables, co-morbidities, behavioral factors and other covariates are described in Appendix1 and 2. HbA1c value was added to the model as a continuous variable as described in Appendix 3.

[3] Cancer will be a) all cancers for primary outcome and b) specific cancers as secondary outcome (see Exposure, Outcomes and Covariates section)

3 Results

3.1 Study Population

There were a total of 9,007,697 patients in the GPRD dataset during the period of January 1, 1987 and December 31, 2009. After applying inclusion and exclusion criteria, we had a total of 230,330diabetics as our study cohort (Figure 3.1).

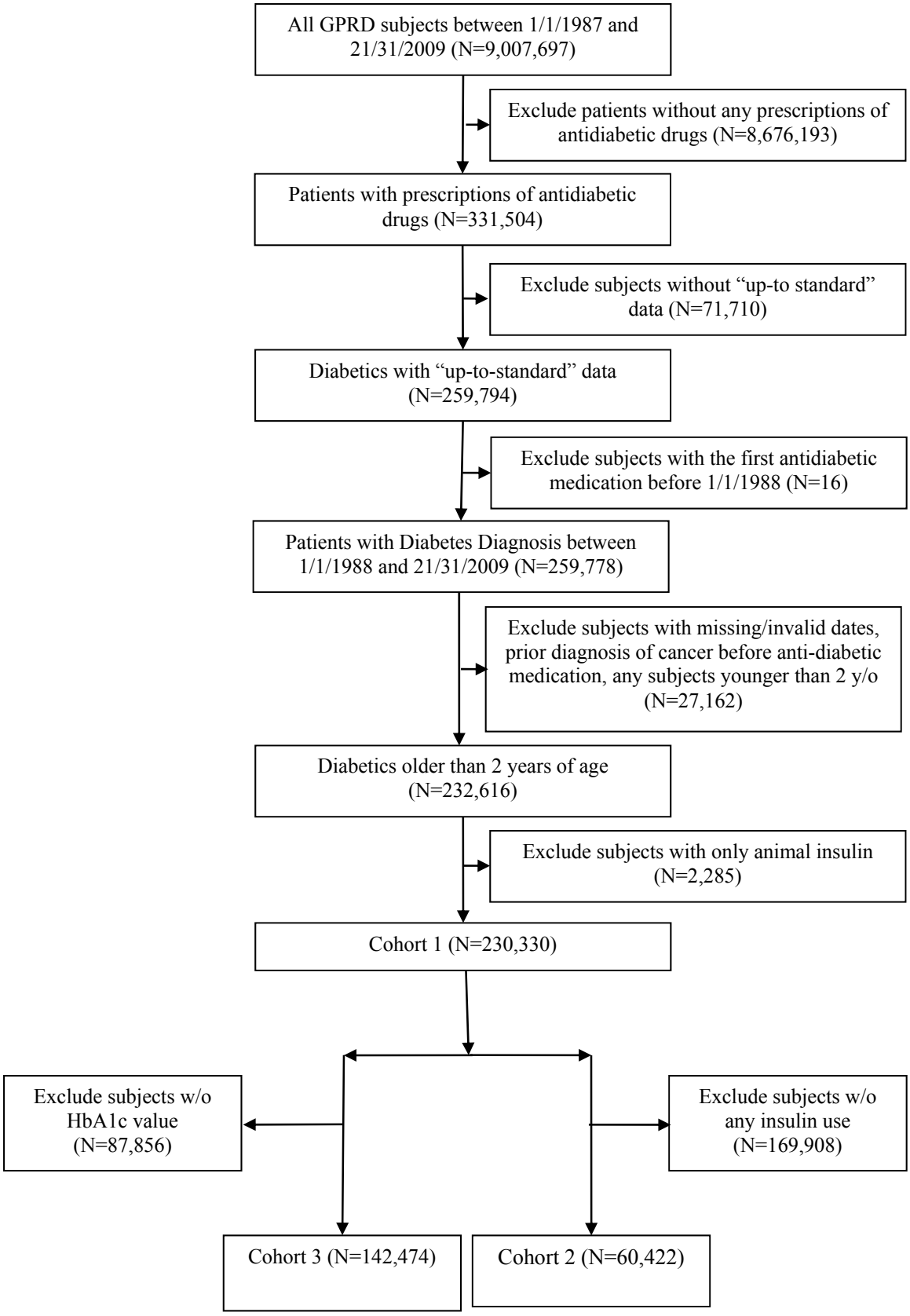

Figure 3.1 Study cohort

Of these patients with diabetes, the age distribution shows that less than 1% of the sample was between 2 and 9 years of age, about 40% were between the ages of 60-79. The rest of the sample fell in the 10-19 (1.70%), 20-39 (13.72%) and 40-59 (30.29%) age categories. Patients' residence was categorized by region; the majority of the patients (83%) lived in England, with the rest (17%) lived in Northern Ireland, Scotland or Wales. After applying for our algorithm to identify diabetes types, 87% of the patients were classified as having type 2 diabetes, 12% as having type 1 diabetes, and the remainder had other types of diabetes (e.g. gestational diabetes). More than one-half of the cohort had a diagnosis of hypertension and/or dyslipidemia. Only 18.0% of the patients were within the normal range of BMI (18.5-24.9). The majority of the diabetes sample (31.46%) was classified as pre-obese. (Table 3.1)

Table 3.1 Baseline Characteristics for All Patients on Diabetes Treatment: Use of Insulin on the Risk of Cancer Compared with Non-insulin Use

	Frequency	Percent (%)
Age group		
2-9	1,584	0.69
10-19	3,918	1.70
20-39	31,600	13.72
40-59	69,790	30.30
60-79	99,707	43.29
80+	23,731	10.30
Gender		
Female	111,241	48.30
Male	119,089	51.70
UK Region		
England	191,329	83.07
Northern Ireland	6,133	2.66
Scotland	15,037	6.53
Wales	17,831	7.74

Diabetes Type		
Type 1	26,312	11.42
Type 2	201,515	87.49
Unknown	2,503	1.09
Hypertension		
Yes	87,738	38.09
No	142,592	61.91
Dyslipidemia		
Yes	32,471	14.10
No	197,859	85.90
Alcohol use		
0-15 Unit Per Week	98,059	42.57
15-42 Unit Per Week	19,478	8.46
>42 Unit Per Week	2,643	1.15
Non Alcohol	16,136	7.01
Unknown	94,014	40.82
Cigarette Smoking		
Current smokers	67,612	29.35
Ex-smokers	52,756	22.90
Non-smokers	82,262	35.71
Unknown	27,700	12.03
BMI		
0-18.4	3,267	1.42
18.5-24.9	40,856	17.74
25.0-29.9	72,470	31.46
30.0-34.9	48,591	21.10
35.0-39.0	20,003	8.68
40.0+	9,643	4.19
Unknown	35,500	15.41
HbA1c*		
Yes	142,474	61.86

*Available in subset of cohort 1

The majority (75%) had only been prescribed oral therapy; 14% had a combination of both insulin and oral agents, only 11% of them were on insulin alone. (Table 3.2)

Table 3.2Drug Use for All Patients on Diabetes Treatment: Use of Insulin on the Risk of Cancer Compared with Non-insulin Use

	Frequency	Percent (%)
Oral only	171702	74.55
Insulin and oral	32618	14.16
Insulin only	26010	11.29

Table 3.3 shows that about 10.0% of the patients with diabetes developed incident cancers of any type, other commonly seen incident cancers include colorectal cancer (1.39%), lung cancer (1.37%), breast cancer (1.02%) and prostate cancer (0.95%).

Table 3.3 Cancer Outcomes for All Patients on Diabetes Treatment: Use of Insulin on the Risk of Cancer Compared with Non-insulin Use

	Frequency	Percent (%)
Any cancer	23064	10.01
Breast cancer	2341	1.02
Colorectal cancer	3198	1.39
Prostate cancer	2196	0.95
Pancreatic cancer	1417	0.62
Bladder cancer	1227	0.53
Lung cancer	3158	1.37
Uterine cancer	0	0.00
Esophageal cancer	0	0.00
Kidney cancer	639	0.28

3.2 Patient characteristics by drug exposure

Table 3.4 lists characteristics of patients by drug exposure. The majority of the patients fell in the 60-79 age category for oral alone, 20-39 age category for insulin alone, and 40-59 age category for a combination of both insulin and oral agents.

