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Diabetes and Cancer in Lithuania: Epidemiology, Interaction and Importance for Disease Control

DOCTORAL DISSERTATION

Medical and Health Sciences,
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LINKEVIČIŪTĖ-ULINSKIENĖ

Diabetas ir vėžys Lietuvoje: epidemiologinė situacija, šių ligų tarpusavio sąsajos ir jų svarba ligų klinikinei kontrolei

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ABBREVIATIONS

ATP – adenosine triphosphate
AMPK – adenosine monophosphate-activated kinase
CI – confidence interval
CVD – cardiovascular diseases
DNA – deoxyribonucleic acid
DPP-4 – dipeptidyl peptidase-4
GLP-1 – glucagon-like peptide 1
HR – hazards ratio
IDF – International Diabetes Federation
IGF-1 – insulin-like growth factor-1
IGF-1R – insulin-like growth factor-1 receptor
IR – insulin receptor
JAK/STAT – Janus kinase/signal transducers and activators of transcription
LKB1 – liver kinase B1
MAPK – Ras-Raf-mitogen activated protein kinase
mTOR – mammalian target of rapamycin
OR – odds ratio
PI3K – phosphoinositide 3-kinase
PPAR – peroxisome proliferator–activated receptor
SGLT-2 – sodium-glucose co-transporter-2
SIR – standardized incidence ratio
SMR – standardized mortality ratio
T2DM – type 2 diabetes mellitus
TZDs – thiazolidinediones
VEGF – vascular endothelial growth factor

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LIST OF PUBLICATIONS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. **Linkeviciute-Ulinskiene D**, Patasius A, Zabuliene L, Stukas R, Smailyte G. *Increased Risk of Site-Specific Cancer in People with Type 2 Diabetes: A National Cohort Study*. Int J Environ Res Public Health. 2019 Dec 30;17(1):246. https://doi.org/10.3390/ijerph17010246

II. Kincius M, Patasius A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Smailyte G. *Reduced risk of prostate cancer in a cohort of Lithuanian diabetes mellitus patients.* Aging Male. 2020 May 15:1-6. https://doi.org/10.1080/13685538.2020.1766013

III. Dulskas A, Patasius A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Urbonas V, Smailyte G. *Positive effect of metformin treatment in colorectal cancer patients with type 2 diabetes: national cohort study*. Eur J Cancer Prev. 2019 Sep 16. https://doi.org/10.1097/CEJ.0000000000000547

IV. Dulskas A, Patasius A, Kaceniene A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Smailyte G. *A Cohort Study of Antihyperglycemic Medication Exposure and Gastric Cancer Risk.* J Clin Med. 2020 Feb 5;9(2):435. https://doi.org/10.3390/jcm9020435

V. **Linkeviciute-Ulinskiene D**, Kaceniene A, Dulskas A, Patasius A, Zabuliene L, Smailyte G. Increased Mortality Risk in People with Type 2 Diabetes Mellitus in Lithuania. Int J Environ Res Public Health. 2020;17(18):6870. https://doi.org/10.3390/ijerph17186870

VI. **Linkeviciute-Ulinskiene D**, Patasius A, Kincius M, Zabuliene L, Smailyte G. *Preexisting diabetes, metformin use and long-term survival in patients with prostate cancer.* Scand J Urol. 2020 Aug 4:1-7. https://doi.org/10.1080/21681805.2020.1798502

VII. Dulskas A, Patasius A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Urbonas V, Smailyte G. *Metformin increases cancer specific survival in colorectal cancer patients – national cohort study*. Cancer Epidemiology. 2019 Sep 3;62:101587. https://doi.org/10.1016/j.canep.2019.101587

VIII. Dulskas A, Patasius A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Smailyte G. *A cohort study of antihyperglycemic medication exposure and survival in patients with gastric cancer.* Aging-US. 2019 Sep 13;11. https://doi.org/10.18632/aging.102245

1. INTRODUCTION

1.1. The Research Problem and Relevance of the Study

For the past two centuries, life expectancy has steadily increased by a quarter of a year per year, more than doubling the expected life span of a person. This has led to longer and probably better lives, increased population size and fuelled the economy (1). Nevertheless, from the healthcare point of view, aging has contributed to a higher amount of chronic diseases and patients with multimorbidities, which may affect up to 95% primary care patients aged 65 years and older (2). Both cancer and type 2 diabetes mellitus (T2DM) are age-related diseases. According to a study from the United States, diabetes mellitus (diabetes) is among the 10 most common co-occurring chronic conditions among patients with cancer aged 65 years or older (3). Additionally, about 8 to 18% of patients with cancer are estimated to have diabetes (4).

Patients with multimorbidity are an extra burden for healthcare resources and raise addition treatment difficulties, which is why improvement of the strategies for the management and raising awareness of multimorbidity is prioritized across the globe (5). Currently, there is a trend of shift from the traditional disease-centered approach, to the individual, patient-based strategy of problem solving among health researchers and clinicians. However, the evidence on prevalence, multimorbidity trends, and determining factors is limited (2). Thus, there is substantial lack of knowledge to support decision-making and health policy establishment, concerning patients with multiple illnesses.

The Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases in 2011 acknowledged that "the global burden and threat of non-communicable diseases constitutes one of the major challenges for development in the twenty-first century which undermines social and economic development throughout the world and threatens the achievement of internationally agreed development goals" and recognized "the urgent need for greater measures at the global, regional and national levels to prevent and control non-communicable diseases" (6). However, the measures taken have not yet been adequate enough and the importance of situation analysis as one of the major tools for better management of these diseases has been highlighted in following meetings (7).

Diabetes and cancer are both complex and growing worldwide health problems, which negatively affect both the quality of life and survival of millions of patients. According to the International Diabetes Federation (IDF) data, there were approximately 463 million adults with diabetes in 2019 and the numbers are growing. Furthermore, there are currently over 25 million more people diagnosed with T2DM than the 2010 IDF prognosis for 2025 (8).

Diabetes and its complications have been an increasing burden of mortality and disability globally. The Global Burden of Disease Study 2013 identified diabetes as the ninth major cause of reduced life expectancy (9). Furthermore, it was estimated that diabetes caused 4.2 million deaths in adults aged 20–79 years during 2019, which is 11.3% of global mortality. In addition, half of these deaths are estimated to occur in working-age adults, younger than 60 years (10). Whereas, according to the Global Burden of Disease Cancer Collaboration, there were 24.5 million incident cancer cases and 9.6 million deaths in 2017, making cancer the second leading cause of death globally. Even more, since 2007, cancer incidence increased by one third in ten years (11). In Lithuania, there were 110 thousand people living with diabetes and 86 thousand people with a cancer diagnosis in 2019 (12).

Since the incidence of cancer and diabetes, particularly T2DM, is predicted to increase in the following decades, this emphasizes the relevance of increased attention to both diseases and adaptation of adequate prevention and management strategies in Lithuania and worldwide.

Various research exploring the relationship between cancer and diabetes has been conducted over the previous years, with the identification of a link between both diseases in population-based studies as early as in the 1960s (13). The interactions of cancer and diabetes, mainly T2DM, have been investigated in a wide range of epidemiological studies, leading to several

meta-analyses published in the recent decades. It has been shown that people with T2DM are more likely to develop liver, pancreas, endometrium, colorectal, breast, bladder and kidney cancer. However, the risk of prostate cancer is observed to be lower compared to those without T2DM. For other sites there appears to be no association or the evidence is inconclusive (14, 15).

Cancer development in patients with T2DM is likely to result from general mechanisms that promote cancer initiation or progression due to abnormalities in homeostasis (hyperglycemia, hyperinsulinemia, inflammation) that affect all tissues, and specific, organ-related tumorigenesis (16).

How T2DM influences survival of cancer patients is less clear than the association between cancer risk and T2DM, although some epidemiological studies have shown that cancer mortality risk is higher in patients with diabetes (17, 18). Since diabetes is associated with complications, comorbidities and higher overall mortality (19), this may explain excess mortality in diabetic cancer patients, however, it is still uncertain how much diabetes may affect cancer-specific survival. It is hypothesized that diabetes may directly negatively affect the course of cancer. Furthermore, it is possible that clinicians may avoid certain cancer treatment in diabetes patients (4, 17). The presence of diabetes can also increase cancer recurrence, suggesting a more specific role for diabetes on cancer progression (20).

Additionally, even medications used to treat diabetes can modify the risk of cancer and cancer-related mortality among diabetic patients. So far, there is insufficient data on the effect of diabetes treatment on cancer risk and cancer survival. Individual studies have shown that some antidiabetic drugs such as insulin and secretagogues may be linked with a higher cancer risk, others, for example, incretins are thought to be neutral, and some, such as metformin, may potentially have a protective effect against cancer (21).

Moreover, the increased risk for (and death from) cardiovascular diseases (CVD) in patients with T2DM worldwide is well-recognized (22, 23). Diabetes is also among the leading causes of kidney failure (19, 24). Excess mortality due to infection-related diseases in patients with diabetes has been demonstrated as well (25). Data for other non-vascular causes of death in T2DM patients is insufficient. Indeed, it is a question whether a higher risk for cancer incidence leads to higher risk for cancer-related mortality in patients with T2DM, and what are the other factors that impact mortality risk in T2DM patients.

Good metabolic control, which decreases morbidity and mortality from diabetes-related complications, is an essential part of effective diabetes treatment (26). Selection of adequate medications for each patient is an important clinical decision, so potential drug side effects and comorbidities should be considered. Therefore, scientific evidence on the effect of glucose-lowering drugs on both cancer risk and cancer survival would have important clinical value. Basic research, showing a positive effect of metformin in decreasing cancer risk, suggests a potential opportunity of using this widely available drug in the prevention of cancer in the future.

However, neither diabetes, nor cancer patients can be considered a very homogeneous cohort, with great differences in the disease course and duration, not to mention risk factors, nutritional characteristics, nationality, ethnicity, medications for the treatment of both diseases and comorbidities, etc., which may impact the course of diabetes and the risk or prognosis of cancer. Even after years of various investigations into the topic of diabetes and cancer, there is concern that unquestionable evidence without significant bias and extensive study heterogeneity is lacking (27). Therefore, the association of the two diseases remains a topic that is relevant now and will probably be so in the years to come.

This thesis is based on eight published research articles. Its overall aim was to examine the correlations between T2DM and cancer, as well as mortality in patients with T2DM in Lithuania. Paper I analyzes the risk of all-site and site-specific cancer in the T2DM patient population. Papers II-IV investigate the association between diabetes treatment and risk for some of the most common and deadly cancers: prostate, colorectal and gastric cancer. Paper V analyzes mortality risk in patients with T2DM and factors that affect patient mortality. Papers VI-VIII investigate prostate, colorectal and gastric cancer survival in patients with preexisting T2DM and survival associations with diabetes treatment.

1.2. The Aim of the Study

Hypothesis: Diabetes may influence cancer risk and mortality. Diabetes treatment might affect both cancer risk and survival.

The aim of this thesis: A detailed analysis of the relationship between T2DM and cancer, as well as T2DM mortality in the Lithuanian population.

1.3. The Objectives of the Study

1. To evaluate the risk of different types of cancer in patients with T2DM (Paper I).
2. To investigate the risk of prostate cancer in T2DM patients with regard to medications used for the treatment of T2DM (Paper II);
3. To investigate the risk of colorectal cancer in T2DM patients with regard to medications used for the treatment of T2DM (Paper III);
4. To investigate the risk of gastric cancer in T2DM patients with regard to medications used for the treatment of T2DM (Paper IV);
5. To evaluate T2DM specific mortality risk (Paper V).
6. To investigate the impact of T2DM on prostate cancer survival with regard to medications used for the treatment of T2DM (Paper VI);
7. To investigate the impact of T2DM on colorectal cancer survival with regard to medications used for the treatment of T2DM (Papers VII);
8. To investigate the impact of T2DM on gastric cancer survival with regard to medications used for the treatment of T2DM (Paper VIII).

1.4. The Scientific Novelty of the Study

This doctoral research, which resulted in a total of eleven published papers, is the first study of such magnitude in Lithuania, and to our knowledge, in Europe, that analyzed both the mortality risk, cancer risk and cancer survival of all the nation's T2DM patients by using real-life data from three well-developed registries. Earlier cohort studies usually focused on one specific cancer site, investigated a specific part of a population, or specific region, while other studies relied on self-reports. Furthermore, the investigation of T2DM medication and their possible benefits, other than for glucose-lowering, is an emerging field of interest in the academic world. The strength of this study is that with the help of the insurance database, drug ever-users were identified as users. In many other studies, drug-use was only recorded once at study entry.

1.5. The Practical Value of the Study

This detailed analysis has increased the existing scientific knowledge about the interplay between T2DM and oncological diseases worldwide, as

well as provided new information on the epidemiological situation on Lithuanian patients specifically. More precise risk estimates have been added to the current literature on T2DM and cancer incidence for some of the less common and less studied cancers. Higher risk groups within T2DM patients for increased mortality have been identified and cancer control issues in patients with T2DM in Lithuania have been evaluated. Therefore, this study has created preconditions for the development of disease prevention and better management of both T2DM and cancer patients.

1.6. Defended Statements of the Thesis

1. People with T2DM have a higher risk for cancer of several sites.
2. The risk of prostate cancer is lower in men with T2DM, and metformin use may have a beneficial effect.
3. People with T2DM have a higher risk of colorectal cancer, however, metformin use may have a beneficial effect.
4. People with T2DM do not have a higher risk of gastric cancer, and metformin use may have a beneficial effect.
5. People with T2DM have an excess risk of mortality.
6. Long-term prostate cancer survival is affected by diabetes status and metformin use.
7. Colorectal cancer survival is affected by diabetes status and metformin use.
8. Gastric cancer survival is not affected by diabetes status and metformin use.

2. LITERATURE REVIEW

2.1. Mechanisms of the Association between T2DM and Cancer

T2DM is a chronic progressive disease that is characterized by hyperglycemia. The disease usually begins after several years of insulin resistance and hyperinsulinemia and is usually associated with abdominal obesity, dyslipidemia, and hypertension (28, 29). Insulin resistance in tissues, which are metabolically important, such as fat, liver, and skeletal muscle, leads to an overproduction of insulin and development of hyperinsulinemia. Pancreatic beta-cells, the producers of insulin, eventually decompensate, resulting in the rise of glucose in the blood (30).

The main explanations of the observed relationship between T2DM and cancer are that there may be a causal effect of a combination of hyperinsulinemia, hyperglycemia, and a chronic state of inflammation, factors that affect the complex process of carcinogenesis in several ways (14).

2.1.1. Hyperinsulinemia

Insulin is an essential regulator of cell metabolism and a growth factor (31). Endogenous insulin stimulates hepatic synthesis of insulin-like growth factor-1 (IGF-1), which in turn results in the decrease of IGF-binding proteins, giving rise to bioavailable IGF-1 (21).

Insulin and IGF (1 and 2) are ligands to insulin receptor (IR) isoforms IR-A and IR-B, IGF-1 and IR/IGF-1 receptor hybrids with different affinities and different biologic action (32, 33). In summary, receptor-ligand interaction activates a cascade of processes, which may induce proliferation, anti-apoptosis, invasion and metastasis, all crucial steps in oncogenesis (14). For example, exposure to insulin, through the activation of the IR-A receptor, which is often found to be overexpressed in cancer cells, may provide growth advantage to malignant tumors (34, 35). Additionally, IGF-1, a stronger growth stimulator compared to insulin, can activate the IR, IGF-1 receptors, and hybrid receptors, which are also often overexpressed in cancer cells (36, 37).

When insulin binds to the IR, it principally activates the phosphoinositide 3-kinase/akt-mammalian target of rapamycin (PI3K–mTOR) signal transduction pathway, responsible for insulin’s metabolic actions. Whereas, when IGF-1 and IGF-2 interact with IGF-1R, both PI3K-mTOR and Ras-Raf-mitogen activated protein kinase (MAPK) pathways are activated,

leading to regulation of gene expression and control of cell growth and differentiation (31, 35). Interestingly, insulin resistance primarily affects the metabolic pathway. As a result, the compensatory rise in insulin leads to overstimulation of the mitogenic pathway (38).

2.1.2. Hyperglycemia

Hyperglycemia is usually present together with hyperinsulinemia, making it difficult to assess the role of elevated blood glucose separately. It is thought that hyperinsulinemia is more important in cancer development and progression. On the other hand, cell proliferation is a process that requires a lot of energy, with the main provider being glucose. Cancer cells use the process of glycolysis to generate adenosine triphosphate (ATP), which is used to promote cell proliferation instead of productive energy generation (39). Because of this aberrant metabolism, malignant cells are more susceptible to the lack of nutrients, however, this possibility is minimized in hyperglycemic states (40).

Furthermore, hyperglycemia has been shown to upregulate microRNA-467, a suppressor of the antiangiogenic protein thrombospondin-1, thus leading to endothelial dysfunction and neoangiogenesis and favoring tumor growth (41). Whereas another important metabolic regulation process, promoted by the 5'adenosine monophosphate-activated kinase (AMPK) may be compromised in the state of hyperglycemia, because its activation requires energy deficit. AMPK is responsible for restoration of energy balance by activation of lipid oxidation and glucose uptake, leading to energy production and inhibition of protein synthesis and cell-cycle progression, consumers of energy (42). Finally, cancer may be promoted by oxidative stress and inflammation caused by the interaction of hyperglycemia-associated advanced glycation end products with their receptors (43).

2.1.3. Obesity

Most of T2DM patients are overweight or obese. Hyperinsulinemia induces chronic adipocyte inflammation leading to a rise in cytokines and changes in the levels of adipokines, leptin and adiponectin (44). Leptin overexpression upregulates vascular endothelial growth factor (VEGF), an angiogenic factor which plays an important role in cancer development (45).

Furthermore, cellular structures such as deoxyribonucleic acid (DNA), proteins and lipids may be damaged by reactive oxygen species, which are

overproduced in states of inflammation, contributing to malignant cell transformation (46). Moreover, the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway in cancer cells is activated by local cytokine production, stimulating cell proliferation, differentiation, cell migration and apoptosis (47).

2.1.4. Local mechanisms

Apart from the general mechanisms discussed above, it has been hypothesized that T2DM might increase cancer risk in some sites more than others due to specific organ metabolism and function, like in the pancreas and liver, where cancer risk is up to 3 times higher in diabetic patients. For example, diabetes may be a direct risk factor for liver cancer or maybe the interplay of common risk factors, such as non-alcoholic fatty liver disease, insulin resistance and subsequent inflammation, plays a larger role (48). It is speculated that the pancreas may be extra sensitive to cancer development in hyperinsulinemic states because of exposure to elevated insulin concentrations, due to common blood circulation with insulin-secreting beta cells (49).

Also, hepatic insulin resistance caused by obesity may affect the metabolism of sex hormones, leading to higher levels of bioavailable estrogen, which promotes cell proliferation by estrogen receptor activation in malignant cells, thus increasing breast and uterine cancer risk (50).

Whereas the lower risk for prostate cancer in men with T2DM can be associated with decreased testosterone, which is common in T2DM patients (51). Additionally, HNF1B gene variants that protect carriers against prostate cancer, but predispose to T2DM, have been found, and provide another theory for a possible mechanism (52).

2.2. Other Factors Contributing to the Link between Diabetes and Cancer

In addition to the various biological mechanisms, associated with T2DM, which may lead to cancer development and progression, both of the diseases share common risk factors. To begin with, both diabetes and cancer become increasingly common with age (53, 54). Also, race and ethnicity might contribute, as incidence of cancer and diabetes is different among various populations (55). Moreover, adiposity raises the risk for many types of cancer, such as breast, colorectal, endometrium, pancreas, liver and kidney

(56-58). Other life-style factors, such as smoking and alcohol overconsumption, may increase risk for both T2DM and several types of cancer, whereas physical activity may decrease T2DM and cancer risk or even positively affect the outcomes of both diseases (59-61).

Furthermore, eventually can various chronic T2DM complications arise, reducing cardiovascular, hepatic and renal function and compromising T2DM patient ability to deal with concomitant diseases such as cancer, or to withstand certain treatments like chemo-and radiotherapy (16).

Reverse causality is another potential alternative explanation for the observed associations, such as in T2DM and risk of developing hepatocellular and pancreatic cancer, because these cancers can lead to dysfunction of insulin secretion, glucose metabolism, and gluconeogenesis (62).

Another theory is that ascertainment bias might exist since there is heightened medical investigation of diabetic patients, particularly with a new diagnosis of T2DM, but studies have found significant associations even after the exclusion of the first few years of follow-up after diagnosis (63). Furthermore, some studies have shown that women with diabetes undergo mammographic and cervical cancer screening less often than those without diabetes, while screening rates for colorectal cancer have been inconsistent (64-66)

On the other hand, it has been considered that, since T2DM is typically an underdiagnosed disease, and cancer is more frequent in patients with diabetes, the association between these diseases might be undervalued (14).

2.3. Glucose-Lowering Medications and Cancer

Medications used to treat T2DM can also modify the risk of cancer and cancer-related mortality among diabetic patients. There are several classes of glucose-lowering medications, which act in different ways.

The first class includes insulin and insulin analogs, which may have a similar effect to endogenous insulin. However, different insulin analogs may also have different properties, such as time of action or even ligand-receptor interaction, due to structural variations (67). Indeed, basic research has shown that long-acting insulin analogs, due to stronger cross-reactivity with the IGF-1R and primary activation of the IR-A isoform, have a stronger mitogenic potential on malignant cell lines compared to native insulin (68, 69). Even epidemiologic studies have shown higher risk of cancer among insulin, in particular insulin glargine, users (70).

Nevertheless, the clinical importance of these findings has caused considerable debates and, further studies have both criticized study methods and published inconsistent results (71). Several prospective trials found no increase in cancer risk in insulin glargine users (72, 73). Furthermore, data regarding effects of insulin treatment on cancer-specific outcomes is both inconsistent and scarce.

Secretagogues (sulfonylureas and rapid-acting glinides) are a class of glucose-lowering drugs that lower glucose by stimulating endogenous insulin secretion (14). They have been used for T2DM treatment for over a half century (21). While preclinical *in vitro* and *in vivo* studies have suggested potential anti-cancer mechanisms of sulfonylureas (74, 75), the results in epidemiological studies are conflicting, from beneficial to neutral or detrimental correlations on cancer risk or mortality (76-78). There even seems to be differences among specific sulfonylureas, both in their systemic and off-target effects (79). The evidence is still limited for definitive conclusions.

Incretin-based therapies (glucagon-like peptide 1, GLP-1, agonists and dipeptidyl peptidase-4, DPP-4, inhibitors) act by mimicking or enhancing the effect of gut-derived hormones, called incretins. Incretins improve glucose-induced insulin secretion, inhibit postprandial glucagon secretion, and delay gastric emptying (80). Regarding cancer, concerns have been raised after finding increased incidence of medullary thyroid tumors in rodents (81). Moreover, incretins might have a trophic effect on beta-cells, however, no rise in pancreatic cancer risk has been shown in clinical studies yet (82, 83). Overall, since incretin therapy is comparably new, more time for observation is required to establish whether incretins influence cancer risk or outcomes.

One of the most recent drug classes for diabetes treatment are sodium-glucose co-transporter-2 (SGLT-2) inhibitors, which act in a non-insulin dependent way by preventing the kidneys from reabsorbing glucose back into the blood and removing it via urine. Outside from glucose and body weight lowering, favorable effects on cardiovascular risk and renal disease progression have been recently demonstrated (84). Therefore, they are considered to be among the first-choice medications after metformin for diabetes treatment and their use is predicted to grow in the near future. However, a possible increase in the incidence of malignancies were associated with SGLT-2 inhibitors in rodents, although, through a suggested mechanism considered irrelevant to humans (85, 86). In humans, bladder and breast cancer concerns have been raised (87). However, a most recent meta-analysis of 27 randomized controlled trials with a duration of at least a year did not observe a heightened incidence of any type of cancer in SGLT-2

users (88). In summary, as with all new drugs, data is continued to be collected on the potential long-term side effects of this drug class.

Thiazolidinediones (TZDs) are insulin-sensitizing peroxisome proliferator–activated receptor (PPAR) γ agonists, which act by increasing tissue sensitivity to insulin (14). Rodent studies have issued safety concerns regarding PPAR γ agonists as potential carcinogens (89). On the contrary, PPAR γ is a target of interest for cancer treatment, since data from *in vitro* research has highlighted the anti-cancer properties of PPAR γ agonists, such as the ability to inhibit growth and induce cell differentiation or apoptosis (90-92). Clinical evidence with these drugs is limited: a few meta-analyses have reported that pioglitazone use is associated with an increased risk of bladder, but lower risk of colorectal cancer in patients with T2DM (93, 94). However it is questionable, whether there truly exists an association because of treatment, or the correlation has been observed due to diabetes mellitus itself, differences in patient ethnicities and confounding risk factors or even biases in data analyses (95). Therefore, data on TZDs and cancer is inconsistent as well.

Last, but not least, and of particular interest are biguanides, of which metformin is the most common drug to be used for the treatment of T2DM worldwide. Research, showing a positive effect of metformin in decreasing cancer risk or mortality, suggest a potential opportunity of using this product in the prevention and management of cancer in the future.

Metformin acts by promoting hepatic adenosine 5′-monophosphate-activated protein kinase (AMPK) phosphorylation, leading to the inhibition of gluconeogenesis and decrease in circulating insulin levels (21, 96). It is considered that metformin may exhibit its anti-cancer effect both by direct tumor growth inhibition and indirectly, by reducing hyperglycemia and acting against hyperinsulinemia (97, 98). *In vitro* models suggest that the underlying mechanism of metformin action is suppression of the mammalian target of rapamycin (mTOR), by activation of the liver kinase B1 (LKB1) dependent AMPK pathway, resulting in the inhibition of protein synthesis in cancer cells and cell proliferation (99, 100). This mechanism has been confirmed in experimental rodent models with intestinal polyps (101). Metformin has been reported to inhibit prostate cancer cell proliferation by suppression of cyclin D1, which is important in cell cycle progression and androgen-dependent transcription (102). Metformin also reduces cancer cell viability and enhances apoptosis through down-regulation of androgen receptors in prostate cancer (103). Apart from previously described mechanisms of metformin action against tumorigenesis, metformin has been shown to inhibit epithelial-mesenchymal transition, which is one of the main

agents contributing to tumor spread, in human gastric cell line (104). Also, metformin may activate the immune system, eradicate cancer stem cells, suppress cell proliferation or induce cell cycle arrest and/or apoptosis and many others protective mechanisms (105). However, the experimental models that have shown these antineoplastic effects often used supratherapeutic doses (106).

On the other hand, several meta-analyses of observational studies have shown lower risk for liver, colorectal, and postmenopausal breast cancer in diabetic metformin users (107-109), and no correlation with prostate cancer risk (110). Smaller cohort studies are heterogeneous and have shown mixed results among various cancer sites.

Metformin use has also been associated with lower risk of cancer-related mortality in endometrial cancer, lung cancer, prostate cancer and colon cancer among people with T2DM in some studies (111-114). Interestingly, positive results have been published on metformin use as adjuvant therapy in colorectal and prostate cancer (115). Currently, over 100 clinical trials are evaluating metformin treatment on cancer risk and outcomes in various populations (116).

Therefore, because of its promising qualities, metformin has been the primary focus in the studies of this thesis which investigated specific cancer risk and survival.

2.4. Review of Earlier Clinical Studies

2.4.1. T2DM and Cancer Risk

A retrospective cohort study in Denmark showed an overall 10% higher risk for cancer for both men and women, with highest risk of hepatic, pancreatic, kidney, and corpus uteri cancer (117). Another cohort study from Tyrol, Austria, revealed a neutral risk for all-site cancer, with significantly higher risk for cancer of the pancreas and corpus uteri in women, and of the liver and pancreas in men (118). A recent Finish cohort study showed an 18% higher risk of cancer for diabetic women and 14% for diabetic men, with the liver and pancreas being the sites at highest risk among both sexes (119). According to a recent meta-analysis of 121 cohorts (19,239,302 individuals; 1,082,592 events) on all-site cancer risk, the risk of cancer among patients with diabetes is shown to be higher: the pooled adjusted relative risk (RR) for all-site cancer associated with diabetes was 1.27 (95% CI = 1.21; 1.32) in women and 1.19 (95% CI = 1.13; 1.25) in men (120).

Results on site-specific cancer incidence have been published in several meta-analyses (58, 121-130). A liver cancer risk meta-analysis by Wang et al., 2012, showed a combined risk estimate for hepatocellular cancer of 2.31 (95% CI = 1.87; 2.84) among diabetic individuals (121). A more recent meta-analysis of cohort studies on T2DM and sex differences in liver cancer by Wang et al., 2016, associated T2DM with an elevated liver cancer incidence in both men (summary RR = 2.16, 95% CI = 1.74; 2.69) and women (summary RR = 1.85, 95% CI = 1.40; 2.44) (58). In addition, the study showed that T2DM and liver cancer association is confounded by smoking and body mass index in both men and women. Results revealed a significantly stronger T2DM and liver cancer association in non-Asian than in Asian women and men.

A meta-analysis by Song et al., 2015, found that long diabetes duration was associated with a 1.5- to 1.7-fold higher risk of pancreatic cancer (122). Although reverse causality has been suspected, constant elevated risk of pancreatic cancer after longer periods of follow-up demonstrate that this is doubtful (63, 122).

A meta-analysis on kidney cancer risk by Bao et al., 2013, showed a slightly higher risk association in women (RR = 1.47, 95% CI = 1.18; 1.83) than in men (RR = 1.28, 95% CI = 1.10; 1.48). Analyses indicate that the risk of kidney cancer, associated with T2DM, is independent of alcohol consumption, BMI, obesity, and smoking (123).

A meta-analysis by Yeo et al., 2014, investigated thyroid cancer risk in T2DM. It showed a 30% higher risk of thyroid cancer in women, but not in men (124). However, a later prospective study by Luo et al. performed in the US of 147 thousand postmenopausal women showed no significant association between diabetes and thyroid cancer, even when diabetes treatment and duration was taken into account (131).

Several meta-analyses of cohort and case-control studies demonstrated a higher risk of colorectal cancer in both women and men with diabetes (125-127). The latest meta-analysis of 38 cohort studies suggested that there was no evidence of sex difference for colorectal cancer among patients with diabetes mellitus compared to those without diabetes mellitus (126). T2DM and colon cancer share common risk factors such as obesity and smoking, but even when adjusted for these factors, the positive association remains (127).

Regarding the associations with T2DM treatment, a case–control study from Denmark found long-term metformin use to be protective, but only in women (132). In a large study from China, authors found that a higher dose of metformin, when compared to a lower dose of metformin, was associated

with 80% reduced risk of cancer development (133). Furthermore, an Irish study compared more than 300 diabetic patients with 3500 non-diabetic patients and observed significant association between high-intensity exclusive metformin use and colorectal cancer-specific mortality reduction (134). Additionally, a one-year long low-dose metformin use has been shown to reduce the number of adenomas or polyps after polypectomy in non-diabetic patients in a randomized control trial from Japan (135).

In contrast, a study from Canada which used the UK Clinical Practice Research Datalink, showed that the use of metformin was not associated with the incidence of colorectal cancer in patients with T2DM, though there was an insignificant trend with slightly lower incidence of colorectal cancer among longer-term users (136). No protective effect of metformin use and risk of colorectal cancer was observed in randomized controlled clinical trials ADOPT or RECORD after analysis of extracted data (137), as well as the nationwide cohort studies from the UK and Germany (138, 139).

There are several epidemiologic studies researching gastric cancer risk, conducted mostly in Taiwan. Lee et al. assessed 800,000 patients with various cancers, including gastric cancer, and showed that metformin use might increase gastric cancer risk by 41% (HR = 1.41; 95% CI = 0.42; 4.73) (140). Hsieh et al. found that patients with T2DM had an insignificantly lower risk of gastric cancer and neither metformin, nor sulfonylureas did not seem to effect it (141). Chen et al. found that during the first four years after diabetes diagnosis, the incidence of gastric cancer was relatively low in diabetic patients (HR = 0.63; 95% CI = 0.42; 0.97). However, later, the diabetic group had a 76% (HR = 1.76, 95% CI = 1.06; 2.91) higher risk of developing gastric cancer than the comparison group (142). This study also found that insulin, metformin, sulfonylureas, TZDs, and non-sulfonylurea insulin secretory analogues had no effect on gastric cancer risk, though alpha-glucosidase inhibitors were associated with a significantly decreased risk of gastric cancer (adjusted HR = 0.38; 95% CI = 0.15; 0.96).

Another nationwide population-based study, also from Taiwan, found that patients with diabetes mellitus had a 49% higher risk of gastric cancer, but thiazolidinedione use was associated with decreased risk (HR = 0.11; 95% CI = 0.02; 0.82). Chang et al. found that sulfonylureas had no effect, meanwhile insulin treatment increased the risk of gastric cancer (crude odds ratio, OR = 2.43; 95% CI =1.89; 3.13) (143). In comparison, a recent Korean study by Kim et al. found that the relative risk of gastric cancer development among metformin users was reduced by up to 43% (HR 0.57; 95% CI: 0.37–0.87) after three years or more of metformin use (144).

Concerning sex-specific cancer sites, it is well-recognized that women with diabetes have about a two-fold higher risk of corpus uteri cancer (128, 129), as well as higher risk of breast cancer. A meta-analysis by Liao et al., 2011, found that the association between diabetes and breast cancer was the most obvious in Europe (RR 1.88, 95% CI 1.56–2.25), followed by America (RR 1.16, 95% CI 1.12–1.20), but it was not significant in Asia (RR 1.01, 95% CI 0.84–1.21) (130).

Men, on the other hand, seem to have a lower risk of prostate cancer, as shown in a recent meta-analysis by Bansal, 2013, were there was a 14% risk reduction in diabetic men (RR = 0.86, 95% CI = 0.80; 0.92). Cohort studies by Turner et al. or Xu et al. analyzed the association between T2DM duration and risk of prostate cancer, bud did not find significant difference (145, 146). Whereas a prospective cohort study from the US reported that the risk of prostate cancer was slightly higher during the first 3 years after diagnosis of diabetes, but reduced after 4 years from T2DM diagnosis (147). Another US study showed that prostate cancer risk was not reduced in the first year after diabetes diagnosis, was lower for men diagnosed for 1–6 years, and was even lower for men who had been diagnosed for more than 6 years after diabetes diagnosis (148). Metformin, as the most common medication used in the management of T2DM, has been suggested to decrease the risk of prostate cancer in earlier studies (149).

2.4.2. T2DM and Mortality Risk

An analysis from the Verona Diabetes Study group of over 7 thousand T2DM patients in Italy, followed-up between 1987 and 1991, showed that diabetic patients had a 42% higher risk of mortality from all causes, compared to the general population (19). CVD, cirrhosis, and diabetes contributed to higher mortality. As in our study, mortality risk from cancer was similar in the diabetic cohort and in the general population. Insulin treatment was strongly associated with mortality from all causes.

Moss et al. studied mortality risk for specific causes in both young onset and older onset (presumably T2DM) diabetes patient groups in Wisconsin, USA, between 1980 and 1988 (150). The authors found similar results for mortality risk from CVD (SMR = 2.3; 95% CI = 2.1; 2.5), diabetes (SMR = 16.8; 95% CI = 14; 19.9), and malignancies (SMR = 0.9, 95% CI = 0.8; 1.2). However, there was no risk association for mortality from external causes. A Finnish study of death causes between 1981 and 1985 for people with drug-treated diabetes showed comparable to ours results, with the youngest

diabetes patients having greatest risk for increased mortality and diabetic women having higher excess risk than men (151).

A collaborative multinational diabetes mortality study from the UK, USA, and Northern Europe included data about base glucose levels and several risk factors from 97 prospective studies (152). In addition to CVD, diabetes was associated with premature death from several cancers, infectious diseases, external causes, intentional self-harm, and degenerative disorders, independent of major risk factors. Fasting glucose levels exceeding 5.6 mmol/L, but not normal glucose levels (3.9 to 5.6 mmol/L), were associated with higher risk for death.

Furthermore, a recently published study from a nationwide complex survey, NHANES, which collected health and nutrition data from the non-institutional civilian United States population in 1999–2010 included 15,513 participants of which 2,396 were diagnosed with diabetes (mainly type 2) (153). The findings showed that diabetes at the baseline was associated with higher mortality risk due to CVD, chronic lower respiratory diseases, influenza and pneumonia, and kidney disease, but not with cancer or Alzheimer's disease. Another recent study from the US National Health Interview data on mortality trends found that from 1988–1994 to 2010–2015, all-cause death rates declined by 20% every 10 years among US adults with diabetes, most in men and adults aged 65–74 years of age, but there was no decline in death rates among adults aged 20–44 years (154). The proportion of total deaths among adults with diabetes from vascular causes declined from 47.8 to 34.1%; however, this decline was offset by increases in the proportion of deaths from non-vascular, non-cancer causes, from 33.5% to 46.5%, suggesting upcoming implications for clinical management of diabetes patients. Another, 24-year follow-up prospective study between 1991 and 2014 from the south of Sweden showed mortality risk to be 47% higher in T2DM patients, with excess mortality mainly attributed to endocrine and CVD, with crude subdistributional hazard ratios of 5.06 and 1.22 (155).

A pooled analysis of 22 studies of the Asia Cohort found that people with diabetes had a 1.89 fold risk of all-cause death compared to patients without, with the highest relative risk of death due to diabetes, followed by renal disease, coronary heart disease, ischemic stroke, and several types of cancer (156). The adverse diabetes-mortality associations were more evident among women and younger adults. A meta-analysis that looked into sex differences in the association between diabetes and risk of CVD, cancer, and mortality of 49 prospective studies found that women had a 13% greater risk of all-cause mortality associated with diabetes, and there was a 30% significantly

greater excess risk of CVD mortality in women with diabetes compared to men (157). Interestingly, a study from Taiwan found that among patients with coronary artery disease, the impact of T2DM on mortality was consistently higher in women than in men, but the differences across sexes were not statistically significant after 1996, that is, after the wide application of coronary stents for CVD treatment (158).

2.4.3. T2DM and Cancer Survival

A study from the UK by Currie et al found that, compared to the non-diabetes group, overall cancer mortality was increased in diabetic patients on monotherapy with sulfonylureas (HR = 1.13, 95% CI = 1.05; 1.21) or insulin (HR = 1.13, 95% CI = 1.01; 1.27), but reduced in those on metformin monotherapy (HR = 0.85, 95% CI = 0.78; 0.93) (159). Similarly, Bowker et al. from Canada showed a higher cancer-related mortality risk in patients on insulin or sulfonylurea monotherapy, compared to metformin users (78). In a smaller prospective study from the Netherlands, Landman et al. found that metformin use was associated with a 57% reduction in all-site cancer-specific mortality and diabetes itself was a worse prognostic factor (160).

Some of the earliest clinical studies showed a positive effect of metformin on prostate cancer survival. Margel et al. found that metformin treatment after the diagnosis of cancer was associated with lower risk of prostate cancer-specific and all-cause mortality in a dose-dependent way (114). Spratt et al. evaluated the effect of metformin in localized prostate cancer treated with external-beam radiation therapy and found that metformin use predicted better outcomes in diabetic patients (161). A recent large study by Richards et al. included 87,344 patients from a US Veterans Affairs databases investigated men treated with androgen deprivation therapy. Both overall and cancer-specific survival was better in men with T2DM who were metformin users, compared to both metformin non-users and men without diabetes (162).

On the other hand, other studies did not seem to find such a benefit of treatment with metformin, such as in the study by Mayer et al. which analyzed survival in 2832 men diagnosed with metastatic castration resistant prostate cancer, treated with docetaxel (163). Zaorsky et al. performed a retrospective review of 3217 patients receiving radiation treatment for prostate cancer and divided them into five subgroups according to diabetes status and diabetes treatment. Only the group of T2DM patients not receiving any medication differed significantly and had increased overall and cause-specific mortality (164). A nested case–control study by Bensimon et

al. of a cohort of 935 men with non-metastatic prostate cancer and preexisting T2DM showed no significant association with use of metformin after cancer diagnosis and prostate cancer survival (165).

A few studies collected data on metformin use prospectively. Jarrard et al. included patients with metastatic prostate cancer, treated with androgen-deprivation therapy (ADT) or ADT and docetaxel. In this study, baseline metformin did not improve prostate cancer outcomes and, furthermore, showed a trend for worse overall survival (HR = 1.47, 95% CI = 0.95; 2.27) (166). Randazzo et al. followed up, for an average of 7.6 years, 4,314 men who underwent PSA-screening, of which 150 used metformin, and found that PSA levels and prostate cancer incidence did not differ, but all-cause mortality was significantly higher among those on metformin, compared to metformin non-users (adjusted OR = 2.50, 95% CI = 1.59; 3.82) (167).

Finally, the latest meta-analysis of 30 studies by He et al. on metformin therapy and prostate cancer incidence and survival, showed that overall survival, cancer-specific survival and recurrence-free survival in prostate cancer is better in patients treated with metformin, with largest survival differences among cancer patients treated with radical radiotherapy (168). A possible antineoplastic effect of metformin for locally advanced and metastatic prostate cancer patients, treated with ADT in combination with radiation therapy is currently under evaluation by multi-arm and multi-stage trial STAMPEDE investigators (169).

Several cohort studies have demonstrated that metformin use increases overall colorectal cancer survival. A retrospective study of almost 5000 patients from the US showed that patients with T2DM and colorectal cancer, receiving metformin as one of their diabetes medications, had a 20 month longer survival (76.9 months), than those who did not receive metformin (170). Similarly, a Danish nation-wide cohort study of more than 30,000 patients with colorectal cancer of which 3391 were diagnosed with diabetes demonstrated that overall mortality was 15% lower in patients treated with metformin, compared to insulin, but there was no significant association with exposure and dose of metformin (171). In a study from US of colorectal cancer patients with diabetes, metformin users had a 13% improved overall survival, despite adjustments for diabetes severity and other risk factors, versus patients taking other glucose-lowering medications, while patients not on any anti-diabetic medications did not differ with respect to overall survival (172).

A few other smaller retrospective analyses showed longer cancer-specific survival in diabetes patients using metformin. For example, one earlier study showed that only high-intensity metformin use was associated with

significantly lower colorectal cancer-specific mortality (HR = 0.44; 95% CI = 0.20; 0.95) (134). Interestingly, comparison of 413 patients diagnosed with colorectal cancer and T2DM in South Korea found colorectal cancer-specific survival benefit associated with metformin use, but the difference was statistically significant only among women (HR = 0.50; 95% CI = 0.29; 0.89), not men (HR = 0.85; 95% CI = 0.59; 1.21) (173). A more recent study from Jordanian found that colorectal cancer and T2DM patients who were metformin users lived significantly longer (89 months vs 36 months) and had longer progression-free survival (47 vs 21 months) than patients who used other glucose-lowering drugs (174).

Alternatively, a study of 2066 postmenopausal women with colorectal cancer from the Women's Health Initiative found no metformin effect on overall or cancer-specific survival (175). Similarly, a study from Northern Ireland with almost 1200 colorectal cancer patients with T2DM showed no protective association between metformin or any other glucose-lowering drug and cancer-specific survival in colorectal cancer patients (176). Another large prospective randomized controlled study, which included patients with resected stage III colon cancer receiving adjuvant chemotherapy did not find differences, associated with metformin use, in any colorectal cancer outcomes (177).

However, a recent meta-analysis on metformin as an adjuvant treatment modality for several cancer locations, including colorectal cancer, found metformin use to be beneficiary in all early-stage colorectal cancer outcomes (115). Additionally, results of a clinical phase II trial, which investigated metastatic colorectal cancer treatment, favored metformin use with conventional chemotherapy in diabetic patients (178).

Gastric cancer survival and insulin use in diabetic Taiwanese patients was assessed by Tseng. People with T2DM had a higher risk of gastric cancer mortality, while insulin use had no effect on mortality in gastric cancer patients (179). On the contrary, Coughlin et al. from the US observed no relation between diabetes and increased gastric cancer mortality, but diabetes treatment was not investigated (18).

Gastric cancer specific survival in diabetic patients was assessed by two other studies. Lee et al. found that metformin use was related to higher overall survival (HR = 0.58, 95% CI = 0.36; 0.93), cancer specific survival (HR = 0.57, 95% CI = 0.33; 0.98), and recurrence-free survival (HR = 0.63, 95% CI = 0.41; 0.98), compared to those T2DM patients who did not receive metformin. Furthermore, metformin treatment prolonged survival in diabetic patients to a rate comparable to that in non-diabetic patients. The cumulative use of metformin was shown to reduce the risk of recurrence, all-cause, and

cancer-specific mortality as well (180). Just recently, Baglia et al. showed worse survival in diabetic patients with gastric cancer who used sulfonylureas (HR = 2.05, 95% CI = 1.09; 3.84) or insulin (HR = 1.45, 95% CI = 0.99; 2.10) and no survival difference in metformin users (HR = 1.01, 95% CI = 0.48, 2.12) (181).

3. RESEARCH DESIGN AND METHODS

3.1. Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki. Due to the design of the study, informed consent of the individuals was not obtained. The protocol of the study was approved by the Vilnius Regional Biomedical Research Ethics Committee (Nr. 158200-17-913-423).

3.2. Study Design and Data Source

The studies in this thesis can be divided into three parts, according to the study objectives. The first part are cancer risk analyses (papers I-IV), the second part is a diabetes mortality risk study (paper V) and the third part are cancer-specific and overall survival investigations (VI-VIII).

All eight papers in this thesis are retrospective cohort studies, conducted using different data sets: healthcare service data from the National Health Insurance Fund (NHIF), population-based Lithuanian Cancer Registry data (all papers) and Causes of Death Register data (paper V).

Lithuania has a compulsory health insurance system; therefore, the vast majority of healthcare services are covered by the National Health Insurance Fund. NHIF database was created in 1999 for the management, storage, analysis, and reporting of the services provided by healthcare organizations. The NHIF database contains demographic data, records on prescriptions of reimbursed medications, entries on healthcare services provided and hospital admissions. It is estimated that the NHIF data includes 100 percent of primary health care visits, 90 percent. secondary and tertiary level visits to medical doctors and 99 percent of hospital admissions (182). An assessment performed by independent European experts in 2019 identified NHIF data as high quality (183). All dispensed medications are coded according to the Anatomical Therapeutic Chemical (ATC) medication classification, and the records include information on type of product, date, and quantity. Information on the diagnosis of T2DM (International Statistical Classification of Diseases and Related Health Problems (ICD)-10 code E11), demographic data (age, sex) and prescribed glucose-lowering medications was obtained from this database.

The Cancer Registry is a nationwide population-based cancer registry that contains personal and demographic information (place of residence, sex, date of birth, vital status), as well as information on diagnosis (cancer site, date of diagnosis, method of cancer verification) and death (date of death, cause of

death) on all people diagnosed with cancer in Lithuania since 1978. All recorded cancers in the Cancer Registry are coded according to the ICD-10-AM. It is a statutory requirement to notify the registry of all cases of malignant neoplasms. The data quality, with regard to completeness and validity of case ascertainment, complies with international standards of cancer surveillance (184). From this database, information on age at Ca diagnosis, date of diagnosis, tumor classification (TNM), date of death and cause of death for cancer patients was obtained.

Underlying causes of death for non-cancer patients were obtained from death certificates (Causes of Death Register).

The records from these three databases were linked by using the personal identification number assigned to all Lithuanian citizens. The data was anonymized for further analysis after record linkage.

Table 1 summarizes the study designs, statistical methods and observed outcomes.

Table 1. Summary of study designs, study population and outcomes for the papers.

	I	II	III	IV	V	VI	VII	VIII
Study design	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Study population	People with T2DM *	Men with T2DM	People with T2DM	People with T2DM	People with T2DM	Men with prostate cancer	People with colorectal cancer	People with gastric cancer
Population size	127,290	64,000	111,109	99,992	89,512	6,689	15,052	8,423
Baseline	1st entry of T2DM under observation period	Entry of T2DM under observation period	Entry of T2DM under observation period	Entry of T2DM under observation period	Previously diagnosed with T2DM and alive on 1/1/2010	Cancer diagnosis from 1/1/2001 until 31/12/2005	Cancer diagnosis from 21/1/2001 until 31/12/2012	Cancer diagnosis from 1/1/2003 until 31/12/2013
Observation period	From 1/1/2000 until 31/12/2012	From 1/1/2000 until 31/12/2016	From 1/1/2000 until 31/12/2012	From 1/1/2001 until 31/12/2012	From 1/1/2010 until 31/12/2017	From 1/1/2001 until 31/12/2016	From 1/1/2001 until 31/12/2017	From 1/1/2001 until 31/12/2017
Outcome	Cancer incidence	Prostate cancer incidence	Colorectal cancer incidence	Gastric cancer incidence	Death	Prostate Ca-specific and overall survival	Colorectal Ca-specific and overall survival	Gastric Ca-specific and overall survival
Exclusion criteria	Cancer before T2DM	Prostate cancer before T2DM and within 1 year after T2DM diagnosis	Cancer before T2DM diagnosis and within 6 months after T2DM diagnosis	Cancer before T2DM diagnosis and within 6 months after T2DM diagnosis	-	<6 months of follow-up, T2DM diagnosed after cancer	Other malignancies before colorectal cancer, T2DM diagnosed after cancer, death certificated only cases	Other malignancies before gastric cancer, T2DM diagnosed after cancer, death certificated only cases

Controls	Sex, calendar year and 5 year age-group adjusted national cancer incidence rates	Sex, calendar year and 5 year age-group adjusted national prostate cancer incidence rates	Sex, calendar year and 5 year age-group adjusted national colorectal cancer incidence rates	Sex, calendar year and 5 year age-group adjusted national gastric cancer incidence rates	Sex, calendar year and 5 year age-group adjusted national death rates	Patients without pre-existing T2DM compared with those who had T2DM	Patients without pre-existing T2DM compared with those who had T2DM	Patients without pre-existing T2DM compared with those who had T2DM
Statistical analysis	SIR	SIR, chi square test for trend	SIR, chi-square test for trend	SIR	SMR, chi-square test for trend	chi square analysis for categorical valuables, Kaplan-Meier survival analysis, Cox proportional hazard models	Kaplan-Meier survival analysis, Cox proportional hazard models, log-rank test	Kaplan-Meier survival analysis, Cox proportional hazard models, log-rank test
Stratification by diabetes treatment	No	Yes, 2 treatment groups+ metformin cumulative dose	Yes, 2 treatment groups + metformin cumulative dose	Yes, 4 treatment groups	Yes, 3 treatment groups	Yes, 2 treatment groups	Yes, 2 treatment groups	Yes, 4 treatment groups

*T2DM status was assigned to patients who were reported as T2DM patients, were older than 40 years at T2DM diagnosis and received prescriptions of glucose-lowering medication; SIR, standardized incidence ratio, SMR, standardized mortality ratio.

3.3. Study Population

For the evaluation of cancer risk for people with T2DM, the cohort was established by identifying all male and female patients with the first entry of T2DM diagnosis (ICD-10-AM code E11) in the NHIF database during the planned observation period. As the diagnoses of T2DM are registered manually into the database by healthcare providers, to increase the specificity of T2DM cases, only patients who were diagnosed at the age of 40 or older and had received prescriptions for reimbursed glucose-lowering medications were included into the study.

Cases with a cancer diagnosis before the diagnosis of diabetes were excluded from the cohort. Papers II-IV had other specific exclusion criteria (Table 1). The cohort exit date was defined as either the date of death, emigration or end of study observation period, whichever came first.

The population cohort of paper V were all T2DM patients who were alive at the beginning of follow up on 1 January 2010. Patients with the same recorded date of diagnosis and date of death and patients with missing information on cause of death were excluded from the cohort.

For cancer survival studies, the study population included patients with prostate (Paper VI), colorectal (Paper VII), and gastric (Paper VIII) cancer, identified at the first time of diagnosis from the Cancer Registry. Information on the diagnosis of T2DM and diabetes treatment was obtained from the NHIF.

3.4. Treatment of Type 2 Diabetes Mellitus in Lithuania

According to the Lithuanian diabetes management guidelines, metformin is the initial oral glucose-lowering drug for T2DM. If metformin is contraindicated, causes side effects, or metformin monotherapy fails to achieve the glycemic goal (HbA1c less than 7%), the treatment is intensified by adding a second line medication, which is generally a sulfonylurea. As a third step, combination therapy with more than two classes of glucose-lowering drugs can be used (adding thiazolidinediones, glucagon-like peptide-1 analogs, or dipeptidyl peptidase-4 inhibitors). Insulin treatment can be initiated after failed combination therapy or at any time depending on the clinical situation. Metformin treatment is usually continued together with insulin (16).

3.5. Exposure Definition

Exposure to glucose-lowering medication was investigated in papers II-VIII. Six months were defined as the shortest duration of exposure to medication required for effect.

Papers II and III evaluated the association between the use of metformin and risk of prostate and colorectal cancer. Patients were stratified into metformin-user and never-user groups. The dose-response relationship by cumulative dose of metformin was also evaluated in papers II and III. This stratification of T2DM patients to groups by metformin use was also applied in papers VI and VII, for the analysis of prostate (paper VI) and colorectal (paper VI) cancer survival according to diabetes treatment, the reference group being cancer patients without T2DM.

In papers IV and VIII, all cohort members were classified into four groups according to treatment: "metformin and other" medication (except insulin) users; "insulin and other" medication (except metformin) users; "metformin and insulin" users; and "sulfonylurea" users, as well as a non-diabetes patient group as reference. Other medications included all other oral antihyperglycemic agents, available as reimbursed prescription drugs in Lithuania during 2000-2012. The list of medications for treatment of T2DM is shown in Table 2.

Table 2. List of medications, prescribed to the patients of the study population for the treatment of T2DM

	List of Medications
1	Biguanides (metformin)
2	Sulfonylureas
3	DPP-4 inhibitors
4	GLP-1 receptor agonists
5	Thiazolidinediones
6	Meglitinides
7	Insulin
8	Metformin+ DPP-4 inhibitor
9	Metformin+ Thiazolidinedione
10	Sulfonylurea+ Thiazolidinedione

For evaluation of mortality risk according to treatment in paper V, cohort members were classified into three groups according to treatment: "oral" medication, "insulin and oral" medication, and "insulin" users. To assess cause-specific mortality risk in the study cohort, common causes of death

were classified into ten broad categories and subcategories according to the ICD-10. The time since the diagnosis of diabetes was also stratified into three groups (1–5, 6–10, and >10 years). Patients with a first diabetes diagnosis between 1999 and 2000 included prevalent cases, therefore, they were excluded from the part of analysis by duration of follow-up.

3.6. Outcomes

The primary outcome for Papers I-IV were site-specific cancer incidence in people with pre-existing T2DM.

The primary outcome for Paper V was cause-specific death in people with T2DM.

The primary outcome measure for papers VI–VII was cancer-specific survival, and the secondary outcome was overall survival. Survival was calculated from the date of cancer diagnosis to the date of death or the end or follow-up.

3.7. Statistical Analysis

For cancer risk evaluation (Papers I-IV), standardized incidence ratios (SIRs) were calculated for site-specific and overall cancer as a ratio of observed number of cancer cases in people with T2DM to the expected number of cancer cases in the underlying general Lithuanian population.

Expected number of cancer cases were calculated by multiplication of the exact person-years under observation in the cohort by sex, calendar year and 5-year-age-group-specific national incidence rates (185). The person-time of observation was computed from the date of the first entry of T2DM diagnosis in the NHIF database until the cohort exit date. For analysis of prostate, colorectal, and gastric cancer risk, SIRs by sex, age of diabetes diagnosis, and use of glucose-lowering medications were computed.

For mortality risk analysis (Paper V), sex, age, and calendar period-standardized mortality ratios (SMRs) were calculated by dividing the observed number of deaths among patients with T2DM by the expected number of deaths according to national rates (186).

The chi-square test for trend was performed in order to evaluate changes in mortality risk of diabetic patients over age groups and time since diabetes diagnosis.

95% confidence intervals for the SIRs and SMRs were estimated assuming the number of observed cases follows Poisson distribution.

For survival analysis, patients were categorized by sex, age at diagnosis of cancer, and stage at diagnosis (TNM Classification of Malignant Tumors).

The chi-square test of independence was used to compare demographic and clinical characteristics between groups.

Kaplan-Meier survival analysis, stratified by exposure group was used to generate survival curves for cancer-specific and overall survival. Survival curves were compared using the log-rank test.

Cox proportional hazards models were used to assess simultaneously the relationship between multiple risk factors and patient's survival time. Univariate Cox proportional hazards models were computed to estimate hazard ratios and their 95% confidence intervals and compare cancer-specific and overall survival differences by separate prognostic factors, such as sex, age at diagnosis and stage at diagnosis, and exposure groups. Later, multivariate Cox proportional hazard models for cancer-specific and overall survival were computed including prognostic factors which had a significant impact on survival as determined by a univariate hazard ratio (HR) with a p-value <0.2. Multivariate adjusted Cox proportional hazards models, including factors such as age and stage at diagnosis and tumor histology, where this data was available, were used to estimate the association of diabetes status on survival and to account for differences in cohort characteristics.

The threshold for statistical significance was set at the conventional level of $\alpha = 0.05$.

Statistical analyses were carried out using either STATA 11 or 15 (Software: Release 11.0 and 15.0 College Station, TX, USA).

3.8. Considerations on Patient Populations and Study Design

There are several strengths and limitations of the studies in this thesis to be considered.

The major strength of this thesis is that the investigation is based on real life data from well-established registries. The studies are based on the whole Lithuanian population with a large sample size and long follow-up time, which is usually hard to achieve in prospective studies. Therefore, selection bias was avoided and it was possible to compare the study population with the national population. Also, the diagnosis of T2DM is well defined and data collection did not rely on self-reports.

Furthermore, by linking data from several registries, we could identify all patients with pharmacologically treated T2DM, such as in Paper V, where those patients, which could have been missed by death registry analysis alone, for whom diabetes might not be listed as an underlying cause of death in the death certificate, were included in the analysis.

In addition, not only have the associations between cancer and T2DM diagnoses been investigated, but also the aspects of diabetes treatment, and in some studies, even the dose of metformin on cancer risk and survival has been evaluated.

The limitations of our study are those, typically associated with retrospective observational studies. First, there was not enough clinical data, such as glucose values or insulin resistance, and information on confounding factors that could potentially interact with diabetes and cancer, such as body mass index, glucose control, comorbidities, physical activity and smoking status to name a few. Other medications received by the patient, or cancer treatment were not included in the assessment as well.

In addition, it might have been possible that the impact of T2DM on cancer risk has been underestimated, since the standard for calculation of SIR was given by the whole population, which may also include undiagnosed T2DM patients or those treated outside the national health insurance scheme. Even in the mortality study (Paper V), bias could have been encountered with SMR calculation, where the true relative risk could have been underestimated for relatively common diseases (187).

One could also argue that patients with T2DM are more likely to regularly visit their doctors, therefore, even participate in cancer screening programs or undergo diagnostic tests more often. However, to minimize this probability, prostate cancer cases within one year of T2DM diagnosis and gastric and colorectal cancer cases within 6 months of T2DM diagnosis were excluded from the studies in Papers II, III and IV.

Additionally, in Papers VI and VIII, the power of the study was smaller than anticipated due to a relatively small number of cancer patients with T2DM.

Finally, the interpretation of the results on diabetes treatment and cancer risk and survival itself is complicated, since treatment groups are heterogeneous due to different indications for the prescribed treatment, different duration, different dosage and numerous possibilities for various diabetes drug combinations.

4. RESULTS

4.1. Paper I – T2DM and Cancer Risk of All Sites

Paper I included the largest study population of 127,290 T2DM patients in this thesis. During 12 years of follow-up, 5959 cases of cancer in men and 6661 cases of cancer in women with T2DM were diagnosed.

A statistically significant higher risk for cancer of all sites was observed in women (SIR = 1.16), but not in men (SIR = 1.00). Table 3 presents the observed and expected numbers of cancer cases and standardized incidence ratios with 95% confidence intervals among Lithuanian type 2 diabetic patients between 2000 and 2012 by site. Among men with T2DM, a significantly higher risk was found for cancer of the liver (SIR = 2.11), pancreas (SIR = 1.77), kidney (SIR = 1.46), and thyroid (SIR = 1.83). Colorectal cancer (SIR = 1.23), skin melanoma (SIR = 1.40), non–melanoma skin cancer (SIR = 1.14), male genital organ (SIR = 1.86), and other endocrine organ (SIR = 1.96) cancer risk was elevated significantly as well.

For women with T2DM, similarly to men, significantly higher risk was found for cancer of the liver (SIR = 1.45), pancreas (SIR = 1.74), kidney (SIR = 1.43), and thyroid (SIR = 1.40), as well as breast (SIR = 1.24) and corpus uteri (SIR = 2.07) cancer.

There was also an inverse association with several cancer sites. A lower incidence in cancer of the mouth (SIR = 0.49), esophagus (SIR = 0.50), larynx (SIR = 0.57), lung and trachea (SIR = 0.53) in men, and multiple myeloma (SIR = 0.74) and leukemia (SIR = 0.81) in women was observed.

Table 3. Observed (Obs) and expected (Exp) numbers of cancer cases and standardized incidence ratios (SIR) with 95% confidence intervals (CI) among Lithuanian type 2 diabetic patients during 2000-2012 by site according to the International Classification of Diseases Australian Modification (ICD10-AM).

Primary Site	ICD 10-AM code	Men				Women			
		Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
All Sites	C00-C96	5959	5933.8	1.00	0.98-1.03	6661	5724.1	1.16	1.14-1.19
Lip	C00	21	22.6	0.93	0.61-1.43	9	11.4	0.79	0.41-1.52
Mouth and pharynx	C01-C14	73	148.8	0.49	0.39-0.62	32	39.7	0.81	0.57-1.14
Esophagus	C15	46	92.9	0.50	0.37-0.66	16	20.2	0.79	0.49-1.29
Stomach	C16	325	339.4	0.96	0.86-1.07	303	305.4	0.99	0.89-1.11
Colon, rectum, rectosigmoid, anus	C18-C21	627	507.9	1.23	1.14-1.33	682	639.6	1.07	0.99-1.15
Liver	C22	139	65.9	2.11	1.79-2.49	86	59.4	1.45	1.17-1.79
Gallbladder, bile ducts	C23,C24	28	23.8	1.17	0.81-1.70	66	63.0	1.05	0.82-1.33
Pancreas	C25	265	150.1	1.77	1.57-1.99	325	187.3	1.74	1.5-61.93
Other digestive organs	C17,C26, C48	15	16.9	0.89	0.54-1.47	42	28.9	1.45	1.07-1.97
Nasal cavity, middle ear, accessory sinuses	C30,C31	7	10.4	0.68	0.32-1.42	6	7.9	0.76	0.34-1.69
Larynx	C32	63	111.1	0.57	0.44-0.73	6	7.2	0.83	0.37-1.85
Lung, trachea	C33,C34	436	827.7	0.53	0.48-0.58	183	210.6	0.87	0.75-1.00
Other respiratory tract	C37-C39	4	6.5	0.62	0.23-1.64	5	5.1	0.99	0.41-2.37
Bone and connective tissue	C40,C41,C45-C47,C49	28	28.6	0.98	0.68-1.42	33	36.2	0.91	0.65-1.28
Skin, melanoma	C43	72	51.6	1.40	1.11-1.76	101	111.3	0.91	0.75-1.10
Skin, non-melanoma	C44	566	498.1	1.14	1.05-1.23	1033	1049.3	0.98	0.93-1.05
Breast	C50	10	8.6	1.17	0.63-2.17	1114	899.6	1.24	1.17-1.31
Vulva	C51	_	_	_	_	53	45.4	1.17	0.89-1.53
Cervix uteri	C53	_	_	_	_	198	212.9	0.93	0.81-1.07
Corpus uteri	C54,C55	_	_	_	_	872	421.7	2.07	1.93-2.21
Ovary	C56	_	_	_	_	249	263.7	0.94	0.83-1.07
Other female genital organs	C52,C57-C58	_	_	_	_	13	17.1	0.76	0.44-1.31
Male genital organs	C60,C63	27	14.5	1.86	1.27-2.71	_	_	_	_

Prostate	C61	2164	2073.9	1.04	1.00-1.09	_	_	_	_
Testis	C62	4	3.8	1.04	0.39-2.78	_	_	_	_
Kidney	C64	336	230.8	1.46	1.31-1.62	312	217.9	1.43	1.28-1.60
Urinary bladder	C67	214	207.7	1.03	0.90-1.18	97	85.9	1.13	0.93-1.38
Other urinary tract	C65,C66, C68	10	10.1	0.99	0.53-1.84	13	10.9	1.19	0.69-2.05
Eye and adnexa	C69	8	7.1	1.13	0.56-2.26	12	12.6	0.95	0.54-1.68
Central nervous system	C70-C72	46	60.6	0.76	0.57-1.01	88	89.8	0.98	0.79-1.21
Thyroid	C73	36	19.7	1.83	1.32-2.54	196	139.6	1.40	1.22-1.62
Other endocrine organs	C74,C75	10	5.1	1.96	1.05-3.64	9	6.6	1.36	0.71-2.62
Other and ill-defined sites	C76-C80	138	130.2	1.06	0.90-1.25	173	146.9	1.18	1.01-1.37
Non-Hodgkin lymphoma	C81	5	6.4	0.78	0.32-1.87	7	8.3	0.84	0.40-1.77
Hodgkin lymphoma	C82-C85	72	82.3	0.87	0.69-1.10	145	129.9	1.12	0.95-1.31
Myeloma	C90	40	40.4	0.99	0.73-1.35	55	74.5	0.74	0.57-0.96
Leukemia	C91-C95	123	126.9	0.97	0.81-1.16	126	155.3	0.81	0.68-0.97
Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue	C88,C96	1	3.8	0.26	0.04-1.87	1	3.9	0.25	0.04-1.80

4.2. Paper II – T2DM and Prostate Cancer Risk

Overall, 64,000 men diagnosed with T2DM in Lithuania between 2000 and 2016 were included in the final cohort. They contributed 490,187 person-years of follow-up to the study. 2751 prostate cancer cases were observed, while 3106.5 were expected within the observation period, entailing a SIR of 0.89 (95% CI = 0.85; 0.92).

Significantly lower risk of prostate cancer was found among men with T2DM in all age groups. There were no differences in prostate cancer risk according to T2DM duration. Significantly lower prostate cancer risk was found in both groups of T2DM patients: metformin users and never-users, with lower risk of prostate cancer in ever-users (SIR = 0.71), in comparison to never-users (SIR = 0.88). However, there was no clear trend in the SIRs according to the cumulative dose of metformin (Table 4).

Table 4. Numbers of observed (Obs) and expected (Exp) cases of prostate cancer, standardized incidence ratios (SIR) with 95% confidence intervals (CI) in type 2 diabetes patients by metformin use.

Metformin	**Obs**	**Exp**	**SIR**	**95% CI**		***p* value***
Never-users	464	529.7	0.88	0.80	0.96	0.004
Users	1482	2078.2	0.71	0.68	0.75	<0.001
Cumulative dose (g)						
<846	195	346.7	0.56	0.49	0.65	<0.001
846–1,635	280	431.4	0.65	0.58	0.73	<0.001
1,635–3,060	424	552.6	0.77	0.70	0.84	<0.001
>3,060	583	747.5	0.78	0.72	0.85	<0.001

*For Chi-square

4.3. Paper III – T2DM and Colon Cancer Risk

111,109 patients were included in this study. Within the period of observation, 1213 were diagnosed with colorectal cancer versus 954.9 expected, entailing a SIR of 1.27 (95% CI = 1.20; 1.34).

Significantly higher risk for colorectal cancer was found both in men and women with T2DM in all age groups. Higher risk was seen for both colon (SIR = 1.36, 95% CI = 1.27; 1.46) and rectal cancers (SIR = 1.11, 95% CI = 1.01; 1.22) in this study population.

Cancer risk was elevated irrespectively of the time after T2DM diagnosis. Furthermore, risk for development of colorectal cancer was higher for both metformin users and metformin never-users. However, colorectal cancer risk was lower among metformin users (SIR = 1.47, 95% CI = 1.36; 1.58), compared to metformin never-users, who had a doubled risk compared with the general population (SIR = 2.14, 95% CI = 1.95; 2.35). In addition, colorectal cancer risk significantly decreased with increasing cumulative dose of metformin ($p<0.001$) (Table 5).

Table 5. Numbers of observed (Obs) and expected (Exp) cases of colorectal cancer, standardized incidence ratios (SIRs) with 95% confidence intervals (CI) in type 2 diabetes patients by metformin use.

	Men					Women					Overall				
	Obs	Exp	SMR	95% CI		Obs	Exp	SMR	95% CI		Obs	Exp	SMR	95% CI	
Overall	578	400.59	1.44	1.33	1.57	635	554.32	1.15	1.06	1.24	1213	954.91	1.27	1.20	1.34
Drug															
Metformin	310	250.61	1.24	1.11	1.38	348	198.22	1.76	1.58	1.95	658	448.83	1.47	1.36	1.58
Never users	202	91.18	2.22	1.93	2.54	225	108.21	2.08	1.82	2.37	427	199.39	2.14	1.95	2.35
Cumulative dose of metformin (g)															
<1380	123	74.19	1.66	1.39	1.98	145	60.62	2.39	2.03	2.81	268	134.82	1.99	1.76	2.24
1380-3000	104	78.51	1.32	1.09	1.61	112	56.81	1.97	1.64	2.37	216	135.33	1.60	1.40	1.82
>3000	83	97.90	0.85	0.68	1.05	91	80.78	1.13	0.92	1.38	174	178.68	0.97	0.84	1.13

4.4. Paper IV – T2DM and Gastric Cancer Risk

Overall, 99,992 patients with T2DM were included in the study and 337 gastric cancer cases were observed, compared to the expected number of 400.5 cancer cases, leading to a SIR of 0.84 (95% CI = 0.76; 0.94). The risk of gastric cancer was lower in both men and women, however, it was significantly lower only among men.

Analysis by T2DM treatment revealed a higher gastric cancer risk in the group of diabetic patients treated with sulfonylureas (SIR = 1.31, 95% CI = 1.04; 1.65) as well as insulin and other medications (SIR = 1.16, 95% CI = 0.73; 1.84), although the latter result was insignificant. Whereas significantly lower risk than expected from the general population was found in the group of metformin users (SIR = 0.75, 95% CI = 0.66; 0.86) and insignificantly lower risk was found for metformin and insulin users (SIR = 0.67, 95% CI = 0.40; 1.11).

4.5. Paper V – T2DM and Mortality Risk

The mortality risk analysis included 89,512 T2DM patients, of which 63.6% were women. The mean age at diabetes diagnosis was 61.3 years and the mean time of follow-up was 12.1 years. The study showed a 35% higher overall mortality risk for both sexes combined. The mortality risk was significantly elevated for both men and women, with SMRs of 1.24 and 1.43, respectively.

The greatest mortality risk was for those who were diagnosed with T2DM at a younger age (SMR = 1.68, 95% CI = 1.60; 1.76) and particularly high among those who had died before the age of 50 years (SMR = 22.04, 95% CI = 18.82; 25.81). The SMRs decreased with increasing age, but remained significantly increased even in the oldest age group (SMR = 1.22). Excessive all-cause mortality risk was higher in women than in men, especially in the younger age group.

The risk for mortality increased with increasing time since diabetes diagnosis, with SMRs of 1.09, 1.23, and 1.36 in periods 1–5, 6–10, and >10 years after diagnosis, respectively (test for trend $p < 0.001$).

With regard to T2DM treatment groups (oral glucose-lowering drugs, insulin and oral, only insulin), significantly higher mortality risk than expected from the general population was found in all groups. The mortality risk varied depending on the disease treatment modality from 23% (95% CI 1.22–1.25) among those treated only with oral antidiabetic drugs to nearly 2.5-fold among those treated with insulin only (Table 6).

Table 6. Standardized mortality ratios (SMRs) with 95% confidence intervals (CI) for all causes of death for men, women, and the overall cohort according to sex, age at diagnosis, age at death, time after diagnosis and therapy.

	Male					Female					Overall				
	Obs[1]	Exp[2]	SMR	95% CI		Obs	Exp	SMR	95% CI		Obs	Exp	SMR	95% CI	
Overall	11829	9512.6	1.24	1.22	1.27	18371	12849.9	1.43	1.41	1.45	30200	22362.5	1.35	1.34	1.37
Age at diagnosis															
40–49	1216	823.1	1.48	1.40	1.56	643	284.5	2.26	2.09	2.44	1859	1107.6	1.68	1.60	1.76
50–59	3026	2416.3	1.25	1.21	1.30	2643	1456.1	1.82	1.75	1.89	5669	3872.3	1.46	1.43	1.50
60–69	4267	3452.8	1.24	1.20	1.27	6339	4071.0	1.56	1.52	1.60	10606	7523.8	1.41	1.38	1.44
≥70	3320	2820.4	1.18	1.14	1.22	8746	7038.4	1.24	1.22	1.27	12066	9858.8	1.22	1.20	1.25
Age at death															
40–49	116	6.1	18.97	15.81	22.75	38	0.9	43.64	31.76	59.98	154	7.0	22.04	18.82	25.81
50–59	1112	431.2	2.58	2.43	2.74	554	116.8	4.75	4.37	5.16	1666	547.9	3.04	2.90	3.19
60–69	2858	1873.0	1.53	1.47	1.58	2197	823.5	2.67	2.56	2.78	5055	2696.5	1.87	1.82	1.93
≥70	7743	7202.3	1.08	1.05	1.10	15582	11908.8	1.31	1.29	1.33	23325	19111.1	1.22	1.20	1.24
Time after diagnosis															
1–5	1506	1445.1	1.04	0.99	1.10	1748	1530.3	1.14	1.09	1.20	3254	2975.4	1.09	1.06	1.13
6–10	4321	3734.5	1.16	1.12	1.19	5945	4611.7	1.29	1.26	1.32	10266	8346.2	1.23	1.21	1.25
>10	3025	2361.8	1.28	1.24	1.33	4886	3455.6	1.41	1.37	1.45	7911	5817.4	1.36	1.33	1.39
Glucose-lowering drugs															
Oral	9329	8252.3	1.13	1.11	1.15	14764	11305.4	1.31	1.29	1.33	24093	19557.6	1.23	1.22	1.25
Insulin and oral	1650	872.5	1.89	1.80	1.98	2624	1178.5	2.23	2.14	2.31	4274	2051.0	2.08	2.02	2.15
Insulin	850	387.8	2.19	2.05	2.34	983	366.1	2.69	2.52	2.86	1833	753.9	2.43	2.32	2.55

[1] Obs, observed number; [2] Exp, expected number.

The main causes of death among patients with T2DM were diseases of the circulatory system (65.2%), malignant neoplasms (15.3%), endocrine, nutritional and metabolic diseases (6.2% (mainly due to T2DM- 5.2%)) and diseases of the digestive system (4.3%). As compared to the general population, except for T2DM, the highest statistically significantly increased mortality risk was found for deaths from infection-related causes (SMR = 1.44), particularly septicemia (SMR = 1.78) and diseases of the circulatory system (SMR = 1.42), especially ischemic heart (SMR = 1.46) and cerebrovascular diseases (SMR = 1.38). However, the mortality risk ascribed to malignant neoplasms was elevated only for women with T2DM (SMR = 1.13), but not for men (SMR = 0.93), whereas mortality from all external causes and alcohol-related diseases was even lower in the diabetic cohort than in the general population—results for men were statistically significant.

The observed and expected numbers and the SMRs for each specific cause of death by sex are shown in Table 7.

Table 7. Standardized mortality ratios (SMRs) for causes of death for men, women, and the overall cohort of type 2 diabetes mellitus patients.

	Male					Female					Overall				
Diagnosis (ICD[1]-10 code)	**Obs[2]**	**Exp[3]**	**SMR**	**95% CI[4]**		**Obs**	**Exp**	**SMR**	**95% CI**		**Obs**	**Exp**	**SMR**	**95% CI**	
Overall	11829	9512.6	1.24	1.22	1.27	18371	12849.9	1.43	1.41	1.45	30200	22362.	1.35	1.34	1.37
Certain infectious and parasitic diseases (A00-B99)	172	143.1	1.20	1.04	1.40	248	148.8	1.67	1.47	1.89	420	291.9	1.44	1.31	1.58
Septicemia (A40-A41)	127	73.5	1.73	1.45	2.06	196	108.4	1.81	1.57	2.08	323	181.9	1.78	1.59	1.98
Malignant neoplasms (C00-C97)	2169	2320.2	0.93	0.90	0.98	2437	2151.4	1.13	1.09	1.18	4606	4471.6	1.03	1.00	1.06
Endocrine, nutritional and metabolic diseases (E00-E88)	767	66.1	11.60	10.81	12.46	1114	122.6	9.08	8.57	9.63	1881	188.7	9.97	9.53	10.43
Non-insulin-dependent diabetes mellitus (E11)	618	50.5	12.25	11.32	13.25	953	98.3	9.70	9.10	10.33	1571	148.7	10.56	10.05	11.10
Mental and behavioral disorders (F01-F99)	22	20.5	1.07	0.71	1.63	52	41.2	1.26	0.96	1.66	74	61.7	1.20	0.95	1.51
Diseases of the nervous system (G00-G98)	79	115.7	0.68	0.55	0.85	149	174.3	0.85	0.73	1.00	228	290.0	0.79	0.69	0.90
Diseases of the circulatory system (I00-I99)	7086	5070.4	1.40	1.37	1.43	12614	8770.5	1.44	1.41	1.46	19700	13840.9	1.42	1.40	1.44
Ischemic heart diseases (I20-I25)	4926	3400.1	1.45	1.41	1.49	8277	5665.7	1.46	1.43	1.49	13203	9065.8	1.46	1.43	1.48
Heart failure (I50)	35	38.1	0.92	0.66	1.28	88	72.1	1.22	0.99	1.50	123	110.2	1.12	0.94	1.33
Cerebrovascular diseases (I60-I69)	1506	1107.3	1.36	1.29	1.43	3323	2402.3	1.38	1.34	1.43	4829	3509.6	1.38	1.34	1.42
Diseases of arteries, arterioles and capillaries (I70-I79)	91	121.1	0.75	0.61	0.92	108	106.8	1.01	0.84	1.22	199	227.9	0.87	0.76	1.00
Diseases of the respiratory system (J00-J98)	355	438.7	0.81	0.73	0.90	315	256.8	1.23	1.10	1.37	670	695.5	0.96	0.89	1.04
Pneumonia (J12-J18)	112	129.9	0.86	0.72	1.04	136	105.7	1.29	1.09	1.52	248	235.6	1.05	0.93	1.19
Diseases of the digestive system (K00-K92)	540	436.8	1.24	1.14	1.34	753	518.2	1.45	1.35	1.56	1293	955.0	1.35	1.28	1.43
Diseases of liver (K70-K76)	220	185.1	1.19	1.04	1.36	169	125.1	1.35	1.16	1.57	389	310.2	1.25	1.14	1.39
Diseases of pancreas (K85-K86)	49	41.7	1.18	0.89	1.56	40	43.7	0.92	0.67	1.25	89	85.4	1.04	0.85	1.28

Diseases of the genitourinary system (N00-N98)	97	78.5	1.24	1.01	1.51	145	120.0	1.21	1.03	1.42	242	198.5	1.22	1.07	1.38
Disorders of kidney and ureter (N00-N28)	69	60.4	1.14	0.90	1.45	119	107.2	1.11	0.93	1.33	188	167.6	1.12	0.97	1.29
External causes of mortality (V01-Y98)	385	653.1	0.59	0.53	0.65	300	343.7	0.87	0.78	0.98	685	996.8	0.69	0.64	0.74
Accidents (V01-X59)	228	392.4	0.58	0.51	0.66	211	234.5	0.90	0.79	1.03	439	627.0	0.70	0.64	0.77
Suicides (X60-X84)	104	167.0	0.62	0.51	0.75	55	59.8	0.92	0.71	1.20	159	226.8	0.70	0.60	0.82
Event of undetermined intent (Y10-Y34)	32	60.6	0.53	0.37	0.75	26	30.7	0.85	0.58	1.25	58	91.3	0.64	0.49	0.82
Alcohol-related diseases*	94	157.0	0.60	0.49	0.73	52	65.5	0,79	0.61	1.04	146	222.4	0.66	0.56	0.77

[1]ICD, International Classification of Diseases, [2]Obs, observed; [3]Exp, expected; [4]CI, confidence interval, *F10, G312, G621, G721, I426, K292, K70, K852, K860, X45, X65, Y15.

4.6. Paper VI – T2DM and Prostate Cancer Survival

254 (3.8%) patients with prostate cancer in the study cohort had pre-existing T2DM. During follow-up there were 4807 deaths, including 2084 from prostate cancer.

At prostate cancer diagnosis, there were more men with distant cancer and less with localized cancer in the non-diabetes patient group. After adjustment for age and stage at diagnosis, prostate cancer-specific mortality risk was 19% lower in men with T2DM, but the difference was not statistically significant (HR = 0.81, 95% CI = 0.62; 1.06). When compared by diabetes treatment groups, prostate cancer-specific mortality risk was 26% lower in diabetic men on metformin (HR = 0.74, 95% CI = 0.54; 1.02), compared to non-diabetic men, although the result was also borderline non-significant. Prostate cancer-specific mortality risk in metformin non-users did not differ much from men without T2DM (HR = 1.03, 95% CI = 0.64; 1.66).

Multivariate-adjusted overall survival was significantly lower (HR = 1.24, 95% CI = 1.07; 1.43) in men with T2DM, with highest overall mortality risk for metformin non-users (HR = 1.63, 95% CI = 1.27; 2.10).

4.7. Paper VII – T2DM and Colorectal Cancer Survival

1094 (7.27%) patients with colorectal cancer in the study population had pre-existing T2DM. During follow-up there were 10,927 deaths, including 8559 from colorectal cancer.

Multivariate analysis after adjustment for age and stage at diagnosis showed a 13% significantly lower risk of colorectal cancer-specific mortality (HR = 0.87, 95% CI = 0.80; 0.94) in the T2DM patient population, while there were no differences in overall survival between with and without T2DM.

When metformin users and non-users with T2DM were compared, multivariate-adjusted colorectal cancer-specific survival was 23% higher (HR = 0.77, 95% CI = 0.64; 0.93) and overall survival was 25% higher (HR = 0.75, 95% CI = 0.64; 0.87) in the metformin user group.

4.8. Paper VIII – T2DM and Gastric Cancer Survival

555 (6.59 %) patients with gastric cancer in this study had pre-existing T2DM. During follow-up, there were 7199 deaths, including 6111 from gastric cancer.

Multivariate analysis after adjustment for sex, age and stage at diagnosis did not show significant difference in gastric cancer-specific (HR = 0.93, 95% C I = 0.84; 1.03) and overall survival (HR = 0.97, 95% CI = 0.88; 1.06) in patients with T2DM, as compared to non-diabetic patients.

Furthermore, exposure to glucose-lowering medication among patients with T2DM did not show significant death risk differences in gastric cancer-specific and overall survival. However, the lowest survival was observed in the sulphonylurea user group (Table 8).

Table 8. The association between glucose-lowering medication use, gastric cancer-specific and overall mortality.

Diabetes treatment	**Ca-specific mortality HR[1]**	**95% CI[2]**	***p* value**	**Overall mortality HR**	**95% CI**	***p value***
Metformin	1.00	ref.	ref.	1.00	ref.	ref.
Metformin and other	0.91	0.71; 1.17	0.47	0.92	0.74; 1.16	0.49
Insulin and other	0.85	0.56; 1.29	0.06	0.96	0.78; 1.33	0.11
Sulfonylureas	1.09	0.82; 1.45	0.45	1.02	0.78; 1.33	0.88

[1]HR, hazard ratio; [2]CI, confidence interval.

5. DISCUSSION

The investigations of this thesis were the first of such size and duration to analyze the whole Lithuanian T2DM patient population and the associations between T2DM, its treatment and both cancer risk and survival, as well as cause-specific mortality risk. This thesis has demonstrated that people with T2DM had a substantially higher mortality risk than the general population, with highest risk of death from cardiovascular, infectious, digestive and genitourinary diseases, while women had a higher mortality risk even from cancer and respiratory diseases. Women also had higher risk for cancer of all sites, and both women and men had higher risks for several site-specific cancers. Prostate, colorectal and gastric cancer-specific survival did not seem to be negatively affected by T2DM, while metformin use was beneficial in prostate and colorectal cancer.

The results will be discussed further and compared to previous studies according to the specific papers.

5.1. Paper I – T2DM and Cancer Risk of All Sites

The results of this cancer risk study showed significantly higher site-specific cancer risk among T2DM patients. We found different risk estimates for cancer of all sites among men and women. The male vs. female cancer risk difference observed in the patient cohort can be partly explained by an increased number of the most common sex-specific, corpus uteri and breast, cancer in the female cohort group. When these cancers are excluded from the calculation for all site cancer risk, the risk decreases, yet remains statistically significantly higher in women (SIR 1.06, 95% CI 1.03–1.09). Men, on the other hand, had a higher risk for more types of cancer than women, however, these cancers where less common and did not affect the overall cancer risk.

SIR estimates for all-site cancer risk in T2DM patients obtained in our study are comparable to previously performed European cohort studies (117-119), as well as the meta-analysis of 121 cohorts by Ohkuma et al., though the risk estimate in the meta-analysis was slightly higher and significantly elevated in both women and men (120).

With regards to SIR estimates on site-specific cancer incidence, our results are comparable to previous meta-analyses on site-specific cancer risk (58, 121-130). We, for example, observed a more than 75% higher risk of pancreatic cancer in both men and women with T2DM, similarly to a meta-analysis by Song et al. (122). Although reverse causality for pancreas cancer

has been suspected, constant elevated risk of pancreatic cancer after longer periods of follow-up demonstrate that this is doubtful (63, 122).

We found a two-fold rise in liver cancer incidence among men withT2DM and a 45% rise among women with T2DM compared with the general population. These findings are similar to those observed in the meta-analysis by Wang et al., 2012 and Wang et al., 2016 (58, 121). The more recent meta-analysis showed that T2DM and liver cancer association is confounded by smoking and body mass index in both men and women (58).

This study showed a 23% higher colorectal cancer risk in men, and 7% higher risk in women, though the latter was statistically insignificant. Several meta-analyses of cohort and case-control studies demonstrated a higher risk of colorectal cancer in both women and men with diabetes (125-127). T2DM and colon cancer share common risk factors such as obesity and smoking, but even when adjusted for these factors, the association remains (127).

Similarly, we found a 40% higher risk of kidney cancer in both women and men. This finding is comparable to a meta-analysis by Bao et al. The meta-analysis indicates that the risk of kidney cancer, associated with T2DM, is independent of alcohol consumption, BMI, obesity, and smoking (123).

Thus, the risk of some cancer-sites may be affected by important clinical co-factors, which may differ in different populations. Unfortunately, the analysis of clinical factors in many retrospective studies, as well as ours, is not possible due to the lack of this type of data in the registers.

In our study, women with T2DM had a 40% and men had an 80% higher risk for thyroid cancer, although it remained a rare form of cancer in men. The results on thyroid cancer are inconsistent among studies (124, 131). The risk was higher among women living in areas where thyroid cancer is more common relative to other geographic areas (124). We hypothesize that the higher estimates for thyroid cancer, especially among men, similarly to increasing rates of thyroid cancer in the whole population, can be explained by the fact that diabetic patients in Lithuania usually undergo thyroid ultrasound scanning routinely, and ultrasound guided fine needle biopsy if needed, therefore even micro-carcinomas can be detected early (188).

There was no reduction in prostate cancer risk among men with T2DM in this study, in contrast to a recent meta-analysis, which showed a 14% lower risk of prostate cancer in diabetic men (189). In Lithuania an official nationwide prostate cancer early detection program was introduced in 2006, resulting in subsequent prostate cancer incidence peaks (190). Therefore, the obtained risk excess of prostate cancer in our study group could in part be

explained by surveillance bias since patients with diabetes are under increased surveillance and are more likely to undergo additional medical examinations including prostate-specific antigen (PSA) testing. The use of PSA testing as an early detection tool may cause over-diagnosis or detection of indolent tumors (191).

We found a lower risk of lung, tracheal, esophageal, mouth, and laryngeal cancer in diabetic men. In comparison, a meta-analysis of 13 studies indicates that DM is positively correlated with esophageal cancer, although there were limitations on potential clinical confounding factors in each study included in the meta-analysis (192). Cancers of the oral cavity, pharynx, esophagus, and larynx, together with cancers of the trachea and lungs, are commonly associated with smoking and alcohol use (193). Lower risk of some cancers in our study may be explained by a different distribution of well-known risk factors in diabetic patients compared to the general population.

5.2. Paper II – T2DM and Prostate Cancer Risk

To account for surveillance bias, as suspected in Paper I, and to be able to analyze the possible effect of treatment with metformin, this analysis included men with more than 1 years' duration of T2DM. In this study, we found an 11% lower risk of developing prostate cancer compared to the general population.

Our findings were in accordance with the results of the meta-analysis by Bansal et al. (189). Furthermore, our study, similarly to the data published by Turner et al. or Xu et al. did not show any association between T2DM duration and risk of prostate cancer (145, 146).

Another interesting observation in literature is that younger diabetic patients have a lower risk of prostate cancer. Two studies showed that patients diagnosed with diabetes mellitus before 30 might had a relatively lower risk of prostate cancer than those diagnosed with diabetes after 30 (148, 194). However, these studies included all types of diabetes mellitus and very young patients, therefore, since prostate cancer is predominantly a disease of the elderly, it is possible that studying a younger cohort and with shorter follow-up these results could be inaccurate. Our T2DM cohort data demonstrated that prostate cancer risk was reduced similarly through all age groups starting from 40 years of age.

Studies with hypogonadal men and testosterone substitution therapies showed that testosterone plays a crucial role in the development of prostate

cancer (195, 196). Testosterone levels at the day of diabetes diagnosis and during treatment would be helpful to evaluate confounding factors for development of prostate cancer.

We found a significantly lower risk of prostate cancer in patients who were metformin users compared to never-users, 29% versus 12% respectively. A Taiwanese study also suggested that metformin use may be beneficial, showing that the higher the cumulative metformin dose, the more pronounced the protective effect of metformin against prostate cancer can be seen (197). However, in a study from Sweden, men with T2DM on metformin had no further decrease in risk compared to men with T2DM who were not taking anti-diabetic drugs (198).

The relationship between diabetes and metformin use and prostate cancer may be suspected to be causal due to evidence of decreasing prostate cancer risk with increasing diabetes duration and longer duration of metformin use, or higher cumulative dose of metformin, however, our study did not show a relationship between the duration of diabetes or cumulative dose of metformin.

5.3. Paper III– T2DM and Colon Cancer Risk

Colorectal cancer is commonly associated with insulin resistance and T2DM, while metformin seems to have the ability to suppress tumorigenesis by several mechanisms, as demonstrated in basic research, which was discussed in the literature review. Our study with a duration of up to 10 years of follow-up showed that T2DM was associated with a higher risk of colorectal cancer in both sexes and in all age groups. Meanwhile, metformin use in large cumulative doses was associated with decreased colorectal cancer risk, which supports a positive effect of metformin against cancer. These results are similar to studies from Denmark, China and Ireland (132-134), however, no protective metformin effect was observed in other studies from Canada, UK or Germany, as well as the randomized controlled clinical trials ADOPT and RECORD (136-139).

Time-related biases, which are difficult to avoid in retrospective studies, may explain some of differences in study results (98). A recent cohort study that used methods to minimize these biases reported long- term metformin use to be associated with lower colorectal cancer risk. Additionally, switching from sulfonylureas or adding metformin decreased colorectal cancer risk in that study (199).

5.4. Paper IV – T2DM and Gastric Cancer Risk

For this study, not only metformin, but several glucose lowering therapies were investigated to determine possible associations with diabetes treatment and cancer risk. The results revealed that T2DM was not associated with increased risk of gastric cancer, on the contrary, T2DM patients had a lower risk of gastric cancer, although the result was insignificant in women.

Furthermore, there were significant differences in cancer risk according to glucose-lowering medication use. The results showed that metformin in combination with other oral glucose lowering drugs might decrease the risk of gastric cancer in patients with T2DM by 25%, while sulfonylureas might increase it by 31%.

Many of the epidemiologic studies researching gastric cancer risk were conducted in Taiwan, with both similar and contrasting results (140-143). Due to different study populations, study design and duration of observation and treatment, as well as various glucose-lowering treatment combinations, it is difficult to compare the studies directly with one another and draw definitive conclusions.

However, two recent meta-analyses have shown results, similar to ours (200, 201). A meta-analysis by Miao et al. of 22 studies found that people with diabetes had little or no change in the risk of gastric cancer or gastric cancer mortality (200). Another meta-analysis by Zhou et al., which included seven studies, found that metformin therapy was associated with a reduction in the risk of gastric cancer in patients with T2DM, compared to other therapies (201).

5.5. Paper V – T2DM and Mortality Risk

Paper V showed that people with T2DM had a 35% excess risk of mortality from all causes, with an even higher risk for women compared to men, especially in the youngest age group. Excess mortality associated with T2DM was substantially higher in people who were diagnosed with T2DM at a younger age, in those who died at a younger age, those who had a longer diabetes duration, or those who required treatment with insulin.

This nationwide study involved more than 89 thousand people with T2DM, followed-up for over 592 thousand person-years. Over 30 thousand deaths were analyzed during the observational period. The large study cohort allowed us to investigate a wide range of mortality outcomes and compare it to the national population.

Our study showed that both men and women with diabetes had not only a higher risk of death from diabetes itself and from CVD, but substantially higher mortality risk from infectious, digestive, and genitourinary diseases. The mortality risk due to cancer, however, was significantly elevated for women with diabetes, but not for men, probably because of the higher corpus uteri and breast cancer risk that we found in Lithuanian diabetic women (Paper I). In addition, higher risk for mortality from respiratory diseases was also seen in diabetic women.

Similar studies from across the world, both earlier (19, 150-152) and recent (153-155, 202), even with advances in diabetes treatment over the years, have also consistently shown that T2DM increases all-cause mortality; however, the association with nonvascular causes of death slightly differs among various populations. Interestingly, in our population, mortality from all external causes and alcohol-related diseases, as well as diseases from the nervous system, were lower in the diabetic cohort than in the general population. Information about these less-common causes of death in other studies is lacking and variable, therefore our analysis adds important data to less-studied fields.

With regard to T2DM and risk for death from external causes, some studies found comparable risk (19, 150, 151) while others showed increased risk (152, 203); however, most of the studies have not reported deaths attributable to these factors. The inconclusive results warrant further investigation. It is most likely that these causes of death may be highly affected by social, economic, and cultural differences of the study populations.

While most of these epidemiological studies come from the western part of the globe, the trends of excessive diabetes mortality do not seem to differ in the east, with the risk seeming to be even higher, as well as the risk of mortality from several cancer localizations (156). Consistent with our findings, the adverse diabetes-mortality associations were more evident among women and younger adults (157).

Regarding diabetes treatment, we found that patients treated with insulin had a greater mortality risk than those treated with oral glucose-lowering medications or combination therapy. The association has been reported in other studies (19). This may be related more to the severity of the disease than the treatment itself, as insulin is usually started when the disease cannot be managed by diet and oral medications alone or if there are contraindications for oral therapy, such as kidney or liver failure.

5.6. Paper VI – T2DM and Prostate Cancer Survival

Prostate cancer tends to progress more slowly than many other cancer types, therefore the duration of prostate cancer survival studies should be long, in order to collect significant results, therefore, our national prostate cancer patient cohort study followed patients up to 10 years.

The study showed that patients with prostate cancer and T2DM had a higher risk of overall mortality, but prostate cancer-specific survival did not differ significantly between diabetes and non-diabetes patient groups, with a trend towards lower mortality risk in T2DM patients. Additionally, there was a clear trend towards higher prostate cancer-specific survival in metformin users compared to both non-diabetic and diabetic metformin non-user groups. Furthermore, overall survival of diabetic metformin users did not differ from the non-diabetic population of prostate cancer patients, but was significantly decreased in diabetes patients who did not use metformin. This could more likely be explained by worse metabolic control and overall increased mortality risk in this T2DM patient group.

The interpretation of the effect of metformin therapy on non-diabetes associated outcomes is complicated in clinical research due to heterogeneity between various study populations and methods. Evidence in literature regarding the beneficial effect of metformin in prostate cancer survival is conflicting (168). Some of the earliest retrospective clinical studies showed a positive effect of metformin on prostate cancer survival (114, 161, 162), while other studies did not seem to find such a benefit of treatment with metformin (163-165). The few prospective studies did not find benefit of metformin treatment as well (166, 167). However, a relatively small number of men using metformin is a limitation of these studies.

5.7. Paper VII – T2DM and Colorectal Cancer Survival

This study is one of the largest cohort studies so far to show that overall and colorectal cancer-specific survival was significantly higher in the metformin-treated group compared with non-metformin group and even non-diabetes group.

Earlier cohort studies have demonstrated that metformin use increases survival in colorectal cancer patients (170-172). However, these studies are hindered by assessing only all-cause mortality and not cancer specific survival. A few smaller retrospective analyses, similarly to our findings, showed longer colorectal cancer-specific survival in diabetes patients using

metformin (134, 174), while several others (175-177) did not find significant differences, associated with metformin use, in colorectal cancer outcomes.

However, a recent meta-analysis on metformin as an adjuvant treatment modality for several cancer locations, including colorectal cancer, found metformin use to be beneficiary in all early-stage colorectal cancer outcomes (115). Additionally, results of a clinical phase II trial, which investigated metastatic colorectal cancer treatment, favored metformin use with conventional chemotherapy in diabetic patients (178).

Differences in results can be explained by study designs, heterogeneous study populations, different diabetes and cancer treatments, observation periods and many other factors that influence study outcomes.

5.8. Paper VIII – T2DM and Gastric Cancer Survival

The results demonstrated no significant association between antihyperglycemic medication use and gastric cancer survival in diabetic patients in Lithuania. However, better survival trends were observed in the groups treated with metformin and insulin combinations, while the lowest survival (and lower than in non-diabetic patients) was observed in diabetic patients who were sulphonylurea users.

Several studies investigated the influence of diabetes and different treatment combinations on all-site cancer survival (78, 159, 160) and only a few previous studies have assessed the links between antihyperglycemic medication use and survival in gastric cancer specifically (179-181), showing favorable results in metformin users, similarly to our findings.

Regarding gastric cancer survival, it seems too early to draw definite conclusions from the available evidence in literature. The assessment of confounding factors, drug doses, information on indications for specific diabetes treatment, cancer treatment, as well as investigations from multiple centers and countries would be appreciated in future research.

6. CONCLUSIONS

1. There is a higher risk of cancer of all sites in women with T2DM, but not in men. Significantly higher risk is found for cancers of the liver, pancreas, kidney and thyroid in both men and women. Risk of colorectal cancer and skin cancer is elevated among men, and risk of breast and corpus uteri cancer - among women.

2. Prostate cancer risk is lower in men with preexisting T2DM for at least 1 year before cancer diagnosis. Metformin use is associated with lowest risk for prostate cancer.

3. People with pre-existing T2DM for at least 6 months have a higher risk of colorectal cancer. Colorectal cancer risk decreases with increasing cumulative dose of metformin.

4. T2DM is not associated with higher gastric cancer risk. Metformin and other oral glucose-lowering medication use is associated with lower, while sulfonylurea use is associated with higher gastric cancer risk.

5. People with T2DM in Lithuania have an excess risk of mortality from all causes. Both men and women with T2DM have a higher risk of death from diabetes itself, cardiovascular, infectious, digestive, and genitourinary diseases. Women have an elevated mortality risk due to cancer and respiratory diseases as well. Excess mortality is substantially higher in people who are diagnosed with T2DM at a younger age, die at a younger age, have a longer diabetes duration, and those who need treatment with insulin. Women have a higher mortality risk than men in all groups according to age, time after diagnosis, and therapy.

6. Long-term prostate cancer-specific survival is higher, although insignificantly, in people with T2DM and metformin users. Whereas overall survival is lower in T2DM and lowest in the metformin non-user group.

7. People with T2DM have a lower colorectal cancer-specific mortality risk. Metformin users have significantly better colorectal cancer-specific and overall survival, compared to metformin non-users.

8. There is no difference in gastric cancer survival between people with or without T2DM and among different diabetes treatment groups.

7. FUTURE PERSPECTIVES/PRACTICAL RECOMENDATIONS

This thesis confirms that there is an association between T2DM and cancer which needs to be highlighted and made known both for patients and clinicians.

In particular, screening for cancers, according to standard protocols for the general population and, moreover, with clinical suspicion, in diabetic patients should be emphasized in clinical practice.

Furthermore, investigation and management of preventable comorbidities and complications in T2DM patients, as well as optimal metabolic control should be implemented as early as possible in the disease course to prevent premature mortality.

The possibility that metformin may have a positive effect on cancer prevention and outcomes should also be taken account for while choosing the best therapy for diabetes control. It seems that metformin might have the most beneficial effect in the management of cancers, associated with insulin resistance, and it would be interesting to test this hypothesis in our Lithuanian population on survival of liver, breast and corpus uteri cancers to begin (or continue) with. There are also many unanswered questions regarding the long-term effect of other glucose-lowering medications, such as TZDs and GLP-1 analogues, which could be the focus of future studies.

In conclusion, although this thesis gives some answers on possible connections of T2DM and cancer, two widespread and complicated diseases, it cannot yet answer if the relationship is causal. However, the results of the thesis may be used as the initial study generating hypotheses to be investigated further by larger, more expensive prospective studies and randomized controlled interventional trials which could confirm these findings with consideration of confounding variables, dose-related and exposure time effects.

SUMMARY IN LITHUANIAN

Ši daktaro disertacija parengta mokslinių publikacijų, kurios tolesniame tekste žymimos romėniškais skaitmenimis, rinkinio pagrindu:

I. **Linkeviciute-Ulinskiene D**, Patasius A, Zabuliene L, Stukas R, Smailyte G. *Increased Risk of Site-Specific Cancer in People with Type 2 Diabetes: A National Cohort Study*. Int J Environ Res Public Health. 2019 Dec 30; 17(1): 246. https://doi.org/10.3390/ijerph17010246

II. Kincius M, Patasius A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Smailyte G. *Reduced risk of prostate cancer in a cohort of Lithuanian diabetes mellitus patients.* Aging Male. 2020 May 15: 1–6. https://doi.org/10.1080/13685538.2020.1766013

III. Dulskas A, Patasius A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Urbonas V, Smailyte G. *Positive effect of metformin treatment in colorectal cancer patients with type 2 diabetes: national cohort study*. Eur J Cancer Prev. 2019 Sep 16. https://doi.org/10.1097/CEJ.0000000000000547

IV. Dulskas A, Patasius A, Kaceniene A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Smailyte G. *A Cohort Study of Antihyperglycemic Medication Exposure and Gastric Cancer Risk.* J Clin Med. 2020 Feb 5; 9(2): 435. https://doi.org/10.3390/jcm9020435

V. **Linkeviciute-Ulinskiene D**, Kaceniene A, Dulskas A, Patasius A, Zabuliene L, Smailyte G. *Increased Mortality Risk in People with Type 2 Diabetes Mellitus in Lithuania.* Int J Environ Res Public Health. 2020; 17(18): 6870. https://doi.org/10.3390/ijerph17186870 - 20 Sep 2020

VI. **Linkeviciute-Ulinskiene D**, Patasius A, Kincius M, Zabuliene L, Smailyte G. *Preexisting diabetes, metformin use and long-term survival in patients with prostate cancer.* Scand J Urol. 2020 Aug 4: 1–7. https://doi.org/10.1080/21681805.2020.1798502

VII. Dulskas A, Patasius A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Urbonas V, Smailyte G. *Metformin increases cancer specific survival in colorectal cancer patients – national cohort study*. Cancer Epidemiology. 2019 Sep 3; 62: 101587. https://doi.org/10.1016/j.canep.2019.101587

VIII. Dulskas A, Patasius A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Smailyte G. *A cohort study of antihyperglycemic medication exposure and survival in patients with gastric cancer.* Aging-US. 2019 Sep 13; 11.
https://doi.org/10.18632/aging.102245

1. ĮVADAS

1.1. Daktaro disertacijos tema ir jos aktualumas

Per paskutinius du šimtmečius vidutinė žmogaus gyvenimo trukmė pailgėjo daugiau nei dvigubai. Tai lėmė ilgesnį žmogaus gyvenimą ir galbūt geresnę jo kokybę, išaugusį gyventojų skaičių ir pakilusį ekonomikos lygį (1). Tiesa, žvelgiant iš sveikatos priežiūros perspektyvos, dėl senstančios visuomenės pagausėjo lėtinių ligų ir keliomis gretutinėmis ligomis sergančių pacientų, kurie šiuo metu sudaro iki 95 proc. pirminės sveikatos priežiūros įstaigų pacientų, vyresnių nei 65-eri metai (2). Ir vėžys, ir 2 tipo cukrinis diabetas (2 tipo CD) yra ligos, glaudžiai susijusios su senėjimu. Remiantis amerikiečių mokslininkų atliktų tyrimų duomenimis, CD yra viena iš dešimties labiausiai paplitusių lėtinių gretutinių ligų tarp onkologinėmis ligomis sergančių 65-erių ir vyresnio amžiaus pacientų (3). Be to, nuo 8 proc. iki 18 proc. pacientų, kuriems yra diagnozuotas vėžys, serga ir CD (4).

Pacientai, kuriems diagnozuotos kelios gretutinės ligos, yra nemenka finansinė našta sveikatos priežiūros sistemai ir sukelia papildomų su gydymu susijusių iššūkių, todėl visame pasaulyje daugybinių ligų suvaldymo strategijoms yra skiriamas didelis dėmesys (5). Mokslininkai bei gydytojai vis dažniau yra linkę nuo tradicinės prieigos, kai dėmesio centre yra liga, pereiti prie individualizuotos paciento sveikatos problemų sprendimo strategijos. Tiesa, duomenys apie daugybinių gretutinių ligų paplitimą, susirgimų tendencijas ir visa tai lemiančius veiksnius yra riboti (2). Dėl informacijos stygiaus sudėtinga priimti tinkamus sprendimus ir sveikatos priežiūros sistemą pakreipti linkme, kuri būtų palankesnė pacientams, kenčiantiems nuo daugybinių ligų.

2011-ųjų metų aukšto rango Generalinės Asamblėjos konferencijos paskelbtoje politinėje Neinfekcinių ligų prevencijos ir kontrolės deklaracijoje buvo pripažinta, kad „pasaulinė neinfekcinių ligų našta ir grėsmė yra vienas didžiausių XXI a. medicinos iššūkių, kenkia socialinei bei ekonominei pažangai visame pasaulyje ir kliudo įgyvendinti tarptautiniu

mastu išsikeltus tikslus“, ir pareikšta, kad „būtina nedelsiant imtis griežtesnių neinfekcinių ligų prevencijos ir kontrolės priemonių pasauliniu, regioniniu ir nacionaliniu mastu“ (6). Tiesa, priemonės, kurių iki šiol buvo imtasi, nebuvo pakankamos, todėl epidemiologinės analizės, kaip vienos pagrindinių šių ligų suvaldymo priemonių, tyrimo svarba buvo pažymima vėlesnėse konferencijose (7).

CD ir vėžys – dvi pasaulinio masto itin sudėtingos ir nuolat augančios problemos, neigiamai veikiančios gyvenimo kokybę ir milijonų pacientų gyvenimo trukmę. Tarptautinės diabeto federacijos (TDF) pateiktais duomenimis, 2019 metais suaugusiųjų, sergančių CD, skaičius siekė 463 mln. ir jis nuolat didėja. Be to, šiuo metu jau yra daugiau asmenų, kuriems diagnozuotas 2 tipo CD, nei 2010-aisiais TDF prognozavo 2025 metams (8).

CD ir jo sukeltos komplikacijos visame pasaulyje lėmė išaugusį mirtingumą ir pacientų su negalia skaičių. 2013-iais *Global Burden of Disease Study* duomenimis, CD buvo devintoje vietoje pagal priežastis, lemiančias sumažėjusią gyvenimo trukmę (9). Apskaičiuota ir tai, kad 2019-iais CD tapo net 4,2 mln. suaugusiųjų nuo 20-ies iki 79-erių metų amžiaus mirties priežastimi, o tai sudaro 11,3 proc. visų mirčių atvejų. Be to, pusė šių mirčių ištiko darbingo amžiaus, jaunesnius nei šešiasdešimties metų pacientus (10). *Global Burden of Disease Cancer Collaboration* tyrimų duomenimis, 2017-aisiais vėžio atvejų buvo 24,5 mln., o mirčių nuo vėžio – 9, 6 mln., vadinasi, onkologinės ligos yra antroji dažniausia mirties priežastis visame pasaulyje. Be to, nuo 2007-ųjų sergamumas vėžiu per dešimtmetį išaugo vienu trečdaliu (11). 2019-aisiais Lietuvoje buvo 110 tūkst. asmenų, sergančių CD, ir 86 tūkst. Asmenų, sergančių vėžiu (12).

Paskaičiuota, kad vėžio ir CD, ypač 2 tipo CD, susirgimai per artimiausius dešimtmečius augs, todėl abiem šioms ligoms būtina skirti daugiau dėmesio, imtis tinkamų prevencijos priemonių bei kontrolės strategijų Lietuvoje ir visame pasaulyje.

Siekiant įvertinti ryšį tarp onkologinių ligų ir CD buvo atliktas ne vienas įvairaus pobūdžio tyrimas. Remiantis populiacinių tyrimų, vykdytų nuo XX a. 7-ojo dešimtmečio, rezultatais, buvo nustatytas glaudus ryšys tarp šių dviejų ligų. Kad vėžys ir CD, ypač 2 tipo CD, tarpusavyje susiję buvo nustatyta epidemiologiniais tyrimais, ilgainiui išaugusiais į ne vieną metaanalizę, paskelbtą per paskutinius dešimtmečius. Buvo įrodyta, kad asmenims, kuriems diagnozuotas 2 tipo CD, yra didesnė rizika susirgti kepenų, kasos, gimdos gleivinės, gaubtinės ir tiesiosios žarnos (kolorektaliniu), šlapimo pūslės bei inkstų vėžiu. Tiesa, paaiškėjo ir tai, kad asmenų, sergančių 2 tipo CD, prostatos vėžio rizika yra mažesnė. Tarp CD ir

kitų onkologinių ligų tiesioginių sąsajų dar nenustatyta arba kol kas tam trūksta pakankamai įrodymų (14, 15).

Vėžio vystymąsi asmenims, sergantiems 2 tipo CD, lemia bendri mechanizmai, skatinantys vėžinių ląstelių susidarymą ir vėžio progresavimą: tai susiję su homeostazės sutrikimais (hiperglikemija, hiperinsulinemija, uždegimas), veikiančiais visus audinius, ir skatinančius specifinių organų karcinogenezę (16).

Įtaka, kurią 2 tipo CD daro išgyvenamumui sergant vėžiu, yra mažiau ištirta nei sąsajos tarp rizikos susirgti vėžiu ir 2 tipo CD. Kai kurie epidemiologinių tyrimų rezultatai parodė didesnę mirtingumo nuo vėžio riziką sergant 2 tipo CD (17, 18). Kadangi cukrinis diabetas yra siejamas su gretutinėmis ligomis, komplikacijomis ir didesniu bendruoju mirtingumu (19), vis dar nėra aišku, ar bendrasis CD ir vėžiu sergančių asmenų mirtingumas yra didesnis nei mirtingumas nuo CD. Keliamos hipotezės, kad cukrinis diabetas tiesiogiai neigiamai veikia vėžio eigą. Be to, gali būti, kad cukriniu diabetu sergantiems ligoniams vengiama taikyti tam tikrus vėžio gydymo būdus (4, 17). Šiems pacientams gali būti didesnė vėžio atsinaujinimo tikimybė, todėl spėjama, kad CD daro tiesioginę įtaką onkologinės ligos progresavimui (20).

Be to, net ir vaistai, skiriami CD gydyti, gali paveikti onkologinių ligų riziką ar išgyvenamumą. Kol kas nėra pakankamai duomenų apie CD gydymo poveikį rizikai susirgti vėžiu ar galimybei nuo jo pasveikti. Pavienių tyrimų rezultatai atskleidė, kad kai kurie vaistai nuo CD, tarkim, insulinas ir insulino sekretagogai, gali būti susiję su didesne rizika susirgti vėžiu, kiti, pavyzdžiui inkretinai, kaip manoma, pasižymi neutraliu poveikiu, o treti, kaip metforminas, gali turėti netgi apsauginį poveikį (21).

Visame pasaulyje yra pripažinta, kad pacientams, kuriems yra diagnozuotas 2 tipo CD, būdinga didesnė širdies ir kraujagyslių ligų (ŠKL) bei mirtingumo nuo jų rizika (22, 23). CD yra ir viena pagrindinių inkstų nepakankamumo priežasčių (19, 24). Buvo nustatytas ir su infekcinėmis ligomis susijęs didesnis mirtingumo rodiklis tų pacientų, kuriems diagnozuotas CD (25). Tiesa, kol kas nėra pakankamai duomenų apie 2 tipo CD sergančių pacientų mirtingumą nuo kitų, ne su ŠKL ligomis susijusių, priežasčių ir neatsakyta, ar padidėjusi onkologinių ligų rizika daro įtaką ir didesniam mirtingumui nuo šių ligų bei kokie kiti veiksniai lemia mirtingumo riziką.

Gera metabolinė kontrolė, mažinanti sergamumą ir mirtingumą nuo CD sukeltų komplikacijų, yra svarbus veiksmingo CD gydymo veiksnys (26). Individualizuotai parenkamas gydymas, atsižvelgiant į galimą šalutinį vaistų poveikį bei gretutines paciento ligas, yra svarbus klinikinis sprendimas. Štai

kodėl moksliniai gliukozę mažinančių vaistų poveikio onkologinių ligų rizikai ir išgyvenamumui tyrimai yra itin reikšmingi. Tyrimai, kuriais nustatytas teigiamas metformino poveikis mažinant onkologinių ligų riziką, leidžia manyti, kad ateityje bus galima taikyti šiuos labai paplitusius vaistus onkologinių ligų prevencijai ir gydymui.

Tiesa, nei CD, nei vėžiu sergantys pacientai nėra homogeniška tiriamųjų grupė, nes skiriasi jų ligos eiga ir trukmė, o kur dar skirtingi rizikos veiksniai, mitybos ypatumai, pacientų tautybė, etninė kilmė, vaistai, paskirti abiem šioms ligoms bei gretutinėms ligoms gydyti, ir t. t. Visa tai gali turėti poveikį CD eigai, įvairių onkologinių ligų rizikai bei ligos prognozėms. Net ir atlikus ne vieną įvairaus pobūdžio tyrimą, kuriuo buvo siekiama įvertinti ryšį tarp cukrinio diabeto ir onkologinių ligų, vis dar trūksta pagrįstų įrodymų bei išsamių tyrimų (27). Štai kodėl toliau analizuoti šių dviejų ligų tarpusavio sąsajas išlieka svarbi ne tik dabarties, bet veikiausiai ir ateinančių dešimtmečių užduotis.

Ši daktaro disertacija yra parengta aštuonių tyrimų, paskelbtų mokslinėse publikacijose, pagrindu. Jos tikslas – ištirti sąsajas tarp 2 tipo CD ir vėžio bei įvertinti pacientų, sergančių 2 tipo CD, mirtingumo rodiklius Lietuvoje. I tyrime nagrinėjama bendroji onkologinių ligų ir specifinių lokalizacijų vėžio rizika pacientams, kuriems nustatytas 2 tipo CD. II–IV tyrimuose analizuojamas ryšys tarp cukrinio diabeto gydymo bei prostatos, kolorektalinio ir skrandžio vėžio rizikos. V straipsnyje nagrinėjama asmenų, sergančių 2 tipo CD, mirtingumo rizika ir jai įtaką darantys veiksniai. VI–VIII tyrimuose analizuojama prostatos, kolorektaliniu ir skrandžio vėžiu bei 2 tipo CD sergančių asmenų išgyvenamumas ir jo sąsajos su 2 tipo CD gydymu.

1.2. Tyrimo hipotezė

Cukrinis diabetas (CD) bei diabeto gydymui skiriami vaistai gali turėti įtakos vėžio rizikai ir išgyvenamumui.

1.3. Tyrimo tikslas

Antrojo tipo CD ir vėžio sąsajų bei asmenų, sergančių 2 tipo CD, mirtingumo rizikos analizė Lietuvos populiacijoje.

1.4. Tyrimo uždaviniai

1. Įvertinti pacientų, sergančių 2 tipo CD, riziką susirgti skirtingų lokalizacijų vėžiu (I);

2. Ištirti prostatos vėžio riziką 2 tipo CD sergantiems asmenims, priklausomai nuo jiems paskirtų vaistų diabetui gydyti (II);

3. Ištirti kolorektalinio vėžio riziką 2 tipo CD sergantiems asmenims, priklausomai nuo jiems paskirtų vaistų diabetui gydyti (III);

4. Ištirti skrandžio vėžio riziką 2 tipo CD sergantiems asmenims, priklausomai nuo jiems paskirtų vaistų diabetui gydyti (IV);

5. Įvertinti asmenų, sergančių 2 tipo CD, mirtingumo riziką (V);

6. Ištirti 2 tipo CD įtaką prostatos vėžiu sergančių vyrų išgyvenamumui, priklausomai nuo vaistų, paskirtų diabetui gydyti (VI);

7. Ištirti 2 tipo CD įtaką kolorektaliniu vėžiu sergančių ligonių išgyvenamumui, priklausomai nuo vaistų, paskirtų diabetui gydyti (VII);

8. Ištirti 2 tipo CD įtaką skrandžio vėžio ligonių išgyvenamumui, priklausomai nuo vaistų, paskirtų diabetui gydyti (VIII).

1.5. Darbo naujumas

Ši mokslinė disertacija, kurios rezultatas yra vienuolika paskelbtų mokslinių publikacijų, yra pirmasis tokio masto ne tik Lietuvoje, bet ir, kiek žinome, Europoje tyrimas, kuriame nagrinėjama mirtingumo ir onkologinių ligų rizika bei išgyvenamumas sergant vėžiu visoje šalies 2 tipo CD turinčių žmonių populiacijoje, remiantis pacientų duomenimis, gautais iš trijų patikimų registrų. Ankstesni kohortiniai tyrimai paprastai dėmesį telkė į vieną vėžio sritį, atskirą populiacijos grupę ar apibrėžtą regioną, o dar kiti rėmėsi gydymo centrų arba anketų duomenimis. Be to, 2 tipo CD gydymui skirtų vaistų ir galimo jų papildomo poveikio, ne tik gliukozės kiekiui mažinti, tyrimai mokslo pasaulyje kelia vis didesnį susidomėjimą. Šio tyrimo stiprybė ir naujumas yra tai, jog remiantis Privalomojo sveikatos draudimo

fondo pateiktais duomenimis buvo atsižvelgta į pacientų kada nors vartotus vaistus, o daugelyje ankstesnių tyrimų vaistų vartojimas buvo registruojamas tik tyrimo pradžioje.

1.6. Ginamieji teiginiai

1. Asmenims, sergantiems 2 tipo CD, yra didesnė kelių lokalizacijų vėžio rizika.

2. Vyrams, sergantiems 2 tipo CD, prostatos vėžio rizika yra mažesnė, o metformino vartojimas gali turėti teigiamą poveikį.

3. Asmenims, sergantiems 2 tipo CD, yra didesnė kolorektalinio vėžio rizika, tačiau metformino vartojimas gali turėti teigiamą poveikį.

4. Asmenims, sergantiems 2 tipo CD, skrandžio vėžio rizika nėra didesnė, o metformino vartojimas gali turėti teigiamą poveikį.

5. Asmenims, sergantiems 2 tipo CD, mirtingumo rizika yra padidėjusi.

6. Ilgalaikiam prostatos vėžio ligonių išgyvenimui 2 tipo CD ir metformino vartojimas turi įtakos.

7. Kolorektalinio vėžio ligonių išgyvenamumui 2 tipo CD ir metformino vartojimas turi įtakos.

8. Skrandžio vėžio ligonių išgyvenamumui 2 tipo CD ir metformino vartojimas įtakos neturi.

2. TYRIMO METODAI

2.1. Leidimas moksliniam darbui atlikti

Tyrimai buvo atliekami remiantis Helsinkio deklaracijos nuostatomis. Atsižvelgiant į mokslinio darbo pobūdį, nebuvo būtina apie tai informuoti pacientų ir gauti jų sutikimo. Leidimą moksliniam darbui atlikti išdavė Vilniaus regioninis biomedicinos tyrimų etikos komitetas (Nr. 158200-17-913-423).

2.2 Mokslinio darbo struktūra ir duomenų šaltiniai

Šios mokslinės disertacijos tyrimus pagal nagrinėjamą temą galima suskirstyti į tris dalis. Pirmoje dalyje nagrinėjama onkologinių ligų rizika (I–IV straipsniai), antroje – 2 tipo CD sergančių pacientų mirtingumo rizika (V straipsnis) ir trečioje – vėžiu ir 2 tipo CD sergančių pacientų išgyvenamumas (VI–VIII straipsniai).

Visos aštuonios šią daktaro disertaciją sudarančios mokslinės publikacijos yra retrospektyvieji kohortiniai tyrimai, atlikti remiantis skirtingų duomenų bazių: Privalomojo sveikatos draudimo fondo (PSDF) SVEIDRA, Nacionalinio vėžio instituto vėžio registro (visuose tyrimuose) ir Mirties atvejų ir jų priežasčių valstybės registro (V straipsnis) duomenimis.

Lietuvoje galioja privalomojo sveikatos draudimo sistema, todėl dauguma sveikatos priežiūros paslaugų yra apmokamos sveikatos draudimo fondo lėšomis. PSDF duomenų bazė, sukurta 1999 metais, yra surinkusi, saugo ir analizuoja sveikatos priežiūros įstaigų pateiktus duomenis. SVEIDROS duomenų bazėje yra saugomi demografiniai, diagnozių, kompensuojamųjų vaistų skyrimo, sveikatos priežiūros paslaugų teikimo ir gydymo išlaidų duomenys. Iš šios duomenų bazės buvo gauta informacija apie 2 tipo CD diagnozę (Tarptautinė statistinė ligų ir sveikatos sutrikimų klasifikacija, Australijos modifikacija (TLK)-10-AM, kodas E11), demografinius duomenis (amžius, lytis) ir paskirtus gliukozės kiekį mažinančius vaistus.

Nacionalinio vėžio instituto vėžio registras veikia nuo 1978 metų ir renka informaciją apie susirgimus onkologinėmis ligomis visoje Lietuvos teritorijoje. Jame kaupiama visų Lietuvos gyventojų, kuriems nuo 1978-ųjų buvo diagnozuota onkologinė liga, demografinė informacija (gyvenamoji vieta, lytis, gimimo data, gyvas ar miręs), informacija apie diagnozę (vėžio lokalizacija, naviko rūšis, diagnozės nustatymo data, diagnozės nustatymo

metodas) ir mirtį (mirties data, mirties priežastis). Onkologinės ligos koduojamos remiantis TLK-10-AM. Iš šios duomenų bazės buvo gauti duomenys apie paciento amžių diagnozės nustatymo metu, diagnozės datą, naviko rūšį (TNM klasifikacija), mirties datą ir mirties priežastį.

Ne onkologinių pacientų mirties priežasčių duomenys nurodomi mirties liudijime (Mirties atvejų ir jų priežasčių valstybės registre).

Pagal asmens kodą, kuris yra suteikiamas kiekvienam Lietuvos piliečiui, visų šių trijų registrų centrų pateikti duomenