ANTI-DIABETIC TREATMENT AND CANCER OCCURRENCE AMONG PATIENTS WITH TYPE II DIABETES MELLITUS

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ABSTRACT OF THE DISSERTATION

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This is a retrospective cohort study, with nested case-control analyses, of type II diabetes patients, to evaluate the association between anti-diabetic treatment and cancer incidence.

Methods: Patients who were initially stabilized on an oral hypoglycemic agent (OHA) mono-therapy, including metformin, sulfonylurea, TZD, and meglitinides, in the GPRD were included in the cohort. New diagnoses of cancer during cohort follow up were compared among exposure groups. In addition to the cohort analyses, solid tumors, as well as breast cancer and colorectal cancer, identified during the cohort follow-up were matched to controls and case-control analyses were performed within the cohort.

Results: Compared to metformin, there was no difference in risk of malignant solid tumors or hematological malignancy with other major classes of OHAs in the cohort. The case-control analyses further supported the findings that these OHA classes or their combinations did not alter the risk of malignant solid tumors.

In the case-control analyses, exposure to insulin was associated with a 64% (95% CI: 1.24, 2.16) higher risk of malignant solid tumors and this risk was modified when combined with different OHAs. When sulfonylurea was added to insulin, the risk of cancer was increased to almost 3 times (OR = 2.75, 95% CI: 1.51, 5.03), while adding metformin to insulin changed the odds ratio to 1.35 (95% CI: 0.94, 1.94). Similar results were found for breast cancer in which insulin was associated with a significant increase of more than 2 times in risk and other OHAs without insulin were not related to altered risk. For colorectal cancer (CRC), both sulfonylurea and TZD were associated with around a 2-fold significant risk increase compared to metformin. The odds of developing CRC were also elevated after starting insulin (OR = 1.41), although this did not reach statistical significance in these data.

Conclusion: This study provides evidence that neither sulfonylurea nor TZD substantially alter the risk of solid tumor compared to metformin among type II diabetes patients. Insulin is associated with higher risk of cancer and this risk may be diminished by concomitant use of metformin, but appears to be magnified by concomitant use of sulfonylurea.

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CHAPTER I INTRODUCTION

1.1 Background

Diabetes Mellitus (DM) is one of the largest national health burdens. The National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of diabetes was 9.3% (19.3 million), consisting of 6.5% diagnosed and 2.8% undiagnosed, among adults aged ≥ 20 years in 1999 - 2002 [1]. The prevalence (unadjusted by age) of diagnosed diabetes has steadily increased over time, from 5.1% in 1988 – 1994 to 6.5% in 1999 – 2002 [1]. In 2007, an estimated 23.5 million people ages 20 or older in the United States (U.S.), 10.7 percent of the population in this age group, had diabetes [2].

Complications of DM, including multiple cardiovascular, microvascular and neurologic abnormalities, are major causes of morbidity and mortality. The link between diabetes and cancer was investigated as early as the middle of the 20th century [3, 4]. A number of studies have focused on the relationship between diabetes and various cancers. Most studies, although not all, as well as meta-analyses, have found that DM is associated with increased risks for one or more types of malignancies.

Colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer related deaths for both men and women in the U.S. [5]. The relationship between diabetes and colorectal cancer (CRC) has been studied by many investigators. Larsson and colleagues [6] conducted a meta-analysis on 15 studies (6 case–control and 9 cohort studies with 2,593,935 subjects) focused on DM and CRC incidence. It was found that DM was associated with an increased risk of CRC with a summary relative risk (RR) = 1.30 (95% Confidence Interval [CI]: 1.20-1.40), compared with no diabetes. This

association did not differ by sex or by cancer sub sites. Diabetes was also positively associated with CRC mortality with summary RR = 1.26 (95% CI: 1.05-1.50). This association also did not differ by gender.

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer death among women [5]. A meta-analysis [7] with 20 studies (5 case–control and 15 cohort studies) showed that women with diabetes had a statistically significant 20% increased risk (95% CI: 1.12–1.28) of breast cancer. In the same paper, meta-analysis of 5 cohort studies with breast cancer mortality yielded a summary RR=1.24 (95% CI: 0.95–1.62).

Pancreatic cancer is the fourth leading cause of cancer-related death in US and the eighth worldwide, causing 227,000 deaths annually. Diabetes was widely considered to be associated with pancreatic cancer, but whether this represents a causal or consequential association is unclear. A meta-analysis [8] on 17 case–control and 19 cohort or nested case–control studies with information on 9,220 individuals with pancreatic cancer reported a summary odds ratio (OR) as 1.82 (95% CI: 1.66–1.89), with evidence that individuals in whom diabetes had only recently been diagnosed (<4 years) had a 50% greater risk of the malignancy compared with individuals who had diabetes for ≧5 years (OR 2.1 vs. 1.5; P=0.005).

In contrast with the increased risks for the cancers cited above, diabetes is associated with a decreased risk of prostate cancer. A meta-analysis published in 2006 [9] on 19 studies of the association between DM and prostate cancer gave a relative risk estimate of 0.84 (95% CI: 0.76-0.93). There was significant heterogeneity that appeared to be related to

the years during which the studies were conducted. For studies conducted before prostate-specific antigen (PSA) screening was introduced as a common procedure, the RR was 0.94 (95% CI: 0.85-1.03), and for studies conducted after this time, the RR was 0.73 (95% CI: 0.64-0.83). Another meta-analysis [10] on 14 studies showed a similar inverse relationship between diabetes and prostate cancer (RR=0.91, 95% CI: 0.86-0.96). PSA screening may introduce a lead time bias in detecting prostate cancer. DM patients may have been focused on glucose control and major DM complications during their physician's office visits, while non-DM patients may have PSA screened routinely during their office visits. Thus, after PSA was introduced as a common screening procedure, prostate cancers in patients with diabetes are more likely to be diagnosed after symptoms are present (with a longer lead time), and prostate cancers in non-diabetic subjects are more likely to be detected from screening.

Although most of the above-cited studies included all types of DM, the participants were largely type II diabetes mellitus (T2DM) patients. In summary, evidence from meta-analysis confirmed that diabetes was associated with 1.2 to 1.8 times risks of several types of cancer, including CRC, breast cancer, and pancreatic cancer. The association of diabetes with various other cancers was less clear, while for prostate cancer a lower incidence has been reported among diabetic patients.

The metabolic defects underlying T2DM include a triad of insulin resistance, pancreatic β-cell dysfunction, and impaired hepatic glucose production. The mechanisms explaining the increased risks of cancer among diabetics may be related to the effects of insulin and insulin-like growth factors (IGFs) on cellular growth. Experimental evidence has

suggested that both insulin and IGFs could stimulate tumor cell proliferation [11-13]. Although insulin and IGFs may also be positively associated with the growth of cancerous prostate cells, decreased testosterone levels in diabetic patients may explain the inverse association with risk of prostate cancer. In both animal and human studies it has been showed that as blood glucose levels increase, there is a simultaneous decrease in testosterone levels [14, 15]. High testosterone levels may increase the risk of prostate cancer and it is therefore low testosterone levels that may be protective. Also, obesity leads to diabetes and obese men are less likely to have prostate cancer [16]. But among prostate cancer patients, obesity is related to higher prostate cancer-specific mortality [17].

1.2. Anti-diabetic Treatment and Cancer

Anti-diabetic treatments, including oral hypoglycemic agents (OHAs) and exogenous insulin, have been widely used for T2DM patients for decades. OHAs are intended to normalize blood sugar levels through three main mechanisms of action: increasing the amount of insulin secreted by the pancreas (insulin secretagogues), increasing the sensitivity of target organs to insulin (insulin sensitizers), and decreasing the rate at which glucose is absorbed from the gastrointestinal tract (alpha-glucosidase inhibitors). Some new anti-diabetic drug classes, glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors, may increase incretin levels, but the experience with these new compounds is still quite limited.

Most T2DM patients have long-term exposure to multiple anti-diabetic treatments. If hyperinsulinemia plays a role in increasing cancer risk in diabetic patients, it is

reasonable to expect that treatments that increase endogenous (sulfonylurea and meglitinides) or exogenous insulin (insulin replacement) may be risk factors for cancer development, and in contrast, those treatments that decrease endogenous insulin (metformin and TZDs) may not be risk factors or even play protective roles in cancer occurrence among diabetics.

OHAs are usually the first line therapy for T2DM. The biguanide metformin, an inexpensive and well tolerated OHA, has been widely used for more than 30 years. Acting as an insulin sensitizer, it reduces serum insulin levels by promoting utilization of insulin in the liver and in muscle. Kaiser Permanente published the results of a 20-month study on metformin in January 1999, which revealed that metformin is associated with good adherence to prescription guidelines, as well as an improvement in glucose control compared to those on sulfonylureas [18]. In recent years metformin has been recommended as the first line drug for T2DM, especially in those who are overweight. Standard care of T2DM now starts with metformin according to guidelines published by the International Diabetes Federation (IDF) in 2005 [19]. Preclinical studies have demonstrated that metformin can inhibit the growth of cancer cells in vitro and in vivo [20]. A recent systematic review [21] of observational studies showed that metformin was associated with a 30% lower cancer incidence in individuals with T2DM compared with other diabetic treatments. Jiralerspong et al. [22] observed that diabetic patients with breast cancer treated with metformin experienced greater pathologic complete response (pCR) rates (OR = 2.95, 95% CI: 1.07-8.07) with neoadjuvant chemotherapy than those treated with other anti-diabetic medications. They also reported that insulin use was

associated with a significantly lower pCR rate in the non-metformin group (0% v 12%; P = .05) but not in the metformin group (27% v 23%; P=.75). A report from the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study in the Netherlands [23] showed an adjusted hazard ratio (HR) of 0.43 (95% CI: 0.23-0.80) for cancer mortality comparing patients taking metformin with those not taking metformin at baseline. A phase III adjuvant trial has recently been initiated to assess the efficacy of adding metformin to standard adjuvant treatment to reduce breast cancer recurrence in more than 3,500 women, including both diabetics and non-diabetics, with stage I and II breast cancer [24].

Thiazolidinediones (TZDs) are insulin sensitizers that reduce insulin resistance in muscle and fat. These compounds have been shown to suppress tumor development in several in vitro and in vivo models. A cohort study [25] using Veterans Administration (VA) data showed a 33% significant reduction of lung cancer among TZD users compared to nonusers. This risk reduction did not reach statistical significance for colorectal and prostate cancers (12% and 14%, respectively). However, a case-control study (breast, colon, and prostate cancers) showed no difference in use of TZDs between cases and matched controls [26].

Sulfonylurea and meglitinides are insulin secretagogues, which stimulate endogenous insulin secretion through direct action on pancreatic beta cells. Sulfonlyurea used to be the first line drug for T2DM. Starting in the early 2000s, evidence has showen that metformin provides better glucose control, and low incidence of hypoglycemia. Since then, sulfonylureas have only been used as first-line therapy in patients of normal weight,

or in those who cannot tolerate metformin. In a cohort study using administrative databases from Canada, sulfonylurea has been found to be associated with an increased cancer mortality compared with metformin (including metformin + sulfonylurea) (hazard ratio [HR] = 1.3, 95% CI: 1.1-1.6) [27]. A retrospective cohort study in the United Kingdom (U.K.) "The Health Information Network" (THIN) database [28] reported that patients treated by sulfonylurea mono-therapy had a 36% significantly increased risk of cancer compared to patients treated by metformin mono-therapy. A case-control study that compared different classes of OHAs and their combinations in diabetic subjects [29] found a significantly lower risk of pancreatic cancer for metformin users (OR=0.38, 95% CI: 0.22-0.69) and significantly increased risk of pancreatic cancer for insulin secretagogues (sulfonylurea and meglitinides) users (OR=2.52) compared to T2DM patients never using the specified classes. A non-significantly lower risk was seen among those who used metformin in combination with either insulin secretagogues or TZD.

Insulin injections directly increase insulin levels through exogenous replacement. Insulin is mostly used when OHAs fail to achieve the goals of blood glucose control. When endogenous insulin declines among T2DM patients, most of these patients require exogenous insulin injection. Prior to studies showing better outcomes with more intensive control, insulin used to be initiated only in late stages of T2DM. However, reports from the U.K. Prospective Diabetes Study (UKPDS) [30] show that more intensive therapy with the goal of achieving near-normal glucose levels could lower the common complication rate among diabetic patients. The UKPDS demonstrated that T2DM patients have an inexorable worsening of metabolic control over time, eventually

requiring the addition of insulin. Thus, insulin has been used increasingly at earlier stages of T2DM.

The role of insulin on risks of cancer among T2DM patients remains controversial. In the THIN study (a database that overlaps the UK GPRD), Currie et al. [28] reported that insulin therapy increased the risk of cancer by 42% (95% CI 1.27 – 1.60) compared to metformin mono-therapy. While this could merely reflect the effect of more advanced diabetes, they also found that concomitant metformin therapy decreased the risk of malignancy associated with insulin (HR 0.54, 95% CI 0.43 – 0.66). In contrast, another recently published matched cohort study reported that insulin was associated with a large decrease in the risk of cancer (HR 0.17, 95% CI 0.09 – 0.32) compared to nonusers, but the reverse direction and magnitude of protection strain the credibility of the findings [31].

Most of these studies compared a group of patients who ever used one drug class versus never having used that class. Since diabetes patients usually have a long disease history, and exposure to multiple anti-diabetic medications and switching between classes is very common, comparisons of ever use versus never use may not be adequate to detect associations between the anti-diabetic treatment and cancer occurrence. Some other studies compared cancer risks of anti-diabetic treatment groups to non-diabetic subjects. The “never use” group may contain a large proportion of patients who had no treatment at all. These patients were usually in early stages of diabetes, or had a form of diabetes that was well controlled by diet and exercise. These non-treated patients, as well as non-diabetic subjects, who carried a different risk of cancer compared to those treated by anti-

diabetic medications, may introduce selection bias and uncontrolled confounders in these studies.

Although it is generally agreed that patients with T2DM have an increased risk of cancer, the evidence supporting the role of OHAs and insulin in promoting cancer is inconsistent. Thus, it is not clear whether the anti-diabetic drugs may promote or prevent cancer initiation or progression, and, if so, whether they act by systemic mechanisms on multiple cancer sites or by site-specific mechanisms in particular organs. The objectives of this study are to compare cancer incidence among anti-diabetic treatments with different mechanisms and action on blood insulin levels.

CHAPTER II THE COHORT STUDY

This was a retrospective cohort study of T2DM patients who were newly exposed to anti-diabetic treatments. In addition, two nested case-control studies of cancer were carried out within the study cohort. The study population was drawn from patients registered to the general practitioners (GPs) contributing to the U.K. General Practice Research Database (GPRD) between 1/1/1995 and 12/31/2008. The objectives of the study were to evaluate the association between anti-diabetic treatment and cancer incidence among patients with T2DM. We supplemented the usual cohort analysis with nested case-control analyses to achieve better matching of elapsed years since the initiation of OHA's.

2.1. Data Source

The U.K. GPRD is one of the world's largest electronic medical record (EMR) databases of anonymized longitudinal clinical records from primary care. It contains detailed information on symptoms, diagnoses, prescriptions, investigations, and hospital referrals, as well as basic demographics. The GPRD began in June 1987 as the Value Added Medical Products (VAMP) Research Databank, which was donated to the U.K. Department of Health in 1994 [32, 33].

In the U.K., GPs act as the gatekeepers to healthcare delivery for the whole population, and 98% of people in the U.K. are registered with a GP [34]. Anonymized patient clinical records for the GPRD are collected from a volunteer group of GPs throughout the U.K.. The data cover more than 35 million patient-years collected from approximately 8.9 million patients, which represents a sample of approximately 5% of all U.K. patients

registered with a GP. Currently, data are being collected incrementally from roughly 3 million patients in 380 practices.

The GPRD has the strengths of population-based data collected prospectively in an unbiased manner in primary care settings. The large size of the data with several years of longitudinal, continuous data recording enables the study of uncommon outcomes and outcomes with substantial latency periods. The comprehensiveness, completeness and quality of the GPRD provide a good resource for studying natural history of disease, as well as its frequency and trends.

The medical signs, symptoms and diagnoses were coded in GPRD using Read Clinical Terms. Historically, GPs used VAMP software and Oxford Medical Information System (OXMIS) codes to enter medical events. OXMIS was later augmented by Read. The validity of the Read coding is variable. Common diseases are more likely to be recorded accurately, and diseases unfamiliar to the majority of GPs, e.g. ophthalmologic diseases, are recorded with less accuracy.

The GPRD is known internationally as a data resource for epidemiologic research, and has been used extensively for pharmaco-epidemiologic studies [35-37]. Prescriptions issued by the practice are coded by drug substance or product using Multilex® which is linked to the British National Formulary (BNF). All prescriptions are issued via the practice computer except those issued when the practitioners are working for the general practice cooperative or making house calls. A survey measuring the validity and utility of electronic patient records in general practice reported that 99.7% of prescriptions were recorded in the electronic records [38]. In the U.K., drugs prescribed by GPs are subject

to a co-payment (£6.85 per prescription; $10.97), but about 88% of prescriptions are exempt from charges. Thus, most medications prescribed by GPs are likely to be filled as recorded. Although dose, route of administration, daily quantity, number of packs, package size, and prescription duration are not available for a majority of prescriptions in the GPRD, detailed prescription dates and coded drug names are recorded in the database [39]. A validation study using the GPRD reported that treatment durations of prescriptions were usually 1 month long [40].

Three large studies demonstrated that information on referrals and hospitalizations is recorded more than 90% of the time [41-43]. Studies that require validation of coded diagnostic outcomes have shown excellent agreement between the recorded diagnoses and the information on paper-based records, including the diagnoses of colorectal cancer and diabetes mellitus [35, 44-46]. Prior studies using the database have also found complete agreement between prescription information received from the GPs and that recorded in the database [43, 44, 47].

Any study using the GPRD that is destined for publication or that is intended to communicate the results to third parties, must receive approval from the Independent Scientific Advisory Committee (ISAC) before proceeding. This study was approved by the ISAC on July 12, 2010.

2.2. Study Cohort

A cohort of T2DM patients who had a new prescription (no prior prescription of anti-diabetic medication prior to identified earliest anti-diabetic prescription in the database) of OHAs between 1/1/1995 and 12/31/2008 was identified from the database.

A diagnosis of diabetes mellitus was determined from the clinical diagnosis using Read codes and related supporting evidence, including age at diagnosis and types of treatment. A set of all possible diabetes-related Read codes was identified and all irrelevant codes (e.g. diabetes insipidus, gestational diabetes, child with diabetes etc.) were excluded. Anti-diabetic therapy was determined using BNF codes as 60101 (insulin) and 60102 (OHAs). OHAs include 6010201 (sulfonylurea), 6010202 (biguanides), and 6010203 (other anti-diabetic drugs with sub-codes for TZDs and meglitinides). The records of all patients in the database with any diabetes-related codes and anti-diabetic treatment codes were then extracted from the database.

In order to exclude mis-coded type I DM patients, Read codes were combined with age at diagnosis and age at which treatment was initiated to define cases of T2DM. Patients who fit the following criteria were included: 1) One or more Read codes for diabetes mellitus were present, and, 2) the earliest diagnosis of diabetes or OHA treatment available in the data was made at an age of at least 35 years old but no more than 80 years old, and, 3) the patient was treated with an OHA (with or without insulin). The effect of this would be to decrease sensitivity of the diagnosis, but would generate a relatively "pure" cohort of T2DM patients.

Eligible patients had to be new users of anti-diabetic agents who were initially stabilized on an OHA mono-therapy. In order to classify the treatment regimen on which each patient was initially stabilized, the first six consecutive prescriptions of the same OHA regimen were identified. (Consecutive prescriptions are defined as prescriptions for the same OHA regimen (mono- or combination therapy) in adjacent prescription dates in the

absence of other anti-diabetic treatment.) Thus, only patients initially stabilized with OHA mono-therapy were included, and the earliest OHA with at least 6 consecutive prescriptions was set as the primary exposure. The 1st prescription date of the primary exposure was set as the OHA index date and the start of follow up of the cohort. Patients who have newly started anti-diabetic treatment may be switched from different medications to find the most efficient therapy to control blood glucose. Thus, in order to identify the therapy on which patients were initially stabilized, eligible patients may have had a few additional prescriptions prior to the OHA index date. In order to exclude potentially mis-coded type I diabetes patients, those whose earliest 6 consecutive prescriptions were insulin only were excluded. Patients whose initial stabilized OHA treatment was combination therapy (multiple classes of OHAs or OHA plus insulin) were not included in the cohort, since a larger proportion of these patients had changed treatment multiple times prior to the OHA index date (see the Results section). These patients might be in later stages of diabetes, or their disease was hard to control, or they switched doctors frequently. These characteristics showed these patients were not representative of the stably controlled diabetes population that initiated treatment at study entry. However, patients who had fewer than 6 consecutive prescriptions of combo-therapy or insulin therapy and were then stabilized (with at least 6 consecutive prescriptions) on an OHA mono-therapy were included in the cohort. To ensure prescriptions were appropriately captured and patients were new users of OHAs, eligible patients had to be registered with GPRD for at least 1 year prior to the earliest prescription of an anti-diabetic treatment. Patients should also have had at least 1 year of

follow-up after the OHA index date. They were also required to be free of malignancy at any time prior to or within 1 year after the OHA index date to exclude cancers that occurred prior to the treatment.

2.2.1 Inclusion Criteria and Exclusion Criteria

Patients were included in the study cohort if they met all of the following criteria:

- Had at least one Read code related to diabetes mellitus; and
- The earliest date of diagnosis of diabetes or anti-diabetic treatment, whichever is earlier, was at 35 years of age or older, but no more than 80 years old; and
- Initially stabilized with OHA mono-therapy (the earliest 6 consecutive prescriptions for the same OHA); and
- Registered in the GPRD for at least 1 year prior to the earliest anti-diabetic (OHA or insulin) prescription date and had been followed up for at least 1 year after the OHA index date; and
- Had no evidence of malignancy (other than non-melanoma skin cancer) at any time prior to or within 1 year after the OHA index date.

Patients were excluded from this study cohort if they met any one of the following criteria:

- Initially stabilized with anti-diabetic treatment as insulin only (the earliest 6 consecutive prescriptions were insulin only); or
- Stabilized with anti-diabetic treatment as combination therapy (the earliest 6 consecutive prescriptions were combination of OHAs or OHA/insulin); or
- Had no OHA therapy; or

- Had at least 1 record, at any time prior to or within 1 year after the OHA index date, consistent with malignancy (other than non-melanoma skin cancer); or
- Had no diagnosis of DM

2.3. Exposure Measurement

Exposures were measured by the presence of prescription records using BNF codes. Prescription dates were captured from the therapy data and there were no missing dates for prescriptions.

The initial six consecutive exposures of OHA mono-therapy were classified as metformin, sulfonylurea, TZDs, or meglitinides. During the cohort follow up, subsequent insulin exposures, switches from one OHA treatment to another, as well as concomitant use of two or more OHAs were captured.

2.4. Outcome Measurement

Cancer cases were defined by the presence of a Read code indicating malignant abnormalities, including invasive solid tumors, other than non-melanoma skin cancer and hematological malignancies. The earliest diagnosis date must have occurred at least 1 year after the OHA index date and within the study period. Only newly diagnosed or incident cases meeting these criteria were considered as cancer cases. The earliest date of diagnosis for a cancer was considered as the cancer index date.

The follow-up period of the study cohort started from one year after the OHA index date until a new diagnosis of cancer, registration end date, or 12/31/2008, whichever occurred first. For overall cancer, the date of a new diagnosis was defined as the earliest diagnosis

of any cancer. Overall cancers were further divided into cancer sub-types as solid tumors and hematological malignancies. For cancer sub-types, the date of a new diagnosis was defined as the earliest diagnosis of a cancer within that sub-type. Patients with more than one sub-type of cancer might have different follow up durations for each cancer sub-type. For example, if a patient had both a solid tumor and a hematological malignancy, the patient would have different follow-up durations for the incidence of solid tumor (ending with the earliest diagnosis of that solid tumor) and for the hematological malignancy (ending with the earliest diagnosis of that hematological malignancy). Overall cancer incidences, as well as incidences of cancer sub-types were compared between exposure groups.

In addition, for sensitivity analyses, a different follow-up period for the duration of the primary exposure, which was defined as the duration from the OHA index date to a) the first date of a new therapeutic regimen minus 1 day or b) the end of the cohort follow-up, whichever occurred first, was calculated. New therapeutic regimens include other mono- or combo- therapies or the addition of another medication to the primary exposure (add-on). The primary exposure follow-up period was defined as extending from one year after the OHA index date until the end of the primary exposure (the first date of a new therapeutic regimen minus 1 day) plus 6 months or the end of the cohort follow up, whichever occurred first. Incidence of overall cancer, as well as solid tumors and hematological malignancies, within the primary exposure follow-up period was compared among the exposure groups.

2.5. Covariates

Multiple demographic and baseline characteristics were considered as potential confounding variables in the cohort. The baseline period was defined as starting one year prior to the OHA index date. Because of the potential for non-linearity of the numeric covariate variables, these covariates were set as categorical variables in the analyses.

Each patient's gender and age at the OHA index date were used as covariates. Age was categorized and the age category was used in the analysis models as a covariate.

The highest value of HbA1c during the entire baseline period was used as the baseline HbA1c. Extremely small (<1%) or large (>50%) values were set as missing. Abnormal HbA1c was defined as a value ≥7%. The baseline HbA1c was categorized as <7%, 7%-<9%, 9%-<12%, and ≥12%. The HbA1c category was used in the analysis models.

BMIs were calculated where height and weight recordings were available. The highest value of weight at baseline was used to calculate BMI. Extremely small (<10) or large (>80) values were set as missing. Patients were grouped by BMI range 10-19, 20-24, 25-29, 30-34, and 35-80 kg/m^2. The range 20-24 kg/m^2 was considered as normal range and the BMI category was used in the analysis models.

Smoking status was assessed at baseline. Patients were categorized as non-smokers, current smokers, ex-smokers or unknown based on the smoking entry closest to the OHA index date.

Cancer screening tests/procedures were also considered as potential confounding factors. Patients who had a mammogram (for women) or a PSA (for men) at baseline, or a

colonoscopy within ten years prior to the OHA index date were considered as having cancer screening measurement. However, the purposes for these tests (screening or diagnosis) were unknown.

The chronic disease score (CDS) is an aggregate co-morbidity measure based on medication use. It is calculated from prescription information for specific drug classes and the scores are summed up from these classes (Table 1). It has been proven to be valid in predicting hospitalization, health resource utilization, and mortality [48]. Prescription information at baseline was used to calculate the CDS.

In addition, hospitalization (yes vs. no), OHA index year, and duration of DM prior to OHA index date (if DM diagnosis was later than the OHA index date, then the duration was set to be missing) were considered as potential confounding variables in the analyses.

2.6. Analyses

Cancer incidences were compared between the primary OHA exposure groups using Cox proportional-hazards regression models. HRs and their 95% CIs were estimated. The time-to-event was modeled in this analysis. The total follow-up time started from one year after the OHA index date until the first date of the diagnosis of a cancer, registration end date, or 12/31/2008, whichever occurred first. Patients who did not meet the case criteria in the cohort were censored at the end of registration or 12/31/2008, whichever occurred first.

Cox models were constructed to estimate HRs adjusted for multiple covariates. The base model only included the primary OHA exposure to estimate the unadjusted HR for

cancer. In the adjusted models, age, gender, baseline HbA1c value, BMI, smoking status, CDS, OHA index year, number of OHA prescriptions prior to the OHA index date, hospitalization, cancer screening test, and duration of DM prior to OHA index date were initially considered. Age and gender were always retained in the final model.

Potential confounders were tested one-by-one by generating two models for each confounder. One model contained the exposure factor only (unadjusted HR) and the other contained the exposure factor and the tested confounder (adjusted HR). Only patients who had a non-missing value for the tested confounder were included in these two models. The confounders were retained in the final model if their inclusion, in a model containing the single covariate and the OHA exposure variable, changed the HR for the OHA exposure variable by 10% or more, relative to the unadjusted HR for OHA exposure (i.e., adjusted HR/ unadjusted HR is either >1.10 or <0.90), the so-called "change in estimate" criterion [49]. Unadjusted HRs and adjusted HRs and their 95% CIs were estimated.

Sensitivity analyses were performed utilizing the same Cox proportional-hazard regression models comparing cancer incidence during the primary exposure follow-up period. In addition, sensitivity analyses were also performed using the cut-off for the OHA index year as 2004. The influence of missing covariates on estimating the risks of cancer was also investigated in sensitivity analyses.

The Cox proportional-hazards regression models were used under the assumption that hazard functions are proportional over time (i.e., constant relative hazard). This was

checked using a proportionality test and "log(-log(survival)) versus log of survival time" plots.

All analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

2.7. Results

2.7.1 Cohort Selection and Baseline Characteristics

There were 180,406 patients registered in the GPRD who initiated anti-diabetic treatment between January 1st, 1995 and December 31st, 2008. Figure 1 shows the cohort selection step-by-step. There were 31,486 patients who were excluded because they did not have a stable anti-diabetic regimen (defined as at least 6 consecutive prescriptions of the same OHA or OHA combinations). Among the remaining 148,920 patients, the initial stable OHA treatment was set as the primary exposure and the first prescription date of the primary exposure was set as the OHA index date. Durations of registrations in the GPRD were accessed and 59,166 patients who had less than 1 year of registration prior to the earliest anti-diabetic treatment date and 11,265 who had less than 1 year of follow up after the OHA index date were excluded. There were 5,164 patients who had a diagnosis of malignancy prior to or within 1 year after the OHA index date and 14 who had a malignancy diagnosis but no associated diagnosis date were also excluded from the cohort. Potential type I diabetic patients (2,647 with a diagnosis of DM or initiated anti-diabetic treatment before 35 years of age and 2,016 who initiated anti-diabetic treatment with at least 6 consecutive prescriptions of insulin only) were excluded. Patients initially stabilized with combination therapy (6,049), those older than 80 years (4,949), and those

with no diagnosis of DM (806) were also excluded. Among the 6,049 patients who were initially stabilized with combination therapy, only 20% were naive to anti-diabetic treatment, and 44% had more than 3 different prescriptions prior to being stabilized on the combination therapy. These patients were excluded because of the complicated treatment history. The final cohort contained 56,844 qualified patients. Among this cohort, 39,070 (68.7%) patients were initially stabilized on metformin, 16,904 (29.7%) on sulfonylurea, 662 (1.2%) on TZDs, and 208 (0.4%) on meglitinides.

Table 2.1.1 shows the demographic and baseline characteristics of the cohort. The sulfonylurea group had the highest proportion (59%) and the TZD group had the lowest proportion (51%) of males. Over one half of individuals in the sulfonylurea group were over 65 years old, while only about a third of the other exposure groups were in this older category. The sulfonylurea group was leaner with 26% and 28% in the normal (BMI 20-<25) and obese (BMI >30) categories, respectively, as compared to the metformin group with only 7% classified as normal weight and over 60% as obese. The mean baseline HbA1c values for all exposure groups were above the normal limit defined as 7%, with the sulfonylurea group having the highest HbA1c. The minimum chronic disease score was 2, which indicated that anti-diabetic treatment was the only treatment for chronic disease at baseline. The sulfonylurea and meglitinides groups had similar proportions (27% and 26%, respectively) in this category. The metformin and TZD groups had lower proportions (11% and 19% respectively). The duration of DM prior to cohort entry was shorter in the metformin and sulfonylurea groups compared to the TZD and meglitinides groups. The proportion of patients with recent cancer screening and smoking status were

similar across the exposure groups. In early study years, patients were more likely to initiate OHA therapy with sulfonylurea. More than half of the metformin group initiated OHA after year 2003. There was no TZD therapy prior to year 2000 and no meglitinide prior to year 1999, since these classes are newer OHAs. The mean total cohort follow-up duration is similar between the sulfonylurea and meglitinides groups (5 years), while it was shorter in the metformin group (3.4 years) and the TZD group (2.6 years).

There were total 20,932 (36.8%) missing baseline HbA1c. Notably, the missing baseline HbA1c was significantly different across exposure groups. Half of the sulfonylurea group had missing baseline HbA1c, and around one-third of the metformin group had missing data for this value. The TZD group had the lowest proportion (13%) of missing. This trend of missing values was similar across other baseline characteristics, including BMI, smoking status, and duration of DM prior to the OHA index date.

In further exploration, it was found that this trend of missing baseline characteristics was mainly due to the difference of the OHA index year. Patients entering treatment in the early years were more likely to be started on sulfonylurea whereas metformin became the dominant initial therapy in the later years. HbA1c was not systematically measured among T2DM patients in earlier years, so it was missing more often in the sulfonylurea group. Table 2.1.2 shows the missing HbA1c across exposure groups stratified by OHA index year. The missing rates decreased by year for all groups. There were more than 60% missing before the year 2000 and more than half were missing between years 2000 – 2001. The missing rate dropped to around one third between years 2002 – 2003. After 2004, there were around 20% missing. The missing rates were similar across exposure

groups, except for the TZD group, by year. Other missing baseline characteristics had similar distributions and were similar across exposure groups by year (data not shown).

Table 2.1.3 lists the duration of the primary exposure and the changes to new therapeutic regimens. The metformin and sulfonylurea groups had similar mean durations (35 and 38 months, respectively, as the primary exposure), while the durations of the primary exposures were shorter for the TZD (31 months) and meglitinides (30 months) groups. Around half of the metformin (56%) and TZD (52%) groups remained on the primary exposure throughout the follow-up. These percentages were lower for the sulfonylurea (35%) and meglitinides (20%) groups. In the metformin group, 22% of patients changed to another mono-therapy and another 22% added one medication (OHA or insulin). These percentages were 36% and 29%, 29% and 19%, and 46% and 31% for the sulfonylurea, TZD, and meglitinides groups, respectively. The most common medication changes were to switch to or add metformin or sulfonylurea.

2.7.2 Anti-diabetic Treatment and Cancer Risk

During the cohort follow up, a malignancy developed in 2,589 subjects (4.6%). Among these cases, 2,403 were solid tumors and 202 were hematological malignancies. Sixteen (16) subjects developed both a solid tumor and a hematological malignancy.

Table 2.2.1 shows the person-years of follow up (started from one year after the OHA index date) and the unadjusted and age standardized (based on U.K. 2001 Census [50]) incidence rates of overall cancers, as well as of solid tumors and hematological malignancies. The incidence rate of death without cancer is also shown in this table.

Incidences of overall cancers were a little higher in the sulfonylurea group and meglitinides group (13/1000 person-years) compared to the metformin and TZD groups (11-12/1000 person-years). After age standardization, the meglitinides group (10/1000 person-years) showed the highest incidence and other groups had similar incidences to each other (7-8/1000 person-years) of overall cancer. For solid tumors, the incidence rate was the lowest in the metformin group (10/1000 person-years) and highest in the sulfonylurea group (13/1000 person-years). Age standardized incidences of solid tumor were similar across all exposure groups. For the hematological malignancies, the incidence was the highest in the meglitinides group (3/1000 person-years crude and 2/1000 person-years age-standardized) compared to those in other exposure groups (0.6 – 1/1000 person-years). However, there was only one hematological malignancy in the TZD group and three in the meglitinides group. The death rate was higher in the sulfonylurea group (31/1000 and 18/1000 person-years for the crude and age-standardized rates, respectively) and the meglitinides group (25/1000 and 24/1000 person-years) as compared to that of metformin (16/1000 and 12/1000 person-years) and TZD (12/1000 and 8/1000 person-years) groups.

Table 2.2.2 shows unadjusted and adjusted hazard ratios and their 95% confidence intervals from Cox proportional hazard models. The metformin group was used as the reference group to estimate the hazard ratios for overall cancer, solid tumor, and hematological malignancies. HRs of death without cancer, as well as death or cancer, were also presented in this table. From unadjusted models, sulfonylurea was associated with a 25% increased risk of overall cancer, solid tumor, and hematological malignancy.

Use of meglitinides was associated with more than a 3-fold risk of hematological malignancies, and no significant risk of cancer was associated with TZD in these unadjusted analyses.

Potential confounders were tested one by one in models containing the single covariate and the exposure variable. Based on the "change in estimate" criterion (i.e., a change in the estimated hazard ratio by 10% or more), adjusting for age changed the estimates of risks for all endpoints. In addition, adjusting for BMI changed the estimate of risk for hematological malignancy. No other potential confounders changed the unadjusted HR by more than 10%. In the final adjusted models, age and gender were retained as covariates for overall cancer, solid tumor, and death without cancer. Age, gender, and BMI were included in the model for hematological malignancy.

After adjusting for potential confounders, the sulfonylurea and TZD groups showed no increased risk of overall cancer, solid tumor, or hematological malignancy. The meglitinides group was not associated with increased risk of solid tumor either. Although there were only three (3) cases in the meglitinides group, it was associated with a more than 4-fold (HR: 4.3, 95% CI: 1.33, 13.57) significant risk of hematological malignancy. Both sulfonylurea (HR=1.39, 95%: 1.31, 1.48) and meglitinides (HR=1.51, 95%CI: 1.02, 2.22) groups were associated with significantly increased risk of death without cancer, compared to metformin. When "death or cancer" was treated as a single endpoint, the increased risks were significant for the sulfonylurea (HR = 1.27) and the meglitinides (HR = 1.40) groups.

Checks on the assumption of constant relative hazard for the Cox proportional-hazard regression models using "log(-log(survival)) versus log of survival time" plots are presented in figures 2.1 to 2.3. The metformin, sulfonylurea, and meglitinides lines were nearly parallel, although the TZD line crossed the metformin line (most likely due to the short follow-up duration and small sample size). The metformin and sulfonylurea lines crossed early in follow-up (i.e., less than 1 week after the first year of follow-up). After excluding these subjects with short follow-up (103 patients), results from the Cox models were the same as those presented in table 2.2.2 (data not shown). The P-values from the proportionality tests were 0.1121, 0.1071, and 0.7340 for overall cancer, solid tumor, and hematological malignancies, respectively, indicating that the proportional hazards assumption seemed reasonable in these models.

2.7.3 Sensitivity Analyses for Anti-diabetic Treatment and Cancer Risk

There were three sets of sensitivity analyses performed.

The first one was to investigate the influence of missing covariates on estimating the odds ratio of cancers. The same unadjusted models shown in table 2.2.2 were repeated, but in this sensitivity analysis, only patients who had non-missing values of each test covariate (HbA1c, BMI, duration of diabetes to OHA start date, and smoking status) were included. The HRs estimated from these test models were compared to the unadjusted HRs in table 2.2.2, to separate out the effect of limiting the dataset to those with non-missing covariate values from the effect of adjusting for covariates.

Table 2.3.1 showed that eliminating patents with missing values of HbA1c, BMI, or DM duration, changed the relative risk of overall malignancies and solid tumors associated with TZD from 1.2 to 1.0. No other relative risk estimates changed for these endpoints. Eliminating missing covariates changed relative risk estimates of hematological malignancies more substantially for all exposure groups. No other hazard ratios shown in Table 2.2.2 were changed by more than 10% by eliminating subjects with missing variables.

The second sensitivity analysis was to compare the incidence of cancers based on the primary exposure follow-up period. Only cancers that occurred during the primary exposure follow-up period (from the OHA index date to the day before the new therapeutic regimen + 6 moths or the end of cohort follow-up, whichever occurred first) were considered as cases. Follow-up was censored at this time point. Table 2.3.2 lists the results from these analyses. The HRs showed similar trends to those shown using the total follow-up duration.

The cohort entry dates of this study spanned 14-years (1995 - 2008). More than half (57%) of the patients entered the cohort after the year 2002. Only a small proportion (22%) of patients initially stabilized on metformin entered before 2002, although the metformin group accounted for 69% of the whole cohort. More than half (57%) of the metformin group entered the cohort at or after 2004. These differences raised the concern about unmeasured differences between the metformin and the other exposure groups, which might have been introduced by the time of entry into the cohort.

The third sensitivity analysis was to stratify the final adjusted models in Table 2.2.2 by OHA index years using the year 2004 as a cutoff (Table 2.3.3). Sulfonylurea was associated with a slightly increased risk (HR=1.16, 95%CI: 1.03 – 1.29) of solid tumor compared to metformin for patients enrolled in early years (before 2004), but not in late years. There was no increased risk of cancer associated with TZD either in early years or in later years. Risks of cancer associated with meglitinides were stronger in later years (HR=1.26 and 6.24 for solid tumor and hematological malignancy, respectively) than in earlier years. However, they were based on small numbers of cases with wide 95% CIs.

2.7.4 Study Power

Based on the results from the cohort analyses and a type 1 error rate of 0.05, the statistical power was calculated for each primary OHA mono-therapy exposure to detect a meaningful relative risk. Ratios of metformin vs. sulfonylureas, TZD, and meglitinides were 1.54, 77.30, and 124.94, respectively. The incidence of malignancies among patients exposed to metformin was 0.007/person-year. For the sulfonylureas group, there was 100% power to detect a relative risk of 1.5 or greater. For the TZD group, there was 42% power to detect a relative risk of 1.5 or greater and 85% power to detect a relative risk of 2 or greater. For the meglitinides group, the power was 31% to detect a relative risk of 1.5 or greater and 80% to detect a relative risk of 2.2 or greater.

CHAPTER III THE CASE-CONTROL STUDY

3.1. Introduction

The cohort study illustrated the incidence of overall malignancies, malignant solid tumors, as well as hematological malignancies, among four exposures of OHA mono-therapy. The cohort entry years were from 1995 to 2008. During this 14-year period, understanding of diabetes management has improved. Both diagnosis and treatment strategies for diabetes have been modified during these years. Major changes include more strict blood glucose control, using HbA1c as an indicator for blood glucose control, and a change in first line treatment from sulfonylurea to metformin. Diagnosis of cancer also improved during these years. The frequencies of the four primary exposures were very different in early vs. late cohort entry years due to the change in practice guidelines and the launch of new drugs on the market. More than half of the metformin group patients started treatment at or after year 2004, while the sulfonylurea group patients were more evenly distributed across these years. TZD and meglitinides were not placed on the market until 1999 – 2000. There is strong potential for various temporal biases due to changes in medical practice on diagnosis and treatment guideline over time, length of available history, and different durations of follow-up for cancer detection. In order to minimize these potential cohort effects and temporal bias, a nested case-control study was carried out to match cases and controls by their cohort entry year and their follow-up duration. Time-varying exposures at different periods were compared for cancer occurrences. Since hematological malignancies were rare and might have different

relationships to DM treatment compared with solid tumors, only invasive solid tumors were included in the case-control study.

3.2. Methods

Cases were defined as all occurrences of malignant solid tumors during the cohort follow-up. Controls were selected from patients in the cohort not experiencing any malignancy during follow-up. For each case, four (4) controls were matched by age ± 2 years, gender, and OHA index year ± 1 year. Eligible controls should have had equal or longer duration of follow up in the cohort as their respective cases and the same duration of follow-up in the cohort was assigned to the controls. If there were more than four patients without cancer fulfilling the matching criteria for a case, four controls were randomly selected among these eligible patients. One control may be matched to more than one case if he/she qualified the matching criteria for each case. For each identified case, the cancer index date was defined as the earliest diagnosis date of the patient's solid tumor, while controls were assigned the index date of the case to which they were matched.

For each case and control in the case-control study, the cancer index date minus 6 months was set as the pre-cancer date. Anti-diabetic treatment history prior to the pre-cancer date was evaluated. As the exposure window was assessed from the pre-cancer date backwards up to 5 years or to the OHA index date, whichever occurred later. The exposure window was divided into recent, past, and distant periods. The recent period was within 1 year prior to the pre-cancer date, the past period was between 1 year and 3 years prior to the pre-cancer date, and the distant period was 3 years and 5 years prior to

the pre-cancer date. The median duration from the OHA index date to cancer diagnosis was 4.8 years. Exposures beyond the distant period (more than 5.5 years prior to the cancer index date) were not assessed due to the small sample size. Figure 3 illustrates the exposure periods.

Prescriptions of metformin, sulfonylurea, TZD, meglitinides, insulin, and their combinations were the exposures of interest in the case-control analyses. Cumulative prescriptions of these medications in each exposure period were calculated. If a patient had at least three prescriptions of one class of the anti-diabetic medication in a period, then this patient was considered to have been exposed to that medication during this period.

For each time period of drug exposure (recent, past, or distant), two classifications of exposures were defined. One classification was based on the pharmacological classes of anti-diabetic medications as metformin only (without other OHA or insulin), sulfonylurea only (without other OHA or insulin), metformin + sulfonylurea (without other OHA or insulin), metformin + insulin (without other OHA), sulfonylurea + insulin (without other OHA), insulin (insulin alone or insulin plus OHAs), TZD (TZD alone, or TZD plus other OHAs), and meglitinides (meglitinides alone, or plus other OHAs). For example, if a patient had 4 prescriptions of metformin and 5 prescriptions of insulin and no other OHAs during the recent period, then this patient was considered to be exposed to metformin + insulin in the recent period. If a patient had 6 prescriptions of metformin and 4 prescriptions of TZD in the past period, then this patient was considered to be exposed to TZD in the past period.

Another classification was made based on the mechanism of action on hyperinsulinemia, as sensitizers only (metformin, or TZD, or metformin + TZD, no insulin), secretagogues only (sulfonylurea, or meglitinides, or sulfonylurea + meglitinides, no insulin), sensitizers + secretagogues (metformin and/or TZD plus sulfonylurea and/or meglitinides, no insulin), sensitizers + insulin (metformin and/or TZD plus insulin), secretagogues + insulin (sulfonylurea and/or meglitinides plus insulin), sensitizers + secretagogues + insulin (metformin and/or TZD plus sulfonylurea and/or meglitinides plus insulin), and insulin only. Metformin and TZDs are insulin sensitizers, and sulfonylurea and meglitinides are insulin secretagogues. Patients classified into one of these single insulin-effect groups (sensitizers or secretagogues) could have either mono- or combo- therapies of the medications within the same insulin-effect group. Prescriptions of medications belong to another insulin-effect group were not allowed in these groups. Patients with prescriptions across insulin-effect groups were classified into the combination group (sensitizers + secretagogues). For example, if a patient had more than 3 prescriptions each of metformin and TZDs, either sequentially or simultaneously, the patient would be in the sensitizer group. If a patient had more than 3 prescriptions each of metformin and sulfonylurea, the patient would be in the sensitizers + secretagogues group.

3.3. Covariates

In addition to the matched factors, multiple characteristics were considered as potential confounding variables in the case-control analyses for each exposure period.

For each exposure period, the highest value of HbA1c and the highest value of BMI within one year prior to the start of the period were used as covariates. HbA1c was

categorized as <7%, 7%-<9%, 9%-<12%, and ≥12%, with abnormal HbA1c defined as a value ≥7%. BMI was categorized as 10-19, 20-24, 25-29, 30-34, and 35-80 kg/m^2, and the range 20-24 kg/m^2 was considered as normal. Categorical variables for HbA1c and BMI were used in the analysis models.

Patients who had a mammogram (for women), or a PSA (for men) within one year or a colonoscopy within ten years prior to each exposure period were considered to have participated in cancer screening. Prescriptions within one year prior to each exposure period were used to calculate CDS for that period.

Smoking status at baseline and duration of diabetes to the OHA index date were also considered as potential confounders.

3.4. Analyses

Conditional logistic regression models, to account for the matching variables, were used to estimate odds ratios (OR) and their 95% CIs by comparing different anti-diabetic treatments to the metformin only group or the sensitizer only group for each exposure period. Other potential confounding factors, including BMI, HbA1c, CDS, cancer screening, smoking status, hospitalization, and duration of DM prior to OHA index date were tested as described in the cohort section. Potential confounders were also controlled based on the "change in estimate" criterion.

3.5. Results

3.5.1 Baseline Characteristics

There were 2,403 malignant solid tumor cases identified from the cohort. Each case was matched to four controls to compose total 9,612 controls. Table 3.1 shows the demographic and baseline characteristics of the cases and their matched controls. There were 61% males and 39% females. Most were between 51 and 75 years old (mean=67) at cohort entry. Just over half the subjects had an HbA1c available. Among these 8%-10% had normal HbA1c and over half had an HbA1c of 7-9% at cohort entry. Fifteen percent (15%) of the patients had a normal BMI, 41% were overweight and 43% were obese. Among these patients 22-23% had anti-diabetic treatment as the only prescription for chronic disease at baseline (CDS=2), and 6% of them had several co-morbidities (CDS>10). Around 6% of the patients had a cancer screening test at baseline. The cases and the controls were well matched for age, gender, and cohort entry year. Other baseline characteristics, including HbA1c, BMI, CDS, cancer screening, and duration of diabetes to OHA index date were well balanced between the cases and the controls. The case group had slightly fewer nonsmokers (37%) and more current smokers (34%) compared to controls (43% and 27%, respectively). Patients with missing values of these baseline characteristic were also balanced between the cases and the controls.

3.5.2 Risks of Cancer Associated with Anti-diabetic Exposures

The unadjusted and adjusted ORs and their 95% CIs comparing anti-diabetic treatments between cases and controls are listed in tables 3.2 and 3.3. The unadjusted ORs were

derived from conditional logistic models with only a single independent variable, but age, gender, OHA index year, and length of follow up in the cohort were accounted for in these analyses through matching. HbA1c was the only additional potential confounder that changed the OR by at least 10%, so it was included in the final models to estimate the adjusted OR.

In table 3.2, exposures were based on the pharmacological classifications. The metformin only group was used as a comparison group. The first five groups, metformin only, sulfonylurea only, metformin + sulfonylurea, TZD, and meglitinides, represent the common OHA treatment regimens (without insulin). When compared to metformin only, none of the other non-insulin exposure groups showed elevated risks of cancer in any exposure period. There were limited numbers of cases (60 - 85) in the meglitinides group. The next three groups, metformin + insulin, sulfonylurea + insulin, and insulin (insulin only or insulin plus other OHA) had in common the use of insulin. Although the metformin + insulin group showed 12% - 81% increased risks of cancer, none of these reached statistical significance. However, the sulfonylurea + insulin group showed the strongest risk (OR = 2.75, 95% CI: 1.51, 5.03) in the recent period. The OR for this group remained elevated in the past period (OR = 1.76, 95%CI: 0.86, 3.22), although it was not statistically significant. This risk disappeared in the distant period. For the insulin group, the risks were also elevated in the recent (OR = 1.64, 95% CI: 1.24, 2.16) and past periods (OR = 1.25, 95% CI: 0.87, 1.78), although these elevated risks were not as large as those for the sulfonylurea plus insulin group.

In table 3.3, exposure groups were based on the mechanism of action on hyperinsulinemia of the OHAs and the sensitizer only group was used as a comparison group. The results were consistent with those discussed above for individual drug types. For the exposure groups without insulin, the secretagogues and the sensitizer + secretagogues groups, there was no elevated risk for cancer in any period. The sensitizer + insulin group showed statistically non-significant 30% - 43% increased risks in the recent and the distant periods. The secretagogues + insulin group showed the strongest risk in both the recent (OR = 2.70, 95% CI: 1.48, 4.92) and the past (OR = 1.58, 95% CI: 0.82, 3.04) periods, although the OR in the past period was not statistically significant. The insulin group was also associated with risks of cancer in the recent (OR = 1.76, 95% CI: 1.29, 2.40) and the past (OR = 1.30, 95% CI: 0.78, 2.07) periods, although it was not as strong as those with the secretagogues + insulin group. When sensitizer was added (the sensitizer + secretagogues + insulin group), the risk was reduced to OR = 1.33 and was not statistically significant.

3.5.3 Study Power

The power to detect a meaningful odds ratio based on the number of solid tumor cases and exposure prevalence in the recent exposure period was calculated for each exposure group compared to metformin group, with a type 1 error rate of 0.05. Prevalence of metformin, sulfonylurea, metformin + sulfonylurea, metformin + insulin, sulfonylurea + insulin, insulin, TZD, and meglitinides groups were 39.6%, 24.7%, 18.7%, 1.9%, 0.5%, 3.1%, 11.0%, and 0.4%, respectively. For the sulfonylurea, metformin + sulfonylurea, and TZD groups, there was greater than 99% power to detect an odds ratio of 1.5 or

greater. The power was over 80% and 90% for the metformin + insulin and the insulin groups, respectively, to detect an odds ratio of 1.5 or greater. The analyses for the sulfonylurea + insulin and the meglitinides groups were under powered (around 30%) to detect an odds ratio of 1.5 or greater.

CHAPTER IV ANTI-DIABETIC TREATMENT AND RISKS OF CANCERS AT SPECIFIED SITES

4.1. Introduction

In addition to studying the risk of malignant solid tumors as a whole disease entity, cancers of the breast and colon-rectum were examined separately. These sites were chosen because of their frequent occurrence and their positive association with T2DM.

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer death among women [5]. Among neoadjuvant chemotherapy- treated breast cancer patients, metformin was found in prior studies to be associated with better response and insulin was associated with worse response. Also, adding metformin may reduce the increase in risk associated with insulin on breast cancer response [22]. A clinical trial is being conducted to test the protective effect of metformin on breast cancer [24].

Colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer related deaths for both men and women in the U.S. [5]. Several studies have reported that insulin and sulfonylurea therapies significantly increased the risk of colorectal cancer among type 2 diabetes mellitus patients [26, 46].

Our case-control approach adds to the existing evidence by studying a number of different analyses comparing different anti-diabetic treatment regimens at different time periods prior to cancer diagnosis.

4.2. Methods

The same case-control method described in the previous chapter was used for these specified cancers. Within the original cohort, patients identified as having a newly diagnosed cancer of the female breast or of the colon/rectum (both sexes) were defined as cases. Patients without malignant abnormalities were eligible to be selected as controls. In order to minimize confounding by indication, if a patient had a diagnosis of malignancy from other sites or had carcinoma-in-situ prior to the diagnosis of cancer from the specified site, the patient was excluded. For breast cancer, only females without any malignancies could be selected as controls. The diagnosis date of the cancer was set as the cancer index date. Each case was individually matched to four controls by age ± 2 years, gender, and OHA index year ± 1 year. Eligible controls should have had equal or longer duration of follow up in the original cohort compared to their matched case and the same duration of follow-up in the cohort was assigned to the controls. If there were more than four patients without cancer who met the matching criteria for a case, four controls were randomly selected among these eligible patients. A pre-cancer date was defined as six months prior to the cancer index date and anti-diabetic treatment history prior to the pre-cancer date was assessed for recent (from pre-cancer date back 1 year), past (1 year to 3 years), and distant (3 years to 5 years) periods (Figure 3). A separate conditional logistic regression including the drug exposure group and potential confounders as independent variables was conducted to estimate the OR and its 95% CI for each of these periods. Age, gender, OHA index year, and duration of follow-up were controlled through matching in these analyses. Exposures in each specified exposure

period were classified as metformin only (without other OHA or insulin), sulfonylurea only (without other OHA or insulin), metformin + sulfonylurea (without other OHA or insulin), insulin (insulin alone or insulin plus OHAs), and TZD (TZD alone, or TZD plus other OHAs). Because of the limited number of cases, no more detailed classification was done.

4.3. Results

There were total 327 breast cancer cases identified from the study cohort. Fifteen (15) of them who either had a cancer at another site or had a carcinoma-in-situ prior to the diagnosis of breast cancer were excluded. The remaining 312 breast cancer cases were matched to 1,248 female controls. Similar to the results for all solid tumors, demographic and baseline characteristics were well balanced between breast cancer cases and their controls. The mean age was 64.7 (±9.2) years. These data are listed in table 4.1.1.

Table 4.1.2 lists the ORs and their 95% CIs from conditional logistic regression models comparing exposures classified based on pharmacological classification at different periods between breast cancer cases and their controls.

Breast cancer risk was compared between metformin only and the several other exposure classes. No additional covariates changed the unadjusted estimate of the OR by 10%. Compared to metformin only, insulin therapy showed more than a two-fold increased risk (OR = 2.4 and 2.3, respectively) of breast cancer in recent and past periods. This risk remained elevated nearly 2 times, although not significant, in the distant period. Exposure to sulfonylureas, alone or combined with metformin, did not alter the risk of breast cancer

in any period. TZD showed lower risk (OR = 0.64, 95% CI: 0.40, 1.01) of breast cancer in the recent period, but not in past or distant periods.

For colorectal cancer, 374 cases were identified from the cohort. Twenty nine (29) of them who had a previous malignant diagnosis or carcinoma-in-situ were excluded. The remaining 345 colorectal cancer cases were matched to 1,380 controls. Demographic and baseline characteristics were also well balanced between the cases and their controls. The mean age was 67.3 (±8.0) year and 66.7% were males. Demographic and baseline characteristics of colorectal cancer are listed in table 4.2.1.

Table 4.2.2 lists the ORs and their 95% CIs from conditional logistic regression models comparing exposures classified based on pharmacological classification at different periods between colorectal cancer cases and their controls. In addition to the potential confounding variables described in the overall solid tumor section, diagnoses of colon polyps or colon-rectum surgical operations prior to the cancer index date were also tested. However, only HbA1c and BMI changed the unadjusted OR by 10%. In the final models, the matching variables were accounted for and the highest HbA1c and the highest BMI within one year prior to each period were used for adjustment.

Compared to metformin, insulin in recent and distant periods was associated with a 40% - 90% increase in risk of CRC, but was not statistically significant. The sulfonylurea only group had a slightly increased non-significant risk of CRC in the recent period. This risk increased to around 2 - 3 times (OR = 3.09 and 1.96, respectively) and became statistically significant in the past and distant periods. Sulfonylurea in combination with metformin also showed around a 2-fold significant increase in risk of CRC compared to

metformin alone. For TZD, there was an increase in risk of more than 50% (non-significant) in the recent period, and that risk increased to more than 2 times and became significant in the past period (OR = 2.39, 95% CI: 1.39, 4.44) and distant period (OR = 2.85, 95% CI: 1.25, 6.52).

CHAPTER V DISCUSSION AND CONCLUSION

Our study identified a cohort of T2DM patients who were newly exposed to anti-diabetic treatment. Relationships between initial mono-therapy of OHAs and cancer occurrences (both solid tumor and hematological malignancy) were investigated in the cohort analyses. In addition, nested case-control analyses were performed to investigate the relationship between OHAs, insulin, and their combinations and occurrence of malignant solid tumor.

Among T2DM patients survived during follow up, compared to metformin as the initial mono-therapy, there was no difference in risk of malignant solid tumors with other major classes of OHA (sulfonylurea, TZD, or meglitinides). Sulfonylurea and TZD were not associated with elevated risk of hematological malignancy either. Although meglitinides showed a 4-fold increased risk, this finding was based on a small sample size (only 3 cases) with a wide 95% confidence interval. The case-control analyses further supported the findings that these OHA classes or their combinations did not alter the risk of malignant solid tumors.

In contrast, exposure to insulin did show an increased risk of malignant solid tumors compared to metformin. Our study found that recent use of insulin was associated with a 64% higher risk of malignant solid tumors compared to metformin mono-therapy. The risk associated with insulin was modified when combined with different OHAs. When sulfonylurea was added to insulin, the short term risk of cancer was increased to almost 3 times, while adding metformin to insulin changed the relative risk to 1.40, which was lower than insulin alone (1.64). These results remained true for past use of anti-diabetic

treatment. Our results are consistent with the reports from a cohort study [28] in which concomitant metformin therapy decreased the risk of malignancy associated with insulin and with another cohort study [22] in which metformin reduced risk from insulin on breast cancer response. These findings support the hypothesis that anti-diabetic treatments with hyperinsulinemia effects (exogenous insulin or insulin secretagogues) increase the risk for cancer or magnify the insulin effect on cancer; while drugs that stimulate insulin utilization (metformin or TZD) do not have this effect and may even be protective for cancer. In further testing of this hypothesis, it was found that combination therapy with insulin sensitizer and insulin, with or without secretagoues, was associated with a 30% higher risk of cancer compared to sensitizer alone. The risk was increased to almost 2 times (1.76) if no sensitizer was added to insulin (insulin alone). The highest risk of cancer, which was almost 3 times (2.70), was found to be associated with insulin secretagoues combined with insulin. This trend was true in both recent and past periods. The increased risk in the recent and past but not distant periods is suggestive of a more promotion effect, and may have its maximal effect on progression of latent cancer.

When cancers from specified sites were studied, similar results were found for breast cancer. Insulin was associated with a significant increase of more than 2 times in risk of breast cancer compared to metformin. Other OHAs without insulin were not related to altered risk of breast cancer. These results were consistent for all exposure periods. Due to limited sample size, different OHA combination of insulin could not be tested separately.

For colorectal cancer (CRC), both sulfonylurea and TZD (mono- or combo- therapies) were associated with around a 2-fold significant risk increase compared to metformin. The odds of developing CRC were also elevated after starting insulin (OR = 1.41 and 1.91 in the recent and past period, respectively) prior to the cancer development, although this did not reach statistical significance in these data. The finding of elevated risk associated with sulfonylurea was consistent with the findings of a cohort study conducted by Currie et al [28], in which sulfonylurea was associated with 80% more risk of CRC than was metformin. The failure to find a significant risk associated with insulin could easily be due to low power. The upper 95% CI were 2.5 or more in all exposure periods. Also, our base cohort was a newly treated T2DM population with a median follow-up time 3.4 years. Since insulin is usually added in later stages of T2DM, the exposure duration of insulin may not have been long enough to maximize its effect on the risk of CRC. Published data [46] showed that only long term (3 years or longer) exposure to insulin was associated with increased risk of CRC, but not short term exposure.

Increased circulating insulin levels and insulin resistance may have direct effects in vitro and in vivo on growth, proliferation and resistance to apoptosis of cancer cells [51]. Insulin has a known cell proliferation effect through two pathways. One pathway is to directly promote increased levels of Insulin-like growth factor I (IGF-I) and the other is to augment levels of bioactive IGF-I by reducing insulin-like growth factor binding proteins (IGFBP) [11, 52]. IGF and IGFBP regulate key cellular functions through a complex axis. These effects on the IGF axis due to hyperinsulinemia are thought to

possibly promote malignant cells by increasing tumor growth and decreasing cellular apoptosis.

Exogenous insulin use in type II diabetes directly increases insulin levels, and insulin secretagogues, including sulfonylurea and meglitinides, promote increases in circulating insulin levels in the body. Currie et al's cohort study [28] found a 42% and 36% increased risk of solid tumors associated with insulin and sulfonylurea use, respectively. Increased cancer-related mortality was also reported to be related to insulin (90% more) and sulfonylurea (30% more) exposures [27]. However, these risks were not universal for all specific cancers. The elevated risks with insulin and sulfonylureas were only shown for colorectal cancer (almost 2 – 4 folds) and pancreatic cancer (almost 5 times), but not for breast cancer or prostate cancer [28] [46]. Metformin was the comparator group in all of these studies.

On the other hand, insulin sensitizers may have opposite effects on cancer risk. Metformin reduces blood glucose by inhibiting hepatic glucose production and increasing the sensitivity of peripheral tissue to insulin [53]. TZDs are a new class of anti-diabetic OHAs that increase insulin sensitivity in peripheral tissues, thereby decreasing insulin and IGF levels [54, 55]. Thus, metformin and TZD may play protective roles for cancer occurrence through reducing insulin resistance and hyperinsulinemia among T2DM patients. In addition to insulin sensitizer effects, both metformin and TZD have direct antiproliferative effects on cell growth.

Metformin may suppress protein synthesis and cell proliferation directly via activation of the AMP-activated protein kinase (AMPK) through liver kinase B1 LKB1[56] [57, 58].

LKB1 is a tumor suppressor that regulates AMPK levels. Metformin's activation of AMPK and LKB1 has been shown to suppress the mammalian target of the raptomycin (mTOR) signaling pathway, leading to antiproliferative and antiangiogenic effects [57] in mice. Human studies found a 30% more significant risk reduction of cancer and a dose-response relationship [59] comparing metformin users to non-users. Multiple studies have found reduced cancer occurrences among metformin exposed populations compared to other treatment [28, 46].

TZDs are peroxisome proliferator-activated receptor-gamma (PPAR-gamma) ligands that inhibit the growth of PPAR-gamma expression on cancer cells. In studies of rodents, the antiproliferative and proapoptotic effects of TZDs have been found to inhibit mammary carcinogenesis [60, 61], but the effects on colon tumorigenesis are controversial. PPAR ligands have been shown to prevent tumor formation or inhibit the early stages of colon neoplasia in some studies [62-64], but other studies found that TZD increased the frequency and size of tumors[65] or polyps [66] in the colon. Data are limited on the effect of TZD therapy on carcinogenesis in humans. A VA study [25] showed a 33% significant reduction of lung cancer among TZD users compared to nonusers. But this risk reduction was not shown for colorectal and prostate cancers. A case-control study of three major cancers, breast, colon, and prostate, showed no difference in use of TZDs compared to other anti-diabetic treatment between cases and matched controls [26]. Another study focused on adenomatous polyps in colon also did not find the protective effect from TZD [67]. A community based case-control study reported that rosiglitazone

(a TZD) use was associated with 75% increased risk of cancer compared to non-users [68].

Patients who were initially stabilized on metformin could have been at lower baseline risk of cancer. Indeed, these patients were younger and had a lower baseline HbA1c, but were less healthy (with more co-morbidity) and heavier (higher baseline BMI). T2DM patients treated by metformin had a much lower rate of mortality (mostly cardiovascular mortality) than those treated by sulfonylurea [69]. Death without cancer might play a role as a competing risk for the sulfonylurea group. This competing risk might bias the results toward the null, if those who died from other causes were also at higher risk of malignancy. When considering death or cancer as a composite endpoint, initiation with sulfonylurea mono-therapy was associated with a statistically significant 27% increased risk compared to metformin initiation mono-therapy.

This is an observational study and patients have not been assigned to therapy in a random manner; therefore, potential residual confounders are not avoidable. Although this limitation is inherent in the observational nature of the study, we tested all known potential confounders and they did not affect the results in a substantial manner, except for age. An uncontrolled cohort effects due to the large difference of cohort entry years across 14-year time span was a major concern. However, the sensitivity analyses stratifying by the OHA index year didn't change the results much for the sulfonylurea group and the TZD group. The risk of cancer associated with meglitinides was stronger in later years than in earlier years. It is most likely due to the small sample size of meglitinides group in earlier years. Also, we matched cases and controls by cohort entry

years and the results were not different from those in the cohort analysis. Although the large difference in median follow-up duration for the cohort analysis may bias the results when there is a certain possible latency period of cancer, the case-control study matching on duration time would be less prone to this bias. There may still have been residual confounding or unknown confounders, but it is unlikely that this could account for the entire risk of cancer associated with insulin and the modification effect from OHAs (60% to almost 3 times) observed.

The U.K. GPRD is a medical records database, which is collected prospectively in an unbiased manner. It provides objective measures of exposures and outcomes. The database has been widely used as a data source for epidemiologic studies [35-37]. Multiple validation studies have confirmed the reliability of coded diagnoses, especially common outcomes like cancer and diabetes mellitus [35, 44-46]. Almost all (99.7%) prescriptions are recorded [38]. Although dispensing of and compliance with the prescribed medications are not captured in the database, most medications are likely to be filled as recorded due to the low co-payment or no co-payment of medications in U.K.

Bearing in mind that known limitations of any observational study, this study provides evidence that neither sulfonylurea (the risks were around 1.00 and the upper 95% CI did not exceed 1.25) nor TZD (the risks were around 1.10 and the upper 95% CI did not exceed 1.85) substantially alter the risk of overall solid tumors among T2DM patients who survived other causes of death (mainly cardiovascular). Compared to metformin, insulin is associated with higher risk of cancer. This risk may be diminished by concomitant use of metformin, but appears to be magnified by concomitant use of

sulfonylurea. It is uncertain whether this increased risk associated with insulin is related to an adverse effect of insulin or a protective effect of metformin, or both. The risk (or protective) effects of insulin or OHAs may be different for specific cancers. However, our study has limited sample size and duration of follow up to investigate in more detail the relationship of anti-diabetic treatment and specific cancers. It must be remembered that the greatly increased mortality among patients with T2DM is mainly related to cardiovascular complications, rather than cancer. The overall benefit-to-risk value of good glycemic control needs to be evaluated in real world medical practice. Further investigation is a priority to address the relationship between insulin, OHAs and cancer from specified sites.

CHAPTER VI TABLES AND FIGURES

Table 1: Chronic Disease Score

Chronic condition	Medication class(es)	Scoring
Heart disease	(a) Anticoagulants, hemostatics	One class = 3
	(b) Cardiac agents, ACE† inhibitors	Two classes = 4
	(c) Diuretic loop	Three classes = 5
Respiratory illness	(a) Isoproterenol	One class = 2
	(b) Beta-adrenergic, miscellaneous	Two or more classes = 3
	(c) Xanthine products	
	(d) Respiratory products including bronchodilators and mucolytics but excluding cromolyn	
	(e) Epinephrine	
Asthma, rheumatism	Glucocorticoids	Score = 3
Rheumatoid arthritis	Gold salts, chloroquine, etc.	Score = 3
Cancer	Antineoplastics	Score = 3
Parkinson's disease	L-dopa	Score = 3
Hypertension	(a) Antihypertensives (except ACE inhibitors) or calcium channel blockers	If class (a) = 2
	(b) Beta-blockers, diuretics	If class (b) and not (a) = 1
Diabetes	(a) Insulin or oral hypoglycemic	Any class = 2
Epilepsy	Anticonvulsants	Score = 2
Asthma, rhinitis	Cromolyn, leukotriene, antirhinitis, etc.	Score = 2
Acne	(a) Antiacne tretinoin	Either class with two or more prescriptions filled = 1
	(b) Topical antiacne antibiotics	
Ulcers	Histamine$_2$-blockers, proton pump inhibitors, sucralfate	Score = 1
Glaucoma	Ophthalmic miotics	Score = 1
Gout, hyperuricemia	Uric acid agents	Score = 1
High cholesterol	Antilipemics	Score = 1
Migraines	Ergot derivatives, etc.	Score = 1
Tuberculosis	Antitubercular agents	Score = 1

Table 2.1.1 Demographic and Baseline Characteristics of the Cohort
(continue on the next page)

	Metformin N = 39,070	Sulfonylurea N = 16,904	TZD N = 662	Meglitinides N = 208
Gender (Male)	22253 (57.0%)	9993 (59.1%)	334 (50.5%)	116 (55.8%)
Age (years) (n=56844)	39070	16904	662	208
35 – 50	7653 (19.6%)	1978 (11.7%)	104 (15.7%)	40 (19.2%)
51-65	17486 (44.8%)	6383 (37.8%)	287 (43.4%)	90 (43.3%)
66 – 75	10825 (27.7%)	6122 (36.2%)	208 (31.4%)	62 (29.8%)
76 – 80	3106 (8.0%)	2421 (14.3%)	63 (9.5%)	16 (7.7%)
Median	61.0	66.0	63.0	61.5
Mean (SD)	60.5 (±10.7)	64.2 (±10.4)	62.2 (±10.6)	60.4 (±10.9)
Min – Max	35-80	35 – 80	35-80	35 – 80
BMI [1] (n=43306)	31397	11151	598	160
10-<20	80 (0.3%)	270 (2.4%)	5 (0.8%)	4 (2.5%)
20-<25	2120 (6.8%)	2891 (25.9%)	67 (11.2%)	29 (18.1%)
25-<30	10005 (31.9%)	4826 (43.3%)	217 (36.3%)	68 (42.5%)
30-<35	10441 (33.3%)	2120 (19.0%)	163 (27.3%)	30 (18.8%)
>35	8752 (27.9%)	1047 (9.4%)	146 (24.4%)	29 (18.1%)
Median	5	5	6	5
Mean (SD)	32.5 (±6.2)	28.1 (±5.2)	31.6 (±6.4)	29.6 (±6.1)
Min – Max	11.9 – 79.1	12.2 – 78.4	18.8 – 67.8	17.8 – 47.4
BMI Missing	7672 (19.6%)	5750 (34.0%)	64 (9.7%)	48 (23.1%)
HbA1c [1] (n=35915)	26768	8453	577	114
<7	2580 (9.6%)	657 (7.8%)	64 (11.1%)	10 (8.8%)
7-<9	14776 (55.2%)	4085 (48.3%)	373 (64.6%)	58 (50.9%)
9-<12	7573 (28.3%)	2826 (33.4%)	116 (20.1%)	37 (32.5%)
≧12	1839 (6.9%)	885 (10.5%)	24 (4.2%)	9 (7.9%)
Median	8.3	8.7	8.0	8.5
Mean (SD)	8.8 (±1.8)	9.2 (±2.1)	8.4 (±1.6)	8.8 (±1.8)
Min – Max	2.9 – 21.0	2.7 – 36.0	5.5 – 16.5	4.9 – 14.1
HbA1c Missing	12302 (31.5%)	8451 (50.0%)	85 (12.8%)	94 (45.2%)
CDS (n=56844)	39070	16904	662	208
2	7392 (18.9%)	4607 (27.3%)	73 (11.0%)	54 (26.0%)
3 – 5	12535 (32.1%)	5029 (29.8%)	219 (33.1%)	65 (31.3%)
6 – 10	16514 (42.3%)	6189 (36.6%)	322 (48.6%)	70 (33.7%)
>10	2629 (6.7%)	1079 (6.4%)	48(7.3%)	19 (9.1%)
Median	31.4	27.2	30.3	28.0
Mean (SD)	5.6 (±3.0)	5.3 (±3.1)	6.2 (±3.0)	5.5 (±3.3)
Min – Max	2 – 19	2 – 18	2 – 21	2 – 16

[1] Percentage for each category was based on subjects with non-missing values in each exposure group. Percentage for missing was based on total subjects in each exposure group.

Table 2.1.1 Demographic and Baseline Characteristics of the Cohort (continue from the previous page)

	Metformin N = 39,070	Sulfonylurea N = 16,904	TZD N = 662	Meglitinides N = 208
Duration of DM Prior to OHA Start (months) [1] (n=56013)	38582	16572	657	202
≦6	12934 (40.8%)	5578 (39.9%)	166 (27.2%)	55 (29.3%)
7-24	8205 (25.9%)	3219 (23.0%)	197 (32.2%)	51 (27.1%)
25-60	7066 (22.3%)	3002 (21.5%)	173 (28.3%)	49 (26.1%)
>60	3480 (11.0%)	2190 (15.7%)	75 (12.3%)	33 (17.6%)
Median	17.2	18.1	27.2	27.1
Mean (SD)	19.6 (± 32.0)	24.6 (± 40.5)	25.9 (± 32.1)	30.7 (± 40.1)
Min-Max	0 – 514.5	0 – 480.7	0 – 243.9	0 – 295.1
Duration Missing	488 (1.3%)	332 (2.0%)	5 (0.8%)	6 (2.9%)
Cancer Screening	2582 (6.6%)	853 (5.1%)	57 (8.6%)	15 (7.2%)
Smoking Status [1] (n=53981)	37753	15381	655	192
No Smoker	15812 (41.9%)	7197 (46.8%)	276 (42.1%)	93 (48.4%)
Current Smoker	13143 (34.8%)	5133 (33.4%)	218 (33.3%)	70 (36.5%)
Previous Smoker	8798 (23.3%)	3051 (19.8%)	161 (24.6%)	29 (15.1%)
Smoking Missing	1317 (3.4%)	1523 (9.0%)	7 (1.1%)	16 (7.7%)
Previous Prescriptions of OHA	39070	16904	662	208
None	37503 (96.0%)	14349 (84.9%)	267 (40.3%)	106 (51.0%)
≦3	1192 (3.1%)	2086 (12.3%)	295 (44.6%)	69 (33.2%)
>3 and ≦6	344 (0.9%)	428 (2.5%)	81 (12.2%)	26 (12.5%)
>6	31 (0.1%)	41 (0.2%)	19 (2.9%)	7 (3.4%)
OHA Start Year				
1996-<1998	1116 (2.9%)	2248 (13.3%)	0	0
1998-<2000	2363 (6.1%)	3511 (20.8%)	0	41 (19.7%)
2000-<2002	5066 (13.0%)	4407 (26.1%)	18 (2.7%)	67 (32.2%)
2002-<2004	8222 (21.0%)	3137 (18.6%)	110 (16.6%)	72 (34.6%)
≧2004	22303 (57.1%)	3601 (21.3%)	534 (80.7%)	28 (13.5%)
Follow up duration (year) [2]				
Median	2.9	4.9	2.5	5.2
Mean (SD)	3.35 (±2.50)	5.02 (±3.02)	2.56 (±1.47)	5.02 (±2.47)
Min – Max	0.002 –11.99	0.002 –12.0	0.03 –7.11	0.02-8.97

[1] Percentage for each category was based on subjects with non-missing values in each exposure group. Percentage for missing was based on total subjects in each exposure group.
[2] Follow up was started from 1 year after the OHA index date.

Table 2.1.2 Missing Baseline Characteristics by Cohort Entry Year

	Metformin N = 39,070	Sulfonylurea N = 16,904	TZD N = 662	Meglitinides N = 208
Missing HbA1c				
1996-<1998	740 (66.3%)	1588 (70.6%)	-	-
1998-<2000	1448 (61.3%)	2310 (65.8%)	-	25 (61.0%)
2000-<2002	2842 (56.1%)	2588 (58.7%)	3 (16.7%)	42 (62.7%)
2002-<2004	2794 (34.0%)	1241 (39.6%)	21 (19.1%)	21 (29.2%)
≧2004	4478 (20.1%)	724 (20.1%)	61 (11.4%)	6 (21.4%)

Table 2.1.3 Change Exposures during Follow-up

	Metformin N = 39,070	Sulfonylurea N = 16,904	TZD N = 662	Meglitinides N = 208
Duration of the Primary Exposure (months)				
Median	29.4	31.3	28.0	23.8
Mean (SD)	35.1 (± 22.5)	38.2 (± 26.0)	31.1 (± 17.4)	30.2 (± 21.6)
Min – Max	1.3 – 155.9	1.6 – 155.5	4.4 – 91.5	4.6 – 109.5
No Change [1]	21862 (56.0%)	5886 (34.8%)	347 (52.4%)	42 (20.2%)
Change to another mono-therapy [1]	8414 (21.5%)	6121 (36.2%)	188 (28.4%)	95 (45.7%)
Metformin [2]	-	4931 (80.6%)	119 (63.3%)	52 (54.7%)
Sulfonylurea [2]	5891 (70.0%)	-	60 (31.9%)	22 (23.2%)
TZD [2]	2030 (24.1%)	562 (9.2%)	-	3 (3.2%)
Meglitinides [2]	127 (1.5%)	34 (0.6%)	4 (2.1%)	-
Insulin [2]	223 (2.7%)	523 (8.5%)	3 (1.6%)	16 (16.8%)
Other [2]	143 (1.7%)	71 (1.2%)	2 (1.1%)	2 (2.1%)
Add-on therapy [1]	8728 (22.3%)	4822 (28.5%)	125 (18.9%)	65 (31.3%)
Metformin [2]	-	4034 (83.7%)	82 (65.6%)	45 (69.2%)
Sulfonylurea [2]	5017 (57.5%)	-	40 (32.0%)	7 (10.8%)
TZD [2]	3392 (38.9%)	577 (12.0%)	-	7 (10.8%)
Meglitinides [2]	98 (1.1%)	16 (0.3%)	-	-
Insulin [2]	99 (1.1%)	129 (2.7%)	2 (1.6%)	6 (9.2%)
Other [2]	122 (1.4%)	66 (1.4%)	1 (0.8%)	-
Change to other double combo-therapy [1]	43 (0.1%)	40 (0.2%)	1 (0.2%)	5 (2.4%)
Change to triple combo-therapy [1]	23 (0.1%)	35 (0.2%)	1 (0.2%)	1 (0.5%)

[1] Percentages were based on the total number of patients in the exposure group.

[2] Percentages were based on the number of patients in the sub-category.

Table 2.2.1 Incidence Rates of Cancer and Death Without Cancer

Exposure	Events (N)	Person-years	Crude Incidence Rate/ 1000 person-years (95% Confidence Interval)	Age Standardized Incidence Rate/ 1000 person-years (95% Confidence Interval)
Overall Malignancies				
Metformin	1389	131186	10.59 (10.05 – 11.16)	7.49 (6.40 – 9.04)
Sulfonylurea	1165	85075	13.69 (12.93 – 14.50)	8.49 (7.09 – 10.36)
TZD	21	1697	12.37 (8.07 – 18.98)	7.32 (2.59 – 23.32)
Meglitinides	14	1050	13.33 (7.90 – 22.51)	10.40 (2.92 – 43.05)
Solid Tumor				
Metformin	1290	130903	9.85 (9.33 – 10.41)	6.97 (5.92 – 8.48)
Sulfonylurea	1082	84812	12.76 (12.02 – 13.54)	7.88 (6.54 – 9.70)
TZD	20	1696	11.79 (7.61 – 18.28)	6.60 (2.49 – 18.21)
Meglitinides	11	1042	10.56 (5.85 – 19.07)	8.35 (2.18 – 35.04)
Hematological Malignancy				
Metformin	110	127547	0.86 (0.76 – 0.98)	0.61 (0.37 – 1.13)
Sulfonylurea	88	81149	1.08 (0.94 – 1,26)	0.70 (0.39 – 1.33)
TZD	1	1661	0.60 (0.08 – 4.27)	0.72 (0.10 – 5.11)
Meglitinides	3	1014	2.96 (0.95 – 9.17)	2.20 (0.31 – 15.62)
Death without Cancer				
Metformin	2097	131186	15.99 (15.32 – 16.69)	11.81 (10.34 – 13.69)
Sulfonylurea	2605	85075	30.62 (29.47 – 31.82)	17.96 (15.62 – 21.22)
TZD	21	1697	12.37 (8.07 – 18.98)	7.97 (3.15 – 21.53)
Meglitinides	26	1050	24.76 (16.86 – 36.38)	23.54 (7.67 – 90.94)

Table 2.2.2 Hazard Ratios for Cancer and Death without Cancer

Exposure	Unadjusted HR (95% CI)	Age Adjusted HR (95% CI) [1]	Final Adjusted HR (95% CI) [2]
Overall Malignancies			
Metformin	1	1	1
Sulfonylurea	1.25 (1.16 – 1.35)	1.08 (0.99 – 1.17)	1.07 (0.98 – 1.15)
TZD	1.22 (0.79 – 1.87)	1.15 (0.74 – 1.76)	1.16 (0.75 – 1.78)
Meglitinides	1.23 (0.73 – 2.08)	1.23 (0.73 – 2.09)	1.25 (0.74 – 2.11)
Solid Tumor			
Metformin	1	1	1
Sulfonylurea	1.25 (1.15 – 1.35)	1.07 (0.99 – 1.17)	1.06 (0.98 – 1.15)
TZD	1.25 (0.80 – 1.95)	1.17 (0.76 – 1.83)	1.19 (0.76 – 1.85)
Meglitinides	1.05 (0.58 – 1.89)	1.05 (0.58 – 1.90)	1.06 (0.59 – 1.92)
Hematological Malignancy			
Metformin	1	1	1
Sulfonylurea	1.24 (0.93 – 1.65)	1.07 (0.80 – 1.42)	0.98 (0.67 – 1.43)
TZD	0.71 (0.10 – 5.08)	0.67 (0.09 – 4.82)	0.72 (0.10 – 5.18)
Meglitinides	3.39 (1.08 – 10.67)	3.46 (1.10 – 10.89)	4.25 (1.33 – 13.57)
Death without Cancer			
Metformin	1	1	1
Sulfonylurea	1.77 (1.67 – 1.88)	1.40 (1.32 – 1.49)	1.39 (1.31 – 1.48)
TZD	0.85 (0.55 – 1.31)	0.80 (0.52 – 1.22)	0.80 (0.52 – 1.23)
Meglitinides	1.47 (1.00 – 2.16)	1.49 (1.01 – 2.19)	1.51 (1.02 – 2.22)
Cancer or Death			
Metformin	1	1	1
Sulfonylurea	1.57 (1.49 – 1.64)	1.28 (1.22 – 1.34)	1.27 (1.21 – 1.33)
TZD	1.01 (0.74 – 1.36)	0.94 (0.69 – 1.28)	0.95 (0.70 – 1.29)
Meglitinides	1.37 (1.01 – 1.88)	1.39 (1.01 – 1.89)	1.40 (1.03 – 1.92)

[1] Adjusted for age only.

[2] For overall cancer, solid tumor, death without cancer, and cancer or death, age and gender were adjusted and 56,844 patients were included in the models. For hematological malignancy, age, gender and BMI were adjusted and 41,623 patients were included in the model.

Table 2.3.1 Sensitivity analyses on missing values of HbA1c, BMI, DM duration, and smoking status

	N	Unadjusted HR (95% CI)
Overall Malignancies		
TZD		
All Cohort	56,844	1.22 (0.79 – 1.87)
Subjects with non-missing HbA1c	35,912	1.01 (0.60 – 1.68)
Subjects with non-missing BMI	43,310	1.09 (0.68 – 1.76)
Subjects with non-missing DM Duration	46,473	1.03 (0.64 – 1.66)
Solid Tumor		
TZD		
All Cohort	56,844	1.25 (0.80 – 1.95)
Subjects with non-missing HbA1c	35,912	1.01 (0.59 – 1.71)
Subjects with non-missing BMI	43,310	1.11 (0.68 – 1.81)
Subjects with non-missing DM Duration	46,473	1.05 (0.64 – 1.71)
Hematological Malignancy		
Sulfonylurea		
All Cohort	56,844	1.24 (0.93 – 1.65)
Subjects with non-missing HbA1c	35,912	1.46 (0.96 – 2.22)
Subjects with non-missing DM Duration	46,473	1.06 (0.77 – 1.46)
TZD		
All Cohort	56,844	0.71 (0.10 – 5.08)
Subjects with non-missing HbA1c	35,912	0.91 (0.13 – 6.54)
Subjects with non-missing BMI	43,310	0.81 (0.11 – 5.81)
Meglitinides		
All Cohort	56,844	3.39 (1.08 – 10.67)
Subjects with non-missing HbA1c	35,912	2.56 (0.35 – 18.45)
Subjects with non-missing BMI	43,310	4.72 (1.49 – 14.96)
Subjects with non-missing smoking status	53,981	3.76 (1.19 – 11.86)

Table 2.3.2 Hazard Ratios for Cancer during the Primary Exposure Follow-up Period

Exposure	Unadjusted HR (95% CI)	Age Adjusted HR (95% CI) [1]
Overall Malignancies		
Metformin	1	1
Sulfonylurea	1.25 (1.12 – 1.39)	1.05 (0.94 – 1.17)
TZD	1.31 (0.80 – 2.15)	1.24 (0.75 – 2.03)
Meglitinides	1.47 (0.66 – 3.28)	1.48 (0.66 – 3.31)
Solid Tumor		
Metformin	1	1
Sulfonylurea	1.24 (1.11 – 1.39)	1.05 (0.93 – 1.17)
TZD	1.32 (0.79 – 2.20)	1.24 (0.75 – 2.07)
Meglitinides	1.33 (0.55 – 3.21)	1.35 (0.56 – 3.25)
Hematological Malignancy		
Metformin	1	1
Sulfonylurea	1.34 (0.91 – 1.96)	1.10 (0.75 – 1.62)
TZD	1.09 (0.15 – 7.84)	1.02 (0.14 – 7.39)
Meglitinides	3.25 (0.45 – 23.42)	3.30 (0.46 – 23.75)

[1] Adjusted for age only.

Table 2.3.3 Hazard Ratios for Cancer for all Years and Stratified by OHA Year 2004

Exposure	All Years Age Adjusted HR (95% CI)	Before Year 2004 Age Adjusted HR (95% CI)	At or After Year 2004 Age Adjusted HR (95% CI)
Overall Malignancies			
Metformin	1	1	1
Sulfonylurea	1.08 (0.99 – 1.17)	1.15 (1.03 – 1.28)	1.08 (0.94 – 1.23)
TZD	1.15 (0.74 – 1.76)	1.03 (0.15 – 7.35)	1.09 (0.70 – 1.70)
Meglitinides	1.23 (0.73 – 2.09)	1.03 (0.49 – 2.17)	1.64 (0.78 – 3.45)
Solid Tumor			
Metformin	1	1	1
Sulfonylurea	1.07 (0.99 – 1.17)	1.16 (1.03 – 1.29)	1.06 (0.92 – 1.22)
TZD	1.17 (0.76 – 1.83)	1.11 (0.16 – 7.90)	1.11 (0.71 – 1.75)
Meglitinides	1.05 (0.58 – 1.90)	0.96 (0.43 – 2.15)	1.26 (0.52 – 3.04)
Hematological Malignancy			
Metformin	1	1	1
Sulfonylurea	1.07 (0.80 – 1.42)	1.01 (0.69 – 1.49)	1.24 (0.78 – 1.97)
TZD	0.67 (0.09 – 4.82)	NE	0.71 (0.10 – 5.10)
Meglitinides	3.46 (1.10 – 10.89)	1.80 (0.25 – 13.06)	6.24 (1.53 – 25.55)

HR was adjusted for age only. NE: not estimable

Table 3.1 Demographic and Baseline Characteristics of Malignancy Solid Tumor Cases and Controls

(continue on the next page)

	Cases N = 2403	Controls N = 9612
Gender (Male)	1455 (60.6%)	5820 (60.6%)
Age (years) (n)	2403	9612
35 – 50	106 (4.4%)	412 (4.3%)
51-65	857 (35.6%)	3458 (36.0%)
66 – 75	1077 (44.8%)	4365 (45.4%)
76 – 80	363 (15.1%)	1377 (14.3%)
Median	68	68
Mean (SD)	66.8 (±8.3)	66.7 (±8.2)
Min – Max	38 – 80	37 – 80
BMI (n) [1]	1697	6898
10-<20	20 (1.2%)	77 (1.1%)
20-<25	256 (15.1%)	1068 (15.5%)
25-<30	686 (40.4%)	2804 (40.7%)
30-<35	469 (27.6%)	1876 (27.2%)
>35	266 (15.7%)	1073 (15.6%)
Median	29.3	29.0
Mean (SD)	30.0 (±5.5)	29.9 (±5.6)
Min – Max	12.2 – 62.5	12.8 – 64.7
BMI Missing	706 (29.4%)	2714 (28.2%)
HbA1c (%) (n) [1]	1277	5209
<7	125 (9.8%)	418 (8.0%)
7-<9	692 (54.2%)	2779 (53.4%)
9-<12	388 (30.4%)	1583 (30.4%)
≧12	72 (5.6%)	429 (8.2%)
Median	8.3	8.4
Mean (SD)	8.8 (±2.0)	8.9 (±1.9)
Min – Max	4.1 – 36.0	2.7 – 19.2
HbA1c Missing	1192 (46.9%)	4671 (45.9%)
CDS (n)		
2	532 (22.1%)	2248 (23.4%)
3 – 5	736 (30.6%)	2965 (30.9%)
6 – 10	987 (41.1%)	3767 (39.2%)
>10	148 (6.2%)	632 (6.6%)
Median	5	5
Mean (SD)	5.5 (±3.0)	5.4 (±3.0)
Min – Max	2-17	2-18

[1] Percentage for each category was based on subjects with non-missing values in each exposure group. Percentage for missing was based on total subjects in each exposure group.

Table 3.1 Demographic and Baseline Characteristics of Malignancy Solid Tumor Cases and Controls (continue from the previous page)

	Cases N = 2403	Controls N = 9612
Cancer Screening	131 (5.9%)	593 (6.2%)
Smoking Status [1]		
No Smoker	887 (36.9%)	4169 (43.4%)
Current Smoker	806 (33.5%)	2558 (26.6%)
Previous Smoker	545 (22.7%)	2183 (22.7%)
Smoking Missing	165 (6.9%)	702 (7.3%)
Duration of DM prior to OHA Start (months) (n) [1]	2391	9553
≦6	14 (0.6%)	38 (0.4%)
7-24	1298 (54.4%)	5304 (55.6%)
25-60	631 (26.4%)	2452 (25.7%)
>60	445 (18.6%)	1744 (18.3%)
Median	20.0	19.6
Mean (SD)	37.8 (±41.0)	37.9 (±41.3)
Min – Max	0 – 526.6	0 – 478.7
Missing	12 (0.5%)	59 (0.6%)
OHA Start Year		
1996-<1998	283 (11.8%)	1155 (12.0%)
1998-<2000	443 (18.4%)	1720 (17.9%)
2000-<2002	612 (25.5%)	2486 (25.9%)
2002-<2004	542 (22.6%)	2238 (23.3%)
≧2004	523 (21.8%)	2013 (20.9%)

[1] Percentage for each category was based on subjects with non-missing values in each exposure group. Percentage for missing was based on total subjects in each exposure group.

Table 3.2: Odds Ratios for Malignant Solid Tumors among Exposures Classified Bases on Pharmacological Classification

Period	**Exposure**	**N**	**Unadjusted OR (95% CI) [1]**	**Adjusted OR (95% CI) [2]**
Recent	Metformin	4549	1	1
	Sulfonylurea	2889	1.11 (0.98 – 1.26)	1.08 (0.93 – 1.25)
	Metformin + Sulfonylurea	2175	1.09 (0.95 – 1.26)	1.14 (0.97 – 1.34)
	TZD	1270	1.07 (0.90 – 1.26)	1.06 (0.88 – 1.27)
	Meglitinides	75	1.10 (0.62 – 1.96)	1.35 (0.72 – 2.53)
	Metformin + Insulin	229	1.37 (0.97 – 1.91)	1.35 (0.94 – 1.94)
	Sulfonylurea + Insulin	67	2.44 (1.46 – 4.08)	2.75 (1.51 – 5.03)
	Insulin	397	1.71 (1.33 – 2.19)	1.64 (1.24 – 2.16)
Past	Metformin	3945	1	1
	Sulfonylurea	2730	1.12 (0.98 – 1.28)	0.96 (0.81 – 1.14)
	Metformin + Sulfonylurea	1854	1.19 (1.02 – 1.39)	1.07 (0.88 – 1.29)
	TZD	926	1.13 (0.94 – 1.37)	0.98 (0.78 – 1.22)
	Meglitinides	85	1.08 (0.63 – 1.86)	1.04 (0.51 – 2.11)
	Metformin + Insulin	112	1.27 (0.78 – 2.06)	1.12 (0.62 – 2.01)
	Sulfonylurea + Insulin	76	1.69 (1.01 – 2.81)	1.67 (0.86 – 3.22)
	Insulin	327	1.34 (1.00 – 1.79)	1.25 (0.87 – 1.78)
Distant	Metformin	2151	1	1
	Sulfonylurea	2008	1.06 (0.90 – 1.24)	0.97 (0.76 – 1.24)
	Metformin + Sulfonylurea	1028	1.11 (0.91 – 1.36)	1.02 (0.75 – 1.39)
	TZD	346	1.01 (0.75 – 1.37)	1.11 (0.74 – 1.67)
	Meglitinides	60	0.58 (0.26 – 1.30)	0.65 (0.21 – 2.01)
	Metformin + Insulin	41	1.83 (0.89 – 3.74)	1.81 (0.73 – 4.51)
	Sulfonylurea + Insulin	35	1.22 (0.55 – 2.70)	0.93 (0.24 – 3.60)
	Insulin	145	1.05 (0.68 – 1.64)	0.92 (0.46 – 1.83)

Conditional Logistic Regression models were used to estimate the ORs and their 95% CIs. Metformin alone group was used as a reference group.

[1] Accounted the matching variables (age, gender, year of OHA index date, and follow up duration).

[2] Adjusted for HbA1c prior to each period.

Table 3.3: Odds Ratios for Malignant Solid Tumors among Exposures Classified Bases on Mechanism of Action on Hyperinsulinemia Effects

Period	**Exposure**	**N**	**Unadjusted OR (95% CI) [1]**	**Adjusted OR (95% CI) [2]**
Recent	Sensitizer	5249	1	1
	Secretagogues	2920	1.10 (0.98 – 1.24)	1.08 (0.94 – 1.25)
	Sensitizer+ Secretagogues	2789	1.06 (0.93 – 1.20)	1.09 (0.95 – 1.26)
	Sensitizer + Insulin	241	1.30 (0.94 – 1.81)	1.30 (0.91 – 1.84)
	Secretagogues + Insulin	67	2.40 (1.44 – 4.01)	2.70 (1.48 – 4.92)
	Sensitizer+ Secretagogues + Insulin	104	1.33 (0.83 – 2.14)	1.33 (0.81 – 2.20)
	Insulin	281	1.85 (1.40 – 2.45)	1.76 (1.29 – 2.40)
Past	Sensitizer	4385	1	1
	Secretagogues	2764	1.11 (0.98 – 1.26)	0.97 (0.82 – 1.15)
	Sensitizer+ Secretagogues	2391	1.18 (1.03 – 1.36)	1.07 (0.90 – 1.27)
	Sensitizer + Insulin	127	1.12 (0.71 – 1.79)	1.07 (0.61 – 1.89)
	Secretagogues + Insulin	80	1.56 (0.94 – 2.60)	1.58 (0.82 – 3.04)
	Sensitizer+ Secretagogues + Insulin	177	1.41 (0.98 – 2.04)	1.33 (0.86 – 2.06)
	Insulin	131	1.44 (0.94 – 2.19)	1.30 (0.78 – 2.07)
Distant	Sensitizer	2279	1	1
	Secretagogues	2033	1.04 (0.88 – 1.22)	0.95 (0.74 – 1.21)
	Sensitizer+ Secretagogues	1281	1.04 (0.86 – 1.26)	0.97 (0.73 – 1.29)
	Sensitizer + Insulin	47	1.48 (0.74 – 2.99)	1.43 (0.59 – 3.45)
	Secretagogues + Insulin	38	1.26 (0.59 – 2.67)	0.84 (0.22 – 3.21)
	Sensitizer+ Secretagogues + Insulin	78	1.06 (0.60 – 1.88)	0.93 (0.41 – 2.12)
	Insulin	58	1.07 (.055 – 2.07)	1.04 (0.31 – 3.45)

Conditional Logistic Regression models were used to estimate the ORs and their 95% CIs. Sensitizer alone group was used as a reference group.

[1] Accounted the matching variables (age, gender, year of OHA index date, and follow up duration).

[2] Adjusted for HbA1c prior to each period.

Table 4.1.1 Demographic and Baseline Characteristics of Breast Cancer Cases and Controls

(continue on the next page)

	Cases N = 312	Controls N = 1248
Age (years) (n)	312	1248
35 – 50	22 (7.1%)	91 (7.3%)
51-65	143 (45.8%)	561 (45.0%)
66 – 75	109 (34.9%)	439 (35.2%)
76 – 80	38 (12.2%)	157 (12.6%)
Median	65.0	65.0
Mean (SD)	64.7 (±9.2)	64.7 (±9.2)
Min – Max	40 – 65	40 – 65
BMI (n) [1]	234	887
10-<20	4 (1.7%)	9 (1.0%)
20-<25	35 (14.9%)	121 (13.6%)
25-<30	69 (29.5%)	290 (32.7%)
30-<35	68 (29.1%)	246 (27.7%)
>35	58 (24.8%)	221 (24.9%)
Median	30.4	30.4
Mean (SD)	31.3 (±6.5)	31.4 (±6.7)
Min – Max	16.1 – 55.5	16.9 – 69.7
BMI Missing	78 (25.0%)	361 (28.9%)
HbA1c (%) (n) [1]	170	679
<7	7 (4.1%)	67 (9.8%)
7-<9	98 (57.7%)	337 (49.6%)
9-<12	60 (35.3%)	212 (31.2%)
≧12	5 (2.9%)	63 (9.3%)
Median	8.5	8.4
Mean (SD)	8.8 (±1.6)	9.0 (±2.0)
Min – Max	5.4 – 16.4	4.9 – 19.0
HbA1c Missing	142 (45.5%)	569 (45.6%)
CDS (n)		
2	73 (23.4%)	237 (19.0%)
3 – 5	94 (30.1%)	444 (35.6%)
6 – 10	124 (39.7%)	494 (39.6%)
>10	21 (6.7%)	73 (5.9%)
Median	5	5
Mean (SD)	5.4 (±3.1)	5.5 (±3.0)
Min – Max	2-17	2-17

[1] Percentage for each category was based on subjects with non-missing values in each exposure group. Percentage for missing was based on total subjects in each exposure group.

Table 4.1.1 Demographic and Baseline Characteristics of Breast Cancer Cases and Controls (continue from the previous page)

	Cases N = 312	Controls N = 1248
Cancer Screening	5 (1.6%)	26 (2.1%)
Smoking Status [1]		
No Smoker	154 (49.4%)	688 (55.1%)
Current Smoker	80 (25.6%)	319 (25.6%)
Previous Smoker	58 (19.6%)	157 (12.6%)
Smoking Missing	20 (6.4%)	84 (6.7%)
Duration of DM prior to OHA Start (months) (n) [1]	310	1239
≦6	14 (0.6%)	38 (0.4%)
7-24	1298 (54.4%)	5304 (55.6%)
25-60	631 (26.4%)	2452 (25.7%)
>60	445 (18.6%)	1744 (18.3%)
Median	18.6	18.3
Mean (SD)	35.8 (±43.9)	32.8 (±32.5)
Min – Max	0 – 374.6	0 – 293.2
Missing	2 (0.6%)	9 (0.7%)
OHA Start Year		
1996-<1998	35 (11.2%)	138 (11.1%)
1998-<2000	56 (18.0%)	235 (18.8%)
2000-<2002	72 (23.1%)	301 (24.1%)
2002-<2004	82 (26.3%)	295 (23.6%)
≧2004	67 (21.5%)	279 (22.4%)

[1] Percentage for each category was based on subjects with non-missing values in each exposure group. Percentage for missing was based on total subjects in each exposure group.

Table 4.1.2: Odds Ratios for Breast Cancer among Exposures Classified Bases on Pharmacological Classification

Period	**Exposure**	N	**Unadjusted OR (95% CI) [1]**
Recent	Metformin	632	-
	Sulfonylurea	308	1.03 (0.72 – 1.47)
	Metformin + Sulfonylurea	258	0.88 (0.59 – 1.31)
	TZD	208	0.64 (0.40 – 1.01)
	Insulin	103	2.38 (1.42 – 3.97)
Past	Metformin	554	-
	Sulfonylurea	273	1.02 (0.70 – 1.49)
	Metformin + Sulfonylurea	222	0.88 (0.58 – 1.34)
	TZD	147	0.92 (0.55 – 1.53)
	Insulin	72	2.28 (1.25 – 4.18)
Distant	Metformin	340	-
	Sulfonylurea	218	0.92 (0.57 – 1.48)
	Metformin + Sulfonylurea	128	1.12 (0.66 – 1.91)
	TZD	52	1.34 (0.64 – 2.78)
	Insulin	30	1.84 (0.74 – 4.54)

Conditional Logistic Regression models were used to estimate the ORs and their 95% CIs. Metformin alone group was used as a reference group.

[1] Accounted the matching variables (age, gender, year of OHA index date, and follow up duration).

Table 4.2.1 Demographic and Baseline Characteristics of CRC Cases and Controls
(continue on the next page)

	Cases N = 345	Controls N = 1380
Gender (male)	230 (66.7%)	920 (66.7%)
Age (years) (n)	345	1380
35 – 50	12 (3.5%)	43 (3.1%)
51-65	113 (32.8%)	460 (33.3%)
66 – 75	160 (46.4%)	649 (47.0%)
76 – 80	60 (17.4%)	228 (16.5%)
Median	69.0	68.0
Mean (SD)	67.4 (±8.1)	67.3 (±8.0)
Min – Max	43 – 80	42 – 80
BMI (n) [1]	229	985
10-<20	2 (0.9%)	16 (1.6%)
20-<25	45 (19.7%)	167 (17.0%)
25-<30	77 (33.6%)	382 (38.8%)
30-<35	70 (30.6%)	273 (27.7%)
>35	35 (15.3%)	147 (14.9%)
Median	29.4	28.9
Mean (SD)	29.6 (±5.1)	29.7 (±5.5)
Min – Max	18.1 – 43.3	16.1 – 52.1
BMI Missing	116 (33.6%)	395 (28.6%)
Cancer Screening	19 (5.5%)	74 (5.4%)
Smoking Status [1]		
No Smoker	152 (44.1%)	585 (42.4%)
Current Smoker	79 (22.9%)	364 (26.4%)
Previous Smoker	85 (24.6%)	343 (24.9%)
Smoking Missing	29 (8.4%)	88 (6.4%)

[1] Percentage for each category was based on subjects with non-missing values in each exposure group. Percentage for missing was based on total subjects in each exposure group.

Table 4.2.1 Demographic and Baseline Characteristics of CRC Cases and Controls (continue from the previous page)

	Cases N = 345	Controls N = 1380
HbA1c (%) (n) [1]	181	771
<7	22 (12.2%)	58 (7.5%)
7-<9	93 (51.4%)	407 (52.8%)
9-<12	56 (30.9%)	246 (31.9%)
≧12	10 (5.5%)	60 (7.8%)
Median	8.2	8.6
Mean (SD)	8.8 (±2.0)	8.9 (±1.8)
Min – Max	4.9 – 16.9	4.7 – 16.7
HbA1c Missing	164 (47.5%)	609 (44.1%)
CDS (n)		
2	91 (26.4%)	336 (24.4%)
3 – 5	97 (28.1%)	399 (28.9%)
6 – 10	135 (39.1%)	558 (40.4%)
>10	22 (6.4%)	87 (6.3%)
Median	5	5
Mean (SD)	5.4 (±3.0)	5.4 (±3.0)
Min – Max	2 - 16	2 – 18
Duration of DM prior to OHA Start (months) (n) [1]	343	1369
≦6	14 (0.6%)	38 (0.4%)
7-24	1298 (54.4%)	5304 (55.6%)
25-60	631 (26.4%)	2452 (25.7%)
>60	445 (18.6%)	1744 (18.3%)
Median	20.5	21.0
Mean (SD)	37.8 (±46.0)	39.7 (±44.7)
Min – Max	3.1 – 526.6	0 – 380.2
Missing	2 (0.6%)	11 (0.8%)
OHA Start Year		
1996-<1998	52 (15.1%)	200 (14.5%)
1998-<2000	65 (18.8%)	274 (19.9%)
2000-<2002	83 (24.1%)	319 (23.1%)
2002-<2004	69 (20.0%)	286 (20.7%)
≧2004	76 (22.0%)	301 (21.8%)

[1] Percentage for each category was based on subjects with non-missing values in each exposure group. Percentage for missing was based on total subjects in each exposure group.

Table 4.2.2: Odds Ratios for Colorectal Cancer among Exposures Classified Bases on Pharmacological Classification

Period	**Exposure**	N	**Unadjusted OR (95% CI) [1]**	**Adjusted OR (95% CI) [2]**
Recent	Metformin	630	-	-
	Sulfonylurea	443	1.18 (0.84 – 1.66)	1.20 (0.81 – 1.78)
	Metformin + Sulfonylurea	301	1.69 (1.15 – 2.47)	1.80 (1.18 – 2.75)
	TZD	187	1.47 (0.95 – 2.28)	1.54 (0.96 – 2.54)
	Insulin	98	1.64 (0.92 – 2.92)	1.41 (0.75 – 2.67)
Past	Metformin	492	-	-
	Sulfonylurea	388	1.69 (1.17 – 2.42)	3.09 (1.89 – 5.06)
	Metformin + Sulfonylurea	275	1.70 (1.12 – 2.58)	2.39 (1.43 – 4.01)
	TZD	148	1.95 (1.21 – 3.13)	2.49 (1.39 – 4.44)
	Insulin	77	1.46 (0.74 – 2.89)	1.91 (0.82 – 4.43)
Distant	Metformin	288	-	-
	Sulfonylurea	282	1.51 (0.97 – 2.37)	1.96 (1.10 – 3.49)
	Metformin + Sulfonylurea	174	2.54 (1.26 – 5.14)	1.96 (1.00 – 3.85)
	TZD	61	2.54 (1.26 – 5.14)	2.85 (1.25 – 6.52)
	Insulin	37	1.25 (0.47 – 3.33)	0.72 (0.15 – 3.53)

Conditional Logistic Regression models were used to estimate the ORs and their 95% CIs. Metformin alone group was used as a reference group.

[1] Accounted the matching variables (age, gender, year of OHA index date, and follow up duration).

[2] Adjusted for HbA1c and BMI.

Figure 1: Cohort Selection

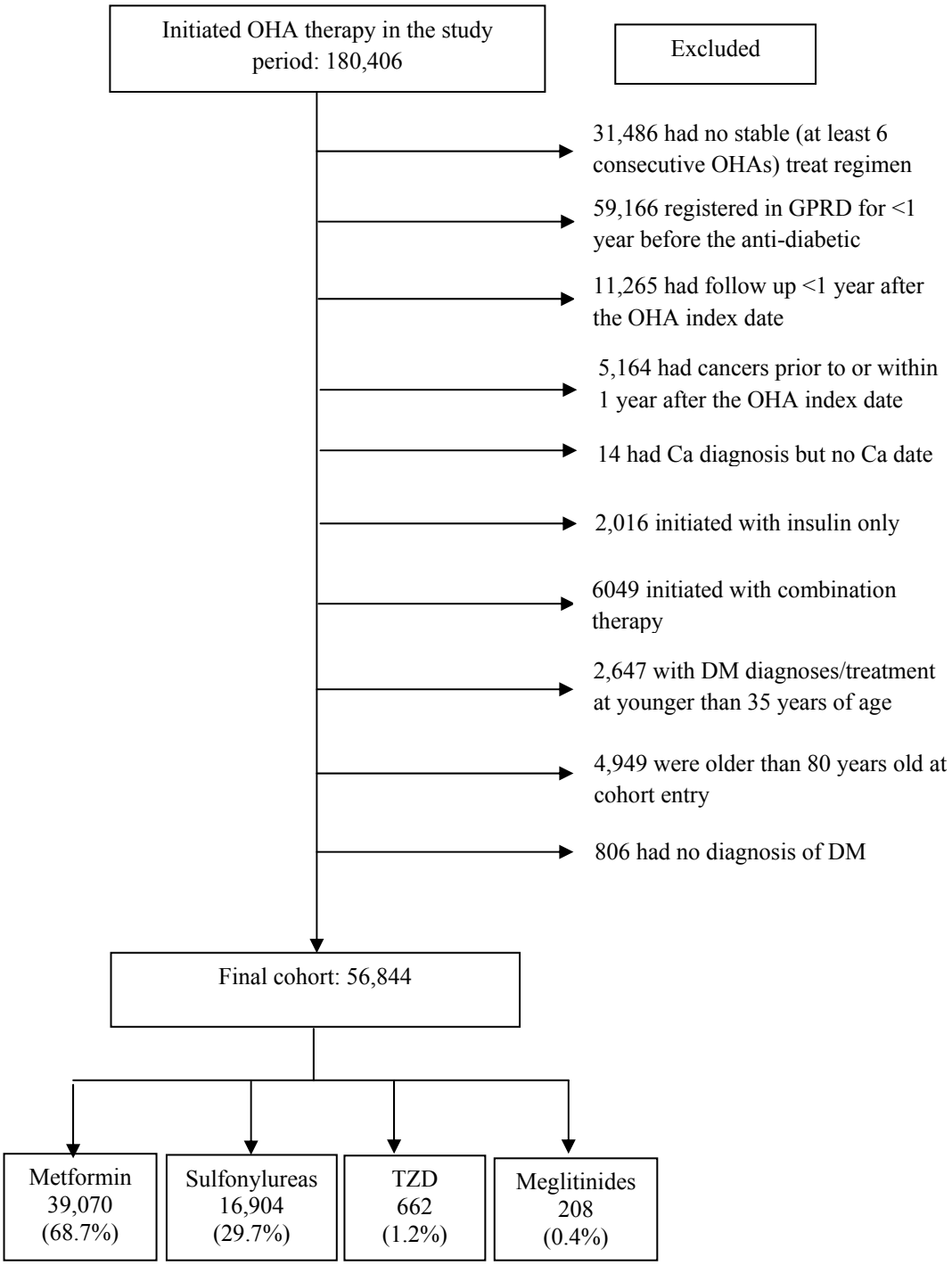


Figure 2.1: Assumption Check Plot for Overall Cancer

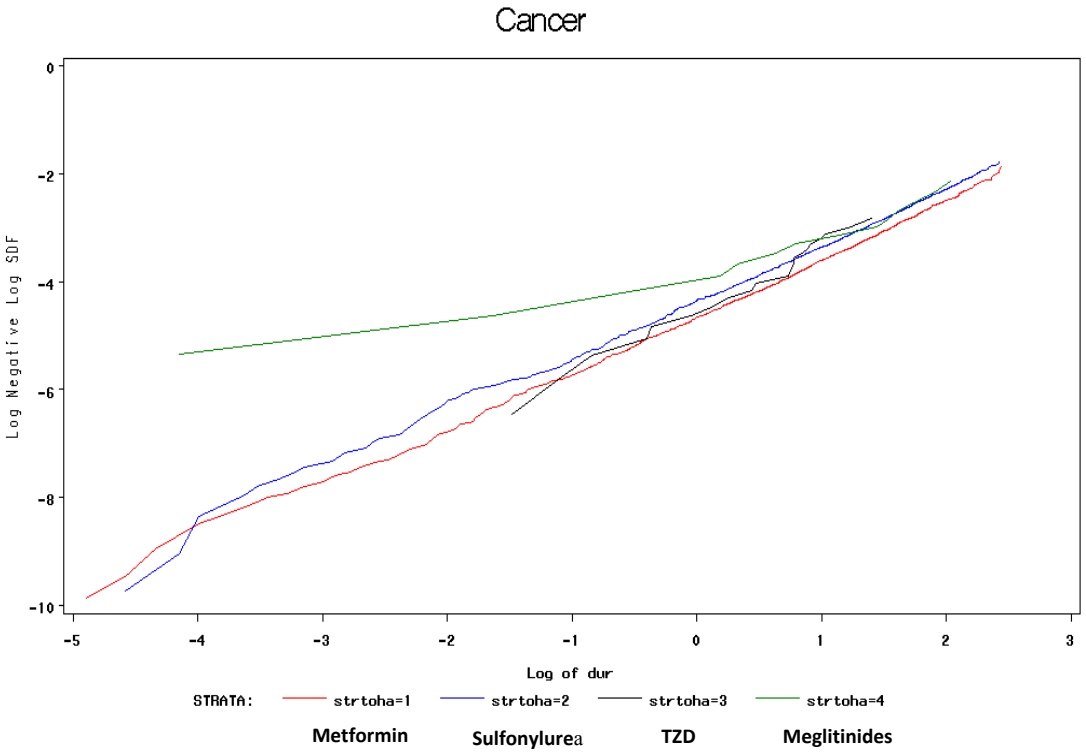


Figure 2.2: Assumption Check Plot for Malignant Solid Tumor

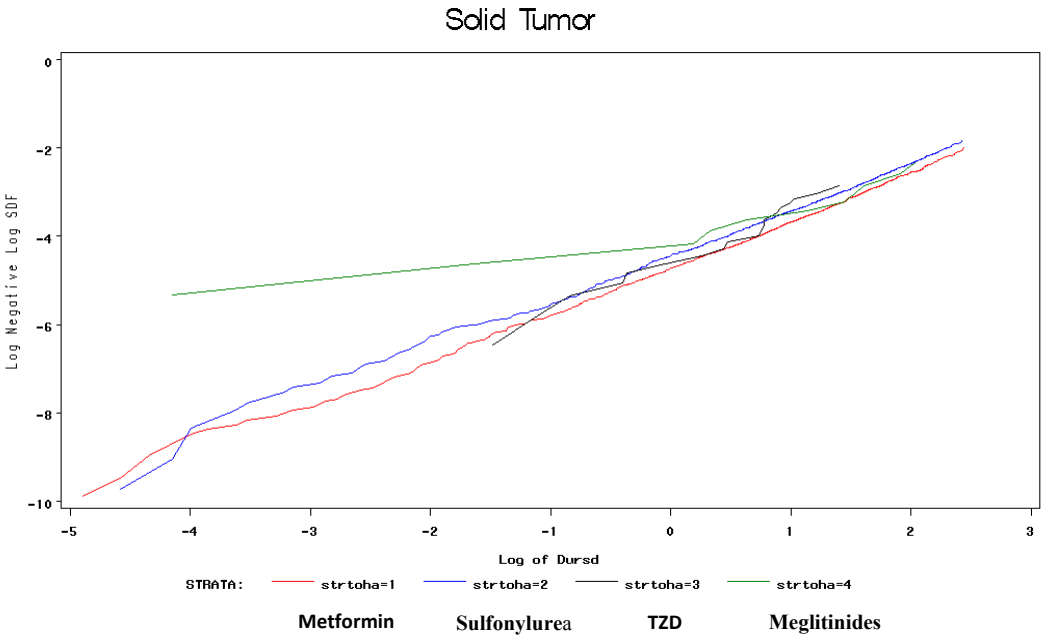


Figure 2.3: Assumption Check Plot for Hematological Malignancy

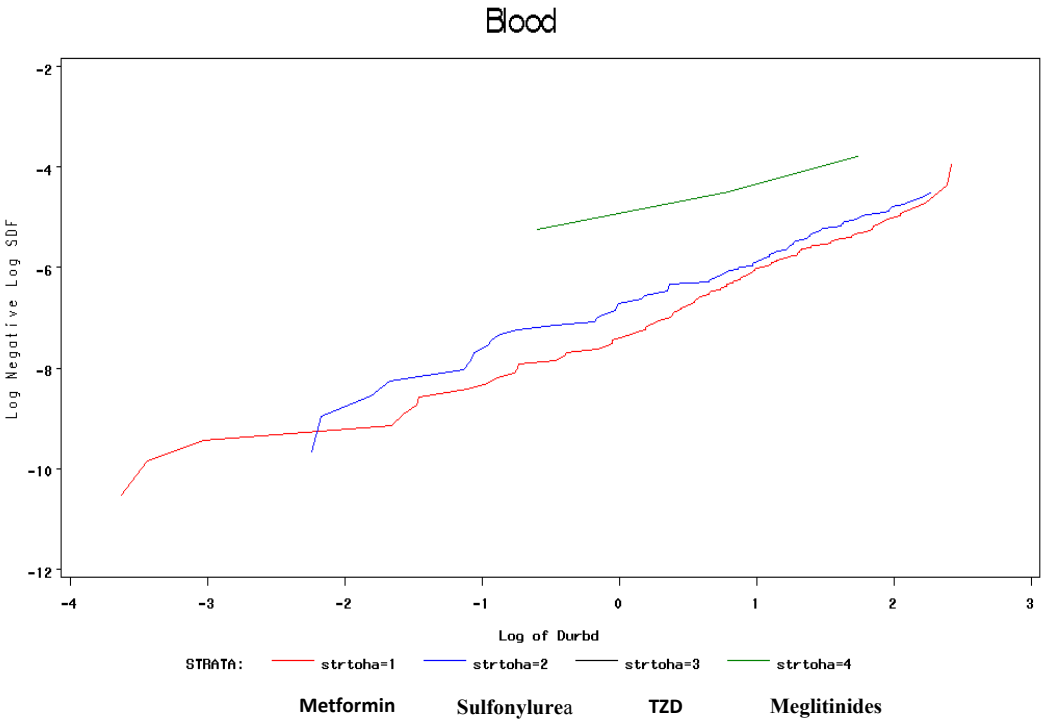
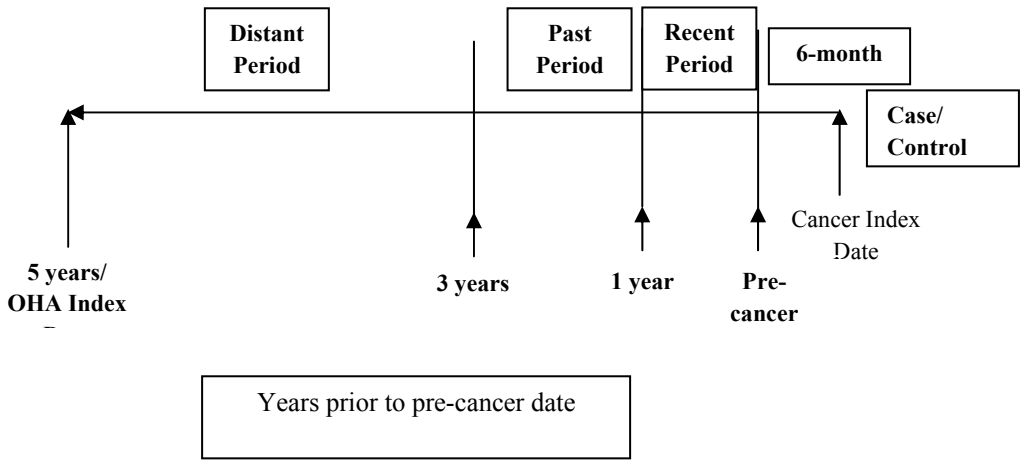


Figure 3: Exposure Windows for the Cases and Controls



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