Table 3.4 Binary Analysis of Patient Characteristics by Drug Use for All Patients on Diabetes Treatment

	Oral only	Insulin only	Insulin and oral	P value
	Percent (%)	Percent (%)	Percent (%)	
Age group				<.0001
2-9	0.03	5.78	0.08	
10-19	0.52	10.93	0.58	
20-39	10.40	37.87	11.93	
40-59	29.84	20.55	40.51	
60-79	47.18	18.84	42.28	
80+	12.03	6.04	4.62	
Gender				<.0001
Female	48.99	45.98	46.50	
Male	51.01	54.02	53.50	
UK Region				<.0001
England	82.78	82.59	84.96	
Northern Ireland	2.72	2.48	2.49	
Scotland	6.58	7.72	5.29	
Wales	7.91	7.21	7.26	
Diabetes Type				<.0001
Type 1	0.11	87.83	10.06	
Type 2	99.89	12.17	82.26	
Unknown	0.00	0.00	7.67	
Hypertension				<.0001
Yes	42.38	14.05	34.68	
No	57.62	85.95	65.32	
Dyslipidemia				<.0001
Yes	15.69	4.68	13.24	
No	84.31	95.32	86.76	
Alcohol use				<.0001
0-15 Unit Per Week	43.71	33.17	44.07	
15-42 Unit Per Week	8.77	7.49	7.57	
>42 Unit Per Week	1.19	1.09	0.95	
Non Alcohol	7.28	4.96	7.17	
Unknown	39.04	53.29	40.24	
Cigarette Smoking				<.0001
Current smokers	29.08	25.76	33.65	
Ex-smokers	24.16	12.23	24.79	
Non-smokers	36.23	35.23	33.40	
Unknown	10.52	26.78	8.17	

BMI					<.0001
	0-18.4	1.16	3.56	1.09	
	18.5-24.9	15.76	31.67	17.06	
	25.0-29.9	32.62	22.81	32.29	
	30.0-34.9	22.70	7.60	23.40	
	35.0-39.0	9.31	2.42	10.38	
	40.0+	4.49	1.06	5.09	
	Unknown	13.97	30.88	10.68	

Table 3.5 lists binary analysis of patient characteristics by outcome of any cancer for all patients on diabetes treatment.

Table 3.5 Binary Analysis of Patient Characteristics by Outcome of Any cancer for All Patients on Diabetes Treatment: Use of Insulin on the Risk of Cancer Compared with Non-insulin Use

	Developed an Incident Cancer (Yes)	Developed an Incident Cancer (No)	P value
	Percent (%)	Percent (%)	
Age group			<.0001
2-9	0.03	0.76	
10-19	0.06	1.88	
20-39	1.8	15.05	
40-59	20.19	31.43	
60-79	66.32	40.73	
80+	11.59	10.16	
Gender			<.0001
Female	41.12	49.1	
Male	58.88	50.9	
UK Region			<.0001
England	82.31	83.15	
Northern Ireland	3.26	2.6	
Scotland	6.27	6.56	
Wales	8.15	7.7	
Diabetes Type			<.0001
Type 1	5.07	12.13	
Type 2	93.91	86.77	
Unknown	1.02	1.09	
Hypertension			<.0001
Yes	56.07	62.56	
No	43.93	37.44	

Dyslipidemia			<.0001
Yes	85.87	85.91	
No	14.13	14.09	
Alcohol use			<.0001
0-15 Unit Per Week	46.06	42.19	
15-42 Unit Per Week	9.61	8.33	
>42 Unit Per Week	1.17	1.15	
Non Alcohol	6.89	7.02	
Unknown	36.28	41.32	
Cigarette Smoking			<.0001
Current smokers	31.49	29.12	
Ex-smokers	30.2	22.09	
Non-smokers	29.24	36.44	
Unknown	9.07	12.36	
BMI			<.0001
0-18.4	0.92	1.47	
18.5-24.9	17.31	17.79	
25.0-29.9	36.83	30.87	
30.0-34.9	22.78	20.91	
35.0-39.0	7.62	8.8	
40.0+	2.73	4.35	
Unknown	11.8	15.81	

The follow-up time for those patients who developed cancer was also assessed (Table 3.6). The average follow-up time was approximately 47 months (2.7 years).

Table 3.6 Follow-up Time for Patients with Incident Cancers (months)

Cancer	Mean	Median	Std Dev	Minimum	Maximum
Any cancer	47.08	35.43	42.76	0.03	251.53
Breast cancer	53.25	42.37	44.68	0.07	251.53
Colorectal cancer	56.52	45.90	46.91	0.03	241.40
Prostate cancer	50.72	39.55	44.21	0.03	245.67
Pancreatic cancer	33.67	18.47	39.97	0.03	229.57
Bladder cancer	55.15	43.73	46.45	0.03	226.37
Lung cancer	56.44	42.93	48.34	0.03	242.63
Kidney cancer	62.05	55.97	44.03	0.03	199.20

3.3 Testing of Hypothesis H1 0: Objectives and Specific Aims

Aim 1: Determine the impact of human recombinant DNA insulin exposure on the risk of cancer;

Hypothesis 1: Diabetics who use human recombinant DNA insulin have a greater cancer incidence than those with oral regimens.

Table 3.7 Cox Proportional Hazards Model for Progression to Any Solid Tumor Cancers in People Treated with Insulin Compared with Oral-agents

Variable	Crude Analysis			Multivariate Analysis		
	Hazard Ratio	**95% Hazard Ratio Confidence Limits**		**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**	
Insulin use						
Oral only (ref)	-	-	-	-	-	-
Insulin and oral	0.928	0.899	0.958	1.054	1.019	1.089
Insulin only	0.432	0.407	0.458	1.160	1.060	1.269
Age group						
2-9	-	-	-	0.297	0.148	0.598
10-19	-	-	-	0.275	0.162	0.467
20-39 (ref)	-	-	-	-	-	-
40-59	-	-	-	4.353	3.930	4.821
60-79	-	-	-	11.671	10.558	12.900
80+	-	-	-	14.891	13.386	16.565
Gender						
Female (ref)	-	-	-	-	-	-
Male	-	-	-	1.260	1.225	1.297
UK Region						
England	-	-	-	0.865	0.804	0.931
Northern Ireland (ref)	-	-	-	-	-	-
Scotland	-	-	-	0.909	0.831	0.993
Wales	-	-	-	0.891	0.819	0.970
Diabetes Type						
Type 1 (ref)	-	-	-	-	-	-
Type 2	-	-	-	1.341	1.224	1.468
Unknown	-	-	-	1.584	1.354	1.853
Hypertension						
Yes	-	-	-	1.035	1.007	1.063
No (ref)	-	-	-	-	-	-

Dyslipidemia						
Yes	-	-	-	0.958	0.922	0.995
No (ref)	-	-	-	-	-	-
Alcohol use						
Non Alcohol (ref)	-	-	-	-	-	-
0-15 Unit Per Week	-	-	-	1.021	0.968	1.078
15-42 Unit Per Week	-	-	-	1.127	1.055	1.205
>42 Unit Per Week	-	-	-	1.232	1.081	1.404
Unknown	-	-	-	1.031	0.975	1.090
Cigarette Smoking						
Non-smokers (ref)	-	-	-	-	-	-
Current smokers	-	-	-	1.292	1.248	1.337
Ex-smokers	-	-	-	1.116	1.078	1.156
Unknown	-	-	-	1.256	1.148	1.376
BMI						
0-18.4 (ref)	-	-	-	-	-	-
18.5-24.9	-	-	-	1.147	0.999	1.318
25.0-29.9	-	-	-	1.135	0.990	1.301
30.0-34.9	-	-	-	1.140	0.993	1.308
35.0-39.0	-	-	-	1.077	0.934	1.243
40.0+	-	-	-	0.977	0.836	1.142
Unknown	-	-	-	1.242	1.063	1.451

First, we conducted a crude analysis with outcome of any cancer. As Table 3.7 shows, before controlling for confounders, it seems that either the combination of insulin-oral therapy or insulin therapy alone was inversely associated with the risk of these cancers, compared to oral therapy. However, after controlling for confounders, use of insulin was associated with an increased risk for overall cancer: HR=1.16, 95% CI (1.060, 1.269); the combination of both insulin and oral agent use, was also associated with the risk of (any) cancer: HR=1.054, 95% CI (1.019, 1.089). Older age, male gender, diabetes other than type 1, hypertension, moderate to intensive alcohol use and cigarette smoking were all associated with cancer risk.

Table 3.8 Cox's Proportional Hazards Model for Progression to Selected Individual Site Cancers in People Treated with Insulin Compared with Oral-agents

Site Cancer	Variable	Crude Analysis			Multivariate Analysis		
		Hazard Ratio	95% Confidence Interval		Hazard Ratio	95% Confidence Interval	
Any Cancer	**Oral only (ref)**	-	-	-	-	-	-
	Insulin and oral	0.928	0.899	0.958	1.054	1.019	1.089
	Insulin only	0.432	0.407	0.458	1.160	1.060	1.269
Breast Cancer	**Insulin and oral**	0.962	0.872	1.061	1.057	0.954	1.172
	Insulin only	0.446	0.371	0.537	1.231	0.932	1.625
Colorectal Cancer	**Oral only (ref)**	-	-	-	-	-	-
	Insulin and oral	0.804	0.738	0.877	0.975	0.892	1.066
	Insulin only	0.386	0.328	0.455	1.639	1.299	2.069
Prostate Cancer	**Oral only (ref)**	-	-	-	-	-	-
	Insulin and oral	0.703	0.631	0.782	0.959	0.860	1.070
	Insulin only	0.223	0.176	0.284	0.814	0.579	1.144
Pancreatic cancer	**Oral only (ref)**	-	-	-	-	-	-
	Insulin and oral	2.739	2.450	3.063	3.034	2.696	3.414
	Insulin only	0.919	0.749	1.127	2.364	1.768	3.160
Bladder Cancer	**Oral only (ref)**	-	-	-	-	-	-
	Insulin and oral	0.902	0.787	1.033	1.019	0.883	1.175
	Insulin only	0.381	0.291	0.499	0.929	0.616	1.401
Lung Cancer	**Oral only (ref)**	-	-	-	-	-	-
	Insulin and oral	0.777	0.711	0.848	0.823	0.750	0.902
	Insulin only	0.341	0.286	0.405	0.883	0.679	1.148
Kidney Cancer	**Oral only (ref)**	-	-	-	-	-	-
	Insulin and oral	0.746	1.080	0.746	0.984	0.813	1.191
	Insulin only	0.272	0.571	0.272	1.495	0.863	2.587

We also assessed the risk of insulin use compared with oral-agent use with respect to the other seven solid tumor cancers. The results in Table 3.8 showed that use of insulin alone was associated with an increased risk of colorectal cancer. Particularly, insulin use (either alone or in combination with other oral agents) appeared to be strongly associated with an additional risk for pancreatic cancer (HR=2.364, 95% CI 1.768, 3.160 for insulin alone and HR=3.034, 95% CI 2.696, 3.414 for insulin with oral agents).

3.4 Testing of Hypothesis H3 0: Objectives and Specific Aims

Aim 3: Determine the role of HbA1c value in modifying the risk of cancer.

Hypothesis 3: Level of HbA1c is directly associated with cancer risk, independent of insulin/oral agent choice.

To test for this hypothesis, we simply restricted our cohort from hypothesis 1 to those patients who had available HbA1c. Table 3.9 and 3.10 demonstrate comparisons between the mean and median of HbA1c value during the follow-up time for each person by medication and diabetes type. Results showed that the median value generally had consistent and smaller standard deviation. Therefore, we used median of HbA1c value as our measure of diabetes control.

Table 3.9 Mean and Median of HbA1c by Different Medication

Insulin Use	Variable	Mean	Std Dev	Minimum	Maximum
Oral only	**HbA1c_Mean**	8.42	2.32	0.50	15.00
	HbA1c_Median	7.26	1.22	0.50	15.00
Insulin and oral	**HbA1c_Mean**	9.27	2.04	2.30	15.00
	HbA1c_Median	8.37	1.42	2.30	15.00

Insulin only	**HbA1c_Mean**	8.74	2.07	2.00	15.00
	HbA1c_Median	8.26	1.69	2.00	15.00

Table 3.10 Mean and Median of HbA1c by Different Types of Diabetes Mellitus

Insulin Use	Variable	Mean	Std Dev	Minimum	Maximum
Type 1 Diabetes Mellitus	**HbA1c_Mean**	8.85	2.07	2.00	15.00
	HbA1c_Median	8.34	1.67	2.00	15.00
Type 2 Diabetes Mellitus	**HbA1c_Mean**	8.57	2.30	0.05	15.00
	HbA1c_Median	7.46	1.32	0.05	15.00
Other Types/Unknown Types of Diabetes Mellitus	**HbA1c_Mean**	8.99	2.12	3.52	14.98
	HbA1c_Median	8.26	1.71	3.40	14.75

Table 3.11 shows the result from Cox proportional hazards model for progression to any solid tumor cancers in people treated with insulin compared with oral-agents after adjusting for diabetes control. The results showed that after adjusting for diabetes control, the increased risk of any cancer due to insulin use was still significant (HR=1.149, 95% CI 1.031, 1.281 for insulin alone and HR=1.056, 95% CI 1.016, 1.098 for insulin with oral agents).

Table 3.11 Cox Proportional Hazards Model for Progression to Any Solid Tumor Cancers in People Treated with Insulin Compared with Oral-agents: Adjusting for Diabetes Control

Variable	Hazard Ratio	95% Confidence Interval	
Insulin use			
Oral only (ref)	-	-	-
Insulin and oral	1.056	1.016	1.098
Insulin only	1.149	1.031	1.281
HbA1c median	1.005	0.991	1.019
Age group			
2-9	0.506	0.125	2.044
10-19	0.197	0.063	0.616
20-39 (ref)	-	-	-
40-59	5.322	4.527	6.256
60-79	14.058	11.971	16.508
80+	18.758	15.865	22.178

Gender			
Female (ref)	-	-	-
Male	1.254	1.213	1.296
UK Region			
England	0.882	0.809	0.960
Northern Ireland (ref)	-	-	-
Scotland	0.917	0.828	1.016
Wales	0.936	0.848	1.032
Diabetes Type			
Type 1 (ref)	-	-	-
Type 2	1.485	1.332	1.656
Unknown	1.704	1.419	2.047
Hypertension			
Yes	1.081	1.048	1.114
No (ref)	-	-	-
Dyslipidemia			
Yes	1.001	0.960	1.042
No (ref)	-	-	-
Alcohol use			
Non-Alcohol (ref)	-	-	-
0-15 Unit Per Week	1.028	0.970	1.089
15-42 Unit Per Week	1.153	1.073	1.239
>42 Unit Per Week	1.271	1.104	1.462
Unknown	1.023	0.963	1.087
Cigarette Smoking			
Non-smokers (ref)	-	-	-
Current smokers	1.330	1.281	1.381
Ex-smokers	1.154	1.111	1.199
Unknown	0.616	0.198	1.913
BMI			
0-18.4	-	-	-
18.5-24.9(ref)	1.166	0.998	1.362
25.0-29.9	1.160	0.995	1.352
30.0-34.9	1.193	1.022	1.392
35.0-39.0	1.144	0.975	1.342
40.0+	1.042	0.876	1.240
Unknown	1.202	1.006	1.436

Table 3.12 shows the result from Cox proportional hazards model for progression to pancreatic cancers in people treated with insulin compared with oral-agents after adjusting

for diabetes control. After adjusting for diabetes control, the association between insulin use and the risk of any cancer remained (HR=1.875, 95% CI 1.261, 2.787 for insulin alone and HR=2.330, 95% CI 2.007, 2.705 for insulin with oral agents). Moreover, our measurement of glucose control, HbA1c was an independent risk factor for pancreatic cancer (HR=1.385, 95% confidence interval (1.324, 1.450).

Table 3.12 Cox Proportional Hazards Model for Progression to Pancreatic cancers in People Treated with Insulin Compared with Oral-agents: Adjusting for Diabetes Control

Variable	Hazard Ratio	95% Confidence Interval	
Insulin use			
Oral only (ref)	-	-	-
Insulin and oral	2.330	2.007	2.705
Insulin only	1.875	1.261	2.787
HbA1c median	1.385	1.324	1.450
Age group			
2-9	0.000	0.000	0.000
10-19	0.000	0.000	0.000
20-39 (ref)	-	-	-
40-59	9.802	3.994	24.056
60-79	39.168	16.045	95.615
80+	56.909	22.781	142.163
Gender			
Female (ref)	-	-	-
Male	1.064	0.921	1.228
UK Region			
England	1.615	0.984	2.651
Northern Ireland (ref)	-	-	-
Scotland	1.316	0.748	2.315
Wales	1.006	0.572	1.768
Diabetes Type			
Type 1 (ref)	-	-	-
Type 2	1.652	1.117	2.443
Unknown	2.975	1.753	5.051
Hypertension			
Yes	1.223	1.070	1.397
No (ref)	-	-	-

Dyslipidemia			
Yes	0.877	0.728	1.057
No (ref)	-	-	-
Alcohol use			
Non Alcohol(ref)	-	-	-
0-15 Unit Per Week	0.986	0.761	1.278
15-42 Unit Per Week	1.855	1.372	2.508
>42 Unit Per Week	2.510	1.525	4.129
Unknown	0.987	0.755	1.291
Cigarette Smoking			
Non-smokers (ref)	-	-	-
Current smokers	1.764	1.504	2.069
Ex-smokers	0.919	0.767	1.101
Unknown	0.000	0.000	.
BMI			
0-18.4	-	-	-
18.5-24.9(ref)	2.688	0.998	7.242
25.0-29.9	3.037	1.133	8.136
30.0-34.9	2.616	0.972	7.038
35.0-39.0	1.800	0.652	4.969
40.0+	1.567	0.532	4.616
Unknown	2.049	0.697	6.025

Because of the concern that the increased risk of pancreatic cancer may be due to the presence of undiagnosed cancer before the drug exposure, we conducted an additional analysis stratified by follow-up time for those patients who developed incident pancreatic cancers. Table 3.13 shows that the link between insulin therapy and pancreatic cancer was not significant among patients whose follow-up time was less than 1 year; though the risk increased sharply for those whose follow-up time was between 1 and 2 years, and it increased even more for those between 2 and 3 years, suggesting that the captured pancreatic cancers were true incident cancers.

Table 3.13 Cox Proportional Hazards Model for Progression to Pancreatic Cancers in People Treated with Insulin Compared with Oral-agents

Follow-up Time*	Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits	
< 1 year	**Insulin use**			
	Oral only (ref)	-	-	-
	Insulin and oral	0.960	0.762	1.209
	Insulin only	1.004	0.529	1.904
1 year- 2 years	**Insulin use**			
	Oral only (ref)	-	-	-
	Insulin and oral	10.780	8.166	14.229
	Insulin only	2.290	1.196	4.385
2 years-3 years	**Insulin use**			
	Oral only (ref)	-	-	-
	Insulin and oral	20.713	14.557	29.473
	Insulin only	9.066	4.306	19.087
3 years- 4 years	**Insulin use**			
	Oral only (ref)	-	-	-
	Insulin and oral	7.601	5.087	11.357
	Insulin only	5.555	2.393	12.892
4 years- 5 years	**Insulin use**			
	Oral only (ref)	-	-	-
	Insulin and oral	4.000	2.330	6.869
	Insulin only	2.964	0.803	10.940
5 years and over	**Insulin use**			
	Oral only (ref)	-	-	-
	Insulin and oral	2.743	2.120	3.551
	Insulin only	1.438	0.657	3.148

To test the robustness of our findings, we conducted a sensitivity analysis by limiting patients to only type 2 diabetes and got similar results (Table 3.14).

Table 3.14 Sub-analysis: Cox's Proportional Hazards Model for Progression to Selected Individual Site Cancers in People with type-2 diabetes mellitus

Site Cancer	Variable	Hazard Ratio	95% Confidence Interval	
	Insulin and oral	1.059	1.018	1.102
Any Cancer	**Insulin only**	1.062	0.919	1.227
	HbA1c_Median	1.006	0.992	1.021
	Insulin and oral	1.029	0.908	1.167
Breast Cancer	**Insulin only**	1.441	0.961	2.162
	HbA1c_Median	1.029	0.984	1.075
	Insulin and oral	0.996	0.898	1.104
Colorectal Cancer	**Insulin only**	1.443	1.050	1.984
	HbA1c_Median	0.979	0.942	1.016
	Insulin and oral	0.990	0.869	1.126
Prostate Cancer	**Insulin only**	0.880	0.537	1.443
	HbA1c_Median	0.961	0.916	1.008
	Insulin and oral	2.301	1.978	2.678
Pancreatic cancer	**Insulin only**	1.905	1.171	3.101
	HbA1c_Median	1.391	1.326	1.460
	Insulin and oral	0.906	0.767	1.071
Bladder Cancer	**Insulin only**	0.897	0.479	1.679
	HbA1c_Median	1.121	1.058	1.189
	Insulin and oral	0.920	0.826	1.024
Lung Cancer	**Insulin only**	0.684	0.429	1.090
	HbA1c_Median	0.962	0.925	1.001
	Insulin and oral	1.071	0.855	1.340
Kidney Cancer	**Insulin only**	0.454	0.113	1.824
	HbA1c_Median	0.858	0.785	0.938

3.5 Testing of Hypothesis H2 0: Objectives and Specific Aims

Aim 2: Determine if the risk of solid tumor differs by insulin sub-types;

Hypothesis 2: Diabetics who use long-acting insulins, or intermediate-acting insulins, or pre-mixed insulins have a greater cancer incidence than those using short-acting insulins.

As results for hypotheses 1 and 3 showed, insulin use posed an additional risk of any cancer and pancreatic cancer. Therefore, we limited our test of hypothesis 2 to these two outcomes (any cancer, pancreatic cancer).

Table 3.15 demonstrated that compared to short-acting insulin, intermediate-acting insulin and premixed-acting insulin were not associated with increased risk of any cancer. Long-acting insulin appeared to have a protective effect for risk of any cancer. HbA1c was associated with an increased risk of cancer.

Table 3.15 Cox Proportional Hazards Model for Progression to Any Solid Tumor Cancers in People treated with Different Types of Insulin: Adjusting for Covariates

Variable	w/o Adjusting for Diabetes Control				Adjusting for Diabetes Control			
	Hazard Ratio	**95% Hazard Ratio Confidence Limits**		**P Value**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**P Value**
Exposure								
Long	0.836	0.761	0.918	0.0002	0.802	0.724	0.888	<.0001
Intermediate	0.947	0.851	1.053	0.3108	0.888	0.788	1	0.0497
Premixed	1.000	0.924	1.082	0.9952	0.919	0.842	1.003	0.0589
HbA1c_Median	-	-	-	-	1.004	1.003	1.005	<.0001

Table 3.16 showed that there was a strong association between insulin use and risk of pancreatic cancer. Specifically, the HR was 2.22, 95% CI (1.461, 3.380) for intermediate-acting insulin, and 1.765, 95% CI (1.225, 2.543) for premixed acting insulin, respectively. Compared to short-acting insulin, long-acting insulin did not pose additional risk for pancreatic cancer. HR=0.896 95% CI (0.585, 1.373).

Table 3.16 Cox Proportional Hazards Model for Progression to Pancreatic cancers in People treated with Different Types of Insulin: Adjusting for Covariates

Variable	w/o Adjusting for Diabetes Control				Adjusting for Diabetes Control			
	Hazard Ratio	**95% Hazard Ratio Confidence Limits**		**P Value**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**P Value**
Exposure								
Long	0.983	0.689	1.402	0.9227	0.896	0.585	1.373	0.6144
Intermediate	2.04	1.436	2.897	<.0001	2.222	1.461	3.38	0.0002
Premixed	1.782	1.321	2.404	0.0002	1.765	1.225	2.543	0.0023
HbA1c_Median	-	-	-	-	0.999	0.991	1.008	0.8249

4 Discussion

Diabetes mellitus is one of the major public health burdens in the U.S., affecting 11% of Americans over the age of 20, and 27% of Americans over the age of 65, with long-term complications of heart disease and stroke, retinopathy, neuropathy, nephropathy and death.[7] In addition, diabetes is reported to be a risk factor for a number of malignancies, including breast cancer, pancreatic cancer, and colorectal cancer.[26-30]

Diabetes related cancer is another public health concern: Information from the American Cancer Society states that cancer ranks as the 2nd leading cause of death in the U.S.[24] Public concern would certainly increase when paticular anti-diabetic medications are linked to additional risk of cancer, as the majority of the patients with diabetes usually receive certain types of therapy for blood glucose control. This study will contribute to the currently unresolved concern over the potential risk of cancer with or without insulin exposure.

The study cohort contained a total of 230,330 patients with claims for antidiabetic therapy. The study found that use of insulin alone or in combination with other oral agents was associated with an increased risk of cancer. Insulin use was strongly associated with a risk for pancreatic cancer (HR=1.875, 95% CI 1.261, 2.787 for insulin alone and HR=2.330, 95% CI 2.007, 2.705 for insulin with oral agents). Moreover, HbA1c appears to be an independent risk factor for pancreatic cancer (HR=1.385, 95% CI, 1.324, 1.450). The risk of pancreatic cancer was similarly increased for premixed and

intermediate-acting insulin when compared with short-acting insulins. The role of HbA1c value in modifying the risk of cancer among patients with diabetes varies across different cancer types.

4.1 Insulin use and other risk factors for incident cancers

In clinical practice, patients usually receive oral agents as their first step of treatment, with insulin added as a second step, or use insulin alone as their treatment as other options are no longer effective. Compared to oral-agent users, the study showed that use of insulin alone or in combination with other oral agents was associated with increased risk of overall cancers. After adjusting for diabetes control, this effect still remained significant. Particularly, use of insulin alone or in combination with other oral agents is associated with a 2 fold increased risk of pancreatic cancer. This increased risk remained strikingly high even after adjusting for diabetes control or stratified by follow-up time, raising a concern for the safety of insulin on the risk of pancreatic cancer. Diabetes mellitus is strongly associated with pancreatic cancer, and whether diabetes is the cause or result of pancreatic cancer is controversial in the literature.[127,128] However, by restricting our cohort to only patients with diabetes, and excluding any diagnosed cancer prior to diabetes, we excluded the possibility that the increased risk of pancreatic cancer was due to diabetes, or resulted from diabetes. To further confirm that this increased risk would not be due to undiagnosed pre-existing pancreatic cancers before insulin use, stratified analysis by follow-up time was conducted. This stratification analysis found that the association between insulin and cancer was not statistically significant when the follow-up time was less than 1 year, increased when the follow-up time was between 1

and 2 years, and became strikingly high when the follow-up time was between 2 and 3 years. This demonstrated that a reversed causal relationship would not be possible. This study raised a safety concern of exogenous insulin on the risk of pancreatic cancer. Hyperinsulinemia, or metabolic syndrome X, is a condition that produces excessively high levels of insulin in the body circulation. It is suggested that hyperinsulinemia, through mitogenic activity, may promote cell proliferation in pancreatic cancer cells, and thus increase the synthesis of insulin-like growth factor-1.[129,130] Furthermore, hyperinsulinemia can simultaneously reduce insulin-like growth factor-binding protein 3 (IGFBP-3) and sex hormone-binding globulin (SHBG), which would lead to alteration in retinoid receptor activity and result in unregulated and/or enhanced tissue growth.[131] There are several approaches to measuring hyperinsulinemia clinically: lab tests of fasting insulin levels over 10 units would generally indicate a possible hyperinsulinemia. Another way is to measure waist and hips: waist measurement larger than hip in mean, or waist over 80% of the hip measurement in women would generally be a good indication of hyperinsulinemia. Lastly, a daily insulin dose of over 30 units could also be linked to hyperinsulinemia. This study suggested that caution should be used when prescribing insulin to patients, particularly those with syndrome X.

When assessing the impact of different types of insulin on the risk of cancer, we found that, after adjusting for diabetes control, pre-mixed insulin or intermediate insulin generally did not pose additional overall cancer risk compared to short-acting insulin. However, the use of premixed insulin or intermediate-acting insulin was associated with increased risk of pancreatic cancer. An observational study using The Health

Improvement Network database (THIN) reported that intermediate-acting insulin have a modest disadvantage in glycaemic control after 12 months compared with other insulins.[132] Qayyum and colleagues conducted a meta-analysis based on numerous clinical trials to explore the effectiveness and safety of premixed insulin. Their study shows that premixed insulin is generally associated with more side effects such as hypoglycemia and greater weight gain compared to other treatment options.[133]

4.2 Other risk factors associated with cancer incidence

Other risk factors for cancer development in diabetes include age, gender, diabetes type, hypertension, intensive alcohol consumption and obesity. As expected, increasing age was a strong risk factor for overall solid tumor cancers. Compared to female, males are generally less likely to develop a solid tumor cancer. Both alcohol use and hypertension were also strong risk factors for incident cancers.

4.3 Use of GPRD database to study the risk of cancer

Because of ethical issues, randomized clinical trials would not be possible for studies to explore the potential risk of cancer due to insulin use, and therefore, large observational studies would be an ideal solution. Unlike other commercial claims datasets, which only include people that are covered under certain insurance, and only contain available prescriptions that are covered under such insurance plans, the population-based General Practice Research Database (GPRD) covers about 6% of the total U.K. population and is nationally representative at patient level. The high quality and validity of the dataset

make it ideal for both clinical and pharmacoepidemiology research. The published studies that investigated the link of insulin exposure and cancer are subject to the following limitations: non-representative study population, small sample size to study certain solid cancer; short follow-up time; inability to adjust important confounding, such as cigarette smoking status/ alcohol use, which are critical for cancer development. In contrast, this study avoided the variety of limitations by using the GPRD dataset with a study period of 22 years (1987-2009). For instance, the GPRD dataset contained 9,007, 697 patients. When using diagnosis information, 372,540 diabetics (4.14%) were identified. In comparison, the literature documents that diabetes prevalence in the U.K. is 4.26% of the whole population, which is very similar to the findings of 4.14% in this study.[134] In addition, the dataset is large enough to conduct sub-analysis of specific solid tumor cancers, while previous studies often had too few of the specific cancers. For instance, we had 23,064 (10%) patients with incident cancers. In addition, we had information on the status of two important risk factors, cigarette smoking and alcohol use, which are generally not available in large population based databases. Thus 12% of the diabetic cohort had missing information on cigarette smoking, and 40% had missing or unknown information on alcohol status.

Lastly, the study period of 22 years enabled us to use long follow-up time, which is critical when investigating incident cancers.

4.4 HbA1c value

Random fasting blood glucose levels are usually a good indicator of one's diabetes status with other diagnosis criteria. However, blood glucose levels usually can vary significantly before and after meals and therefore are not a stable indicator of diabetes severity/control. Alternatively, glycated hemoglobin (hemoglobin A1c, Hb1c, HbA1c, or A1C, or HbA1c) levels are routinely measured to monitor patients with diabetes. HbA1c levels are determined by the blood glucose concentration: higher blood glucose concentration would lead to higher HbA1c levels. Two important advantages of HbA1c level are that 1) it does not vary by daily fluctuations in the blood glucose concentration, and 2) it is the mean glucose level in the prior 2 months. Therefore, HbA1c levels in patients with diabetes are a stable indicator of how well the blood glucose level has been controlled over the past two to three months. In healthy people, the HbA1c level is between 4% - 6% of total hemoglobin. An agreement has not been reached on the optimal threshold for HbA1c in patients with diabetes, but the National Committee for Quality Assurance (NCQA) recommends the target HbA1c level to be less than 7% for patients with diabetes.[135] The American Diabetes Association also recommends that the HbA1c level be below 7.0% for most patients. The ADA guidelines recommend that patients with diabetes measure their HbA1c every 2-3 months. Studies have demonstrated that keeping the HbA1c level under 7% would help to reduce diabetes-related complications, such as cardiovascular disease. However, intensive control may result in increased mortality and no significant reduction in cardiovascular events.[136]

In summary, HbA1c is a good measure of diabetes control. Because it is a marker for glycosylation and/or glycemic control, it can also mirror the overall severity of diabetes by reflecting the overall risk factor profile of the disease.[137] In addition, HbA1c level is regarded as the best marker of microvascular and/or dysglycemic complications among diabetics.[137] A lower HbA1c value is often associated with less severe complications from diabetes.[138,139] Because diabetes is a chronic condition, the majority of the patients usually receive certain types of treatment, adjusting for diabetes control is critical for studies with long follow-ups.

HbA1c is a good measure for mid-to-long-term of diabetes control. The extended length of follow-ups to study cancer risk allows for various measures of HbA1c over time. Because this study had a long study period, it is ideal to use the Median/mean HbA1c as a continuous variable over the follow-up period. Because mean value is subject to change dramatically by certain extreme values (Table 3.6 and Table 3.7), we used the median HbA1c over the follow up period in our data analysis.

4.5 Algorithm for diabetes types

We used algorithms to identify patients with type 1 and type 2 diabetes. Based on the diagnosis codes for diabetes, only 268 diagnosis codes (20%) were specific to diabetes types: 120 diagnosis codes (9%) were specific to type 1 diabetes, and 148 (11%) were specific for type 2 diabetes. We identified 372, 540 patients based on diabetes treatment, among whom 53.78% had pre-specified diabetes types; 46.22% or 172,192 of them did

not have this information and an algorithm was applied to further differentiate diabetes types among those categorized as “unknown types”.

The algorithm did not use age as a cut off in this study to further differentiate between type 1 and type 2 because there were more prescriptions for type 2 diabetes among adolescents and children. As such, the 30 or 35 cut off often used in the literatures is not readily applicable in present days. After applying to our algorithm, we identified 16.05% of patients with type 1 diabetes, 82.87% with type 2 diabetes and only around 1% with unknown or other types of diabetes, which was consistent with the distribution of diabetes types in the U.K. population.[134]

4.6 Diabetes treatment

Most of the published studies use diagnosis information to identify patients with diabetes for their cohort. This study, however, used diabetes medication information to identify diabetics and diabetes diagnosis date. Diabetes drugs are not used to treat other disorders so it is likely that if a patient was taking an antidiabetic medication and was diagnosed with diabetes later, he would have had diabetes when he was prescribed the antidiabetic medication. As a result, when using diagnosis to identify diabetics in the GPRD, we identified 372,540 (4.14%) patients, which included patients solely on dietary or supplementary treatment. When using antidiabetic prescriptions however, we identified 329,558 (3.66%) before applying to other inclusion and exclusion criteria. As our study cohort consisted of only a population on antidiabetic treatment, this method could have

helped us capture diabetics more comprehensively than using diagnosis information, and helped to capture the prescription dates more accurately.

4.7 Other Limitations of the Study

There are several other limitations in this study. The approach to diabetes treatment usually depends on the disease type since type 1 and type 2 diabetes have different standards of care. For instance, type 2 diabetics usually initiate their therapy on oral regimen, and receive insulin when their condition is in progresses, while insulin is the major treatment option for type 1 diabetes. That is, patients on insulin typically have more severe diabetes mellitus than those on oral regimens; and therefore, the increased risk of cancer might not be due to insulin therapies, but due to disease severity, or due to another characteristics of patients whose diabetes cannot be controlled. However, by differentiating diabetes types, limiting all subjects to diabetic patients on regimen and controlling for potential confounding, we were able to minimize this potential bias. Most importantly, by assessing the role of HbA1c in modifying the risk of cancer, we can evaluate the extent of the potential bias since HbA1c, as indicated in the literature, can be a measure of the diabetes control and the best marker for diabetes complications.[136]

In order to measure BMI, we used the median weight and height during the follow-up time for calculation. This approach was better than using baseline information, as patients with diabetes, particularly those on insulin treatment, may gain weight gradually. We were not able to find an association between BMI and cancer, probably because patients with diabetes could lose weight due to diet control or exercise. Particularly, patients with

an incident cancer diagnosis are frequently seen to lose weight some time before cancer diagnosis. For other covariates, such as cigarette smoking status or alcohol use, we used the baseline information for data analysis. Given the assumption that they do not change over time, misclassification bias may be an important issue due to wrong measurement in alcohol, smoking status or missing values. For instance, the literature indicates that the GPRD's information on current smokers is more through than data on former smokers according to a study on agreement of cigarette smoking status derived from a survey of general practitioners vs. a population-based survey.[140]

Other limitations of this study are related to the use of a U.K. based population. Therefore, certain clinical practice or disease management patterns might be different from those in the U.S. Also, the U.K. population is less diverse then the U.S. population and therefore, the study sample is relatively homogeneous in race and ethnicity. While the baseline risk of certain cancer may differ by race/ethnicity, it is less likely that an association between insulin use and cancer risk differs across race/ethnicity. There is no evidence showing that the IGF-I role varies across race/ethnicity. Lastly, certain socioeconomic confounding factors such as education, family income, health insurance status, and marital status were not available in the GPRD. However, since the U.K. has a universal health insurance, the socioeconomic confounding may be less influential on the utilization of healthcare services than in the U.S.

5 Conclusions

In conclusion, the study confirmed that patient demographic factors and clinical factors were associated with cancer development. These risk factors included older age, male gender, certain U.K locations (e.g., England), hypertension, intensive alcohol use or smoking status. The study showed that using insulin (alone or in combination with oral agents) was associated with additional risk for overall cancer, and particularly pancreatic cancer. Use of insulin alone was also associated with an increased risk of colorectal cancer. HbA1c was an independent risk factor for pancreatic cancer. This study also suggests that intermediate-acting insulin or premixed insulin, compared to short-acting insulin, posed an additional risk of pancreatic cancer compared with short-acting insulin. Lastly, the availability of HbA1c measurement in the GPRD dataset made it possible to explore the role of HbA1c in modifying the risk. Our findings suggested that HbA1c was generally a risk factor for cancer development but that it varied across different types of solid tumor cancer.

Future studies should concentrate on:

1) Exploring if the increased risk of pancreatic cancer is a class effect of insulin or only limited to specific insulin products;
2) Exploring the mechanism of increased risk of pancreatic cancer due to exogenous insulin use
3) Exploring the association between hyperinsulinemia and pancreatic cancer.

In summary, Comparative Effectiveness Research (CER), designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options, provides a useful method to assess the potential risk of cancer among patients with diabetes.[141] This comparative effectiveness/safety research brought to light gaps in the literature on insulin treatment alternatives in terms of potential cancer risk and the role of HbA1c value in modifying this risk. The results of the study, combined with other published studies, would be helpful to inform providers, patients, and decision-makers, based on their diabetes condition, of the potential risk/benefit assessment and the role of HbA1c for diabetes management.

Appendices

Appendix 1 Demographic Covariates in the Analysis

Variables	Type of Data	Values	Operational Definitions
Age	Categorical	2-9 10-19 20-39 40-59 60-79 80+	
Gender	Categorical	0, 1	0=female; 1=male
Body Mass Index	Categorical	< =19 20-24 25-29 30.0-34.9(Obese Class I)	BMI=mass (lb)*4.88/height^2(ft^2)

		35.0-39.9(Obese Class II)
		40.0 or over (Obese Class III)
Alcohol intake	Categorical	0 unit/week
		1-15 units/week
		16-42 units/week
		42 units/week or more
		Unknown
Smoking status	Categorical	nonsmoker
		former smoker
		current smoker
		Unknown
Location	Categorical	North
		South
		West
		East

Appendix 2 Comorbidities in the Analysis

Variables	Type of Data	Values	Operational Definitions
hypertension	Dichotomous	0, 1	Value=1: Patients will be defined to have hypertension if they have elevated blood pressure (140/90 mm Hg or over), or a recorded diagnosis
hyperlipidemia	Dichotomous	0, 1	Value=1: Patients will be defined to have hyperlipidemia if they have a recorded diagnosis, or under related treatment

Appendix 3 Definition of HbA1c in the Analysis

Variables	Type of Data	Values	Operational Definitions
HbA1c	Continuous		mean HbA1c from labs
HbA1c	Categorical (Alternative)	<4.0%	
		4.0%-6.0% (normal range)	
		6.1%-7.0% (target range for antidiabetics)	
		7.1%-8.0% (High)	
		8.1%-9.0%	
		9.1%-10.0%	
		10.0%+	
		<4.0%	
		4.0%-6.0% (normal range)	

Appendix 4 Insulin Types by Time of Onset/peak

classify	drug substance	product name
Short-acting	insulin soluble – human	ACTRAPID injection 100 iu/ml [NOVO]
Short-acting	insulin soluble – human	ACTRAPID NOVOLET 100 iu/ml [NOVO]
Short-acting	insulin soluble – human	ACTRAPID PENFILL 100 iu/ml [NOVO]
Short-acting	insulin soluble – human	ACTRAPID VIAL injection solution 100 units/ml [NOVO]
Short-acting	insulin glulisine	APIDRA CARTRIDGE injection solution 100 units/ml [SANOFI/AVE]
Short-acting	insulin glulisine	APIDRA OPTICLIK injection solution 100 units/ml [SANOFI/AVE]
Short-acting	insulin glulisine	APIDRA OPTISET injection solution 100 units/ml [SANOFI/AVE]
Short-acting	insulin glulisine	APIDRA SOLOSTAR injection solution 100 units/ml [SANOFI/AVE]
Short-acting	insulin glulisine	APIDRA VIAL injection solution 100 units/ml [SANOFI/AVE]
Short-acting	insulin human	EXUBERA powder for inhalation 1mg [PFIZER]
Short-acting	insulin human	EXUBERA powder for inhalation 3mg [PFIZER]
Short-acting	insulin soluble – human	HUMAJECT S DISPOSABLE PEN injection solution 100 units/ml [LILLY]
Short-acting	insulin lispro	HUMALOG CARTRIDGE injection solution 100 units/ml [LILLY]
Short-acting	insulin lispro	HUMALOG DISPOSABLE PEN injection solution 100 units/ml [LILLY]
Short-acting	insulin lispro	HUMALOG injection 100 iu/ml [LILLY]
Short-acting	insulin lispro	HUMALOG KWIKPEN injection solution 100 units/ml [LILLY]
Short-acting	insulin lispro	HUMALOG VIAL injection solution 100 units/ml [LILLY]
Short-acting	insulin soluble – human	HUMULIN S CARTRIDGE injection solution 100 units/ml [LILLY]
Short-acting	insulin soluble – human	HUMULIN S injection 100 units/ml [LILLY]
Short-acting	insulin soluble – human	HUMULIN S VIAL injection solution 100 units/ml [LILLY]
Short-acting	insulin aspart	insulin aspart cartridge injection solution 100 units/ml
Short-acting	insulin aspart	insulin aspart disposable pen injection solution 100 units/ml
Short-acting	insulin aspart	insulin aspart human pyr injection 100 iu/ml
Short-acting	insulin aspart	insulin aspart vial injection solution 100 units/ml

Short-acting	insulin glulisine	insulin glulisine cartridge injection solution 100 units/ml
Short-acting	insulin glulisine	insulin glulisine disposable pen injection solution 100 units/ml
Short-acting	insulin glulisine	insulin glulisine injection solution 100 units/ml
Short-acting	insulin glulisine	insulin glulisine vial injection solution 100 units/ml
Short-acting	insulin soluble - human	INSULIN HUM/ACTRAPID
Short-acting	insulin soluble - human	INSULIN HUMAN ACTRAPID (NEUTRAL)
Short-acting	insulin soluble - human	INSULIN HUMAN ACTRAPID (NEUTRAL) 40 I/U INJ
Short-acting	insulin soluble - human	INSULIN HUMAN ACTRAPID PENFILL
Short-acting	insulin human	insulin human powder for inhalation 1mg
Short-acting	insulin human	insulin human powder for inhalation 3mg
Short-acting	insulin soluble - human	INSULIN HUMAN VELOSULIN 100 I/U INJ
Short-acting	insulin soluble - human	INSULIN HUMULIN S (NEUTRAL SOLUBLE)
Short-acting	insulin soluble - human	INSULIN HUMULIN S (NEUTRAL) CARTRIDGE 100 I/U
Short-acting	insulin soluble - human	INSULIN HYPURIN SOLUBLE 100 I/U INJ
Short-acting	insulin lispro	insulin lispro cartridge injection solution 100 units/ml
Short-acting	insulin lispro	insulin lispro disposable pen injection solution 100 units/ml
Short-acting	insulin lispro	insulin lispro human prb injection 100 iu/ml
Short-acting	insulin lispro	insulin lispro vial injection solution 100 units/ml
Short-acting	insulin soluble - human	INSULIN NEUSULIN (NEUTRAL)(PURIFIED) 100 I/U INJ
Short-acting	insulin soluble - human	INSULIN NEUTRAL (HUMAN) 100 I/U INJ
Short-acting	insulin soluble - human	INSULIN NEUTRAL (PURIFIED) 100 I/U INJ
Short-acting	insulin soluble - human	INSULIN NOVO ACTRAPID MC 100 I/U INJ
Short-acting	insulin soluble - human	INSULIN QUICKSOL (SOLUBLE NEUTRAL) 100 I/U INJ
Short-acting	insulin soluble - human	INSULIN SOLUBLE 100 I/U INJ
Short-acting	insulin soluble - human	INSULIN SOLUBLE 40 I/U INJ
Short-acting	insulin soluble - human	insulin soluble human cartridge injection solution 100 units/ml
Short-acting	insulin soluble - human	insulin soluble human crb injection 100 iu/ml
Short-acting	insulin soluble - human	insulin soluble human disposable pen injection solution 100 units/ml
Short-acting	insulin soluble - human	insulin soluble human emp injection 100 units/ml
Short-acting	insulin soluble - human	insulin soluble human prb injection 100 units/ml

Short-acting	insulin soluble - human	insulin soluble human pyr injection 100 units/ml
Short-acting	insulin soluble - human	insulin soluble human vial injection solution 100 units/ml
Short-acting	insulin soluble - human	INSULIN SOLUBLE INJ I/U^2
Short-acting	insulin soluble - human	INSUMAN RAPID CARTRIDGE injection solution 100 units/ml [AVENTIS]
Short-acting	insulin soluble - human	INSUMAN RAPID injection 100 iu/ml [AVENTIS]
Short-acting	insulin soluble - human	INSUMAN RAPID OPTISET injection solution 100 units/ml [AVENTIS]
Short-acting	insulin soluble - human	NOVOPEN injection device 100 units/ml [NOVO]
Short-acting	insulin aspart	NOVORAPID FLEXPEN injection solution 100 units/ml [NOVO]
Short-acting	insulin aspart	NOVORAPID NOVOLET injection 100 iu/ml [NOVO]
Short-acting	insulin aspart	NOVORAPID PENFILL injection solution 100 units/ml [NOVO]
Short-acting	insulin aspart	NOVORAPID VIAL injection solution 100 units/ml [NOVO]
Short-acting	insulin soluble - human	PENJECT injection device 100 units/ml [HYPOGUARD]
Short-acting	insulin soluble - human	PUR-IN NEUTRAL injection 100 units/ml [CP PHARM]
Short-acting	insulin soluble - human	VELOSULIN VIAL injection solution 100 units/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMAJECT M1 pen 100 iu/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMAJECT M2 pen 100 iu/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMAJECT M3 pen 100 iu/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMAJECT M4 pen 100 iu/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMAJECT M5 pen 100 iu/ml [LILLY]
Pre-mixed	insulin lispro protamine/insulin lispro	HUMALOG MIX 25 CARTRIDGE injection suspension 100 units/ml [LILLY]
Pre-mixed	insulin lispro protamine/insulin lispro	HUMALOG MIX 25 DISPOSABLE PEN injection suspension 100 units/ml [LILLY]
Pre-mixed	insulin lispro protamine/insulin lispro	HUMALOG MIX 25 injection 25:75; 100 units/ml [LILLY]
Pre-mixed	insulin lispro protamine/insulin lispro	HUMALOG MIX 25 KWIKPEN injection suspension 100 units/ml [LILLY]
Pre-mixed	insulin lispro protamine/insulin lispro	HUMALOG MIX 25 VIAL injection suspension 100 units/ml [LILLY]
Pre-mixed	insulin lispro protamine/insulin lispro	HUMALOG MIX 50 CARTRIDGE injection suspension 100 units/ml [LILLY]
Pre-mixed	insulin lispro protamine/insulin lispro	HUMALOG MIX 50 DISPOSABLE PEN injection suspension 100 units/ml [LILLY]
Pre-mixed	insulin lispro protamine/insulin lispro	HUMALOG MIX 50 KWIKPEN injection suspension 100 units/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMAN ACTRAPHANE injection 100 iu/ml [NOVO]

Pre-mixed	insulin soluble - human emp/insulin isophane - human emp	HUMAN INITARD 50/50 injection 100 units/ml [NOVO]
Pre-mixed	insulin zinc suspension (amorphous) - human prb/insulin zinc suspension (crystalline) - human prb	HUMULIN LENTE injection 100 units/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMULIN M1 injection 100 units/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMULIN M2 injection 100 units/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMULIN M3 CARTRIDGE injection suspension 100 units/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMULIN M3 DISPOSABLE PEN injection suspension 100 units/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMULIN M3 injection 100 units/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMULIN M3 VIAL injection suspension 100 units/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMULIN M4 injection 100 units/ml [LILLY]
Pre-mixed	insulin soluble - human/insulin isophane - human	HUMULIN M5 injection 100 units/ml [LILLY]
Pre-mixed	insulin aspart protamine/insulin aspart	insulin biphasic aspart cartridge injection suspension 30:70; 100 units/ml
Pre-mixed	insulin aspart protamine/insulin aspart	insulin biphasic aspart disposable pen injection suspension 30:70; 100 units/ml
Pre-mixed	insulin aspart protamine/insulin aspart	insulin biphasic aspart human pyr injection 30:70; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human cartridge injection suspension 10:90; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human cartridge injection suspension 20:80; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human cartridge injection suspension 25:75; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human cartridge injection suspension 30:70; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human cartridge injection suspension 40:60; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human cartridge injection suspension 50:50; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human crb injection 25:75; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human crb injection 50:50; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human disposable pen injection suspension 30:70; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human disposable pen injection suspension 50:50; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human prb injection 10:90; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human prb injection 20:80; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human prb injection 25:75; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human prb injection 30:70; 100 units/ml

Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human prb injection 40:60; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human prb injection 50:50; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human pyr injection 10:90; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human pyr injection 20:80; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human pyr injection 30:70; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human pyr injection 40:60; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human pyr injection 50:50; 100 units/ml
Pre-mixed	insulin soluble - human/insulin isophane - human	insulin biphasic isophane human vial injection suspension 30:70; 100 units/ml
Pre-mixed	insulin lispro protamine/insulin lispro	insulin biphasic lispro cartridge injection suspension 25:75; 100 units/ml
Pre-mixed	insulin lispro protamine/insulin lispro	insulin biphasic lispro cartridge injection suspension 50:50; 100 units/ml
Pre-mixed	insulin lispro protamine/insulin lispro	insulin biphasic lispro disposable pen injection suspension 25:75; 100 units/ml
Pre-mixed	insulin lispro protamine/insulin lispro	insulin biphasic lispro disposable pen injection suspension 50:50; 100 units/ml
Pre-mixed	insulin lispro protamine/insulin lispro	insulin biphasic lispro human prb injection 25:75; 100 units/ml
Pre-mixed	insulin lispro protamine/insulin lispro	insulin biphasic lispro human prb injection 50:50; 100 units/ml
Pre-mixed		INSULIN BP 100 I/U
Pre-mixed	insulin soluble - human/insulin isophane - human	INSULIN HUM/ACTRAPHANE
Pre-mixed		INSULIN HUMALOG MIX 25
Pre-mixed	insulin soluble - human/insulin isophane - human	INSULIN HUMULIN M CARTRIDGE 100 I/U
Pre-mixed	insulin soluble - human/insulin isophane - human	INSULIN HUMULIN M1 VIAL
Pre-mixed	insulin soluble - human/insulin isophane - human	INSULIN HUMULIN M2 VIAL
Pre-mixed	insulin soluble - human/insulin isophane - human	INSULIN HUMULIN M4 100 I/U INJ
Pre-mixed	insulin soluble - human/insulin isophane - human	INSULIN HUMULIN M4 CARTRIDGE 100 I/U
Pre-mixed		INSULIN MIXTARD 30/70 40 I/U INJ
Pre-mixed		INSULIN NOVO MONOTARD MC
Pre-mixed		INSULIN NOVO MONOTARD MC 100 I/U INJ
Pre-mixed		INSULIN PUR-IN MIX 15/85 100 I/U INJ
Pre-mixed		INSULIN PUR-IN MIX 50/50 100 I/U INJ
Pre-mixed	insulin zinc suspension (amorphous) - human prb/insulin zinc suspension (crystalline) - human prb	insulin zinc suspension mixed human prb injection 100 units/ml
Pre-mixed	insulin zinc suspension (crystalline) - human pyr/insulin zinc suspension (amorphous) - human pyr	insulin zinc suspension mixed human pyr injection 100 units/ml

Pre-mixed	insulin soluble - human/insulin isophane - human	INSUMAN COMB 15 injection 100 iu/ml [AVENTIS]
Pre-mixed	insulin soluble - human/insulin isophane - human	INSUMAN COMB 15 OPTISET injection suspension 100 units/ml [AVENTIS]
Pre-mixed	insulin soluble - human/insulin isophane - human	INSUMAN COMB 25 CARTRIDGE injection suspension 100 units/ml [AVENTIS]
Pre-mixed	insulin soluble - human/insulin isophane - human	INSUMAN COMB 25 injection 100 iu/ml [AVENTIS]
Pre-mixed	insulin soluble - human/insulin isophane - human	INSUMAN COMB 25 OPTISET injection suspension 100 units/ml [AVENTIS]
Pre-mixed	insulin soluble - human/insulin isophane - human	INSUMAN COMB 25 VIAL injection suspension 100 units/ml [AVENTIS]
Pre-mixed	insulin soluble - human/insulin isophane - human	INSUMAN COMB 50 CARTRIDGE injection suspension 100 units/ml [AVENTIS]
Pre-mixed	insulin soluble - human/insulin isophane - human	INSUMAN COMB 50 injection 100 iu/ml [AVENTIS]
Pre-mixed	insulin soluble - human/insulin isophane - human	INSUMAN COMB 50 OPTISET injection suspension 100 units/ml [AVENTIS]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 10 NOVOLET 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 10 PENFILL 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 10 PENFILL injection suspension 100 units/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 20 NOVOLET 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 20 PENFILL 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 20 PENFILL injection suspension 100 units/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 30 ge injection 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 30 INNOLET injection suspension 30:70; 100 units/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 30 NOVOLET 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 30 PENFILL 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 30 PENFILL injection suspension 100 units/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 30 VIAL injection suspension 100 units/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 30/70 injection 100 units/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 40 NOVOLET 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 40 PENFILL 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 40 PENFILL injection suspension 100 units/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 50 injection 50:50; 100 units/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 50 NOVOLET 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 50 PENFILL 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	MIXTARD 50 PENFILL injection suspension 100 units/ml [NOVO]

Pre-mixed	insulin zinc suspension (crystalline) - human pyr/insulin zinc suspension (amorphous) - human pyr	MONOTARD injection 100 units/ml [NOVO]
Pre-mixed	insulin aspart protamine/insulin aspart	NOVOMIX 30 FLEXPEN injection suspension 100 units/ml [NOVO]
Pre-mixed	insulin aspart protamine/insulin aspart	NOVOMIX 30 injection 30:70; 100 units/ml [NOVO]
Pre-mixed	insulin aspart protamine/insulin aspart	NOVOMIX 30 PENFILL injection suspension 100 units/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	PENMIX 10/90 pen [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	PENMIX 10/90 PENFILL PENFILL [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	PENMIX 20/80 pen [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	PENMIX 20/80 PENFILL PENFILL [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	PENMIX 30/70 injection 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	PENMIX 30/70 PENFILL injection 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	PENMIX 40/60 injection 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	PENMIX 40/60 PENFILL injection 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	PENMIX 50/50 injection 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	PENMIX 50/50 PENFILL injection 100 iu/ml [NOVO]
Pre-mixed	insulin soluble - human/insulin isophane - human	PUR-IN MIX 15/85 injection [CP PHARM]
Pre-mixed	insulin soluble - human/insulin isophane - human	PUR-IN MIX 25/75 injection [CP PHARM]
Long-acting		HUMULIN ZN injection 100 units/ml [LILLY]
Long-acting	insulin detemir	insulin detemir cartridge injection solution 100 units/ml
Long-acting	insulin detemir	insulin detemir disposable pen injection solution 100 units/ml
Long-acting	insulin detemir	insulin detemir injection solution 100 iu/ml
Long-acting	insulin glargine	insulin glargine cartridge injection solution 100 units/ml
Long-acting	insulin glargine	insulin glargine disposable pen injection solution 100 units/ml
Long-acting	insulin glargine	insulin glargine injection 100 iu/ml
Long-acting	insulin glargine	insulin glargine vial injection solution 100 units/ml
Long-acting		INSULIN HYPURIN PROTAMINE ZINC 100 I/U INJ
Long-acting		INSULIN NEULENTE (ZINC SUSP)(PURIFIED) 100 I/U INJ
Long-acting		INSULIN NOVO ULTRATARD MC 100 I/U INJ
Long-acting		INSULIN ZINC CRYSTALLINE susp 100 I/U INJ
Long-acting		INSULIN ZINC HUMAN SUSPENSION
Long-acting		INSULIN ZINC LENTE PURIFIED SUSPENSION

Long-acting	insulin zinc suspension (crystalline) - human pyr	insulin zinc suspension crystalline human pyr - long acting injection 100 units/ml
Long-acting	insulin glargine	LANTUS CARTRIDGE injection solution 100 units/ml [AVENTIS]
Long-acting	insulin glargine	LANTUS injection 100 iu/ml [AVENTIS]
Long-acting	insulin glargine	LANTUS OPTICLIK injection solution 100 units/ml [AVENTIS]
Long-acting	insulin glargine	LANTUS OPTISET injection solution 100 units/ml [AVENTIS]
Long-acting	insulin glargine	LANTUS SOLOSTAR injection solution 100 units/ml [SANOFI/AVE]
Long-acting	insulin glargine	LANTUS VIAL injection solution 100 units/ml [AVENTIS]
Long-acting	insulin detemir	LEVEMIR FLEXPEN injection solution 100 iu/ml [NOVO]
Long-acting	insulin detemir	LEVEMIR INNOLET injection solution 100 units/ml [NOVO]
Long-acting	insulin detemir	LEVEMIR PENFILL injection solution 100 units/ml [NOVO]
Long-acting	insulin zinc suspension (crystalline) - human pyr	ULTRATARD injection 100 units/ml [NOVO]
Intermediate-acting	insulin isophane - human	HUMAJECT I pen 100 iu/ml [LILLY]
Intermediate-acting	insulin isophane - human	HUMAN PROTAPHANE injection 100 units/ml [NOVO]
Intermediate-acting	insulin isophane - human	HUMAN PROTAPHANE PENFILL 100 units/ml [NOVO]
Intermediate-acting	insulin isophane - human	HUMULIN I CARTRIDGE injection suspension 100 units/ml [LILLY]
Intermediate-acting	insulin isophane - human	HUMULIN I DISPOSABLE PEN injection suspension 100 units/ml [LILLY]
Intermediate-acting	insulin isophane - human	HUMULIN I injection 100 units/ml [LILLY]
Intermediate-acting	insulin isophane - human	HUMULIN I VIAL injection suspension 100 units/ml [LILLY]
Intermediate-acting	insulin isophane - human	INSULATARD FLEXPEN injection 100 iu/ml [NOVO]
Intermediate-acting	insulin isophane - human	INSULATARD ge injection 100 iu/ml [NOVO]
Intermediate-acting	insulin isophane - human emp	INSULATARD injection 100 units/ml [NOVO]
Intermediate-acting	insulin isophane - human	INSULATARD INNOLET injection 100 iu/ml [NOVO]
Intermediate-acting	insulin isophane - human	INSULATARD INNOLET injection suspension 100 units/ml [NOVO]
Intermediate-acting	insulin isophane - human	INSULATARD NOVOLET 100 iu/ml [NOVO]
Intermediate-acting	insulin isophane - human	INSULATARD PENFILL 100 iu/ml [NOVO]
Intermediate-acting	insulin isophane - human	INSULATARD PENFILL injection suspension 100 units/ml [NOVO]
Intermediate-acting	insulin isophane - human	INSULATARD VIAL injection suspension 100 units/ml [NOVO]

Intermediate-acting	insulin isophane - human	INSULIN HUMULIN I (ISOPHANE) 100 I/U INJ
Intermediate-acting		INSULIN INSULATARD (LEO RETARD) 40 I/U INJ
Intermediate-acting		INSULIN ISOPHANE (HIGHLY PURIFIED) 100 I/U INJ
Intermediate-acting		INSULIN ISOPHANE (HUMAN) 100 I/U INJ
Intermediate-acting		INSULIN ISOPHANE (NPH) 100 I/U INJ
Intermediate-acting		INSULIN ISOPHANE (NPH) 40 I/U
Intermediate-acting		INSULIN ISOPHANE (PURIFIED) 100 I/U INJ
Intermediate-acting		INSULIN ISOPHANE 100 I/U
Intermediate-acting		INSULIN ISOPHANE 50%/NEUTRAL 50% 100 I/U INJ
Intermediate-acting		INSULIN ISOPHANE 70%/NEUTRAL 30% 100 I/U INJ
Intermediate-acting	insulin isophane - human	insulin isophane human cartridge injection suspension 100 units/ml
Intermediate-acting	insulin isophane - human	insulin isophane human crb injection 100 iu/ml
Intermediate-acting	insulin isophane - human	insulin isophane human disposable pen injection suspension 100 units/ml
Intermediate-acting	insulin isophane - human emp	insulin isophane human emp injection 100 units/ml
Intermediate-acting	insulin isophane - human	insulin isophane human prb injection 100 iu/ml
Intermediate-acting	insulin isophane - human	insulin isophane human pyr injection 100 iu/ml
Intermediate-acting	insulin isophane - human	insulin isophane human vial injection suspension 100 units/ml
Intermediate-acting		INSULIN MONOPHANE (ISOPHANE) 100 I/U INJ
Intermediate-acting		INSULIN NEUPHANE (ISOPHANE)(PURIFIED) 100 I/U INJ
Intermediate-acting		INSULIN PUR-IN ISOPHANE 100 I/U INJ
Intermediate-acting		INSULIN SEMITARD 100 I/U INJ
Intermediate-acting		INSULIN SEMITARD 40 I/U INJ
Intermediate-acting		INSULIN ZINC SEMILENTE SUSP BP 100 I/U INJ
Intermediate-acting	insulin zinc suspension (crystalline) - human prb	insulin zinc suspension crystalline human prb - intermediate acting injection 100 units/ml
Intermediate-acting	insulin isophane - human	INSUMAN BASAL CARTRIDGE injection suspension 100 units/ml [AVENTIS]
Intermediate-acting	insulin isophane - human	INSUMAN BASAL injection 100 iu/ml [AVENTIS]
Intermediate-acting	insulin isophane - human	INSUMAN BASAL OPTISET injection suspension 100 units/ml [AVENTIS]

Intermediate-acting	insulin isophane - human	INSUMAN BASAL VIAL injection suspension 100 units/ml [AVENTIS]

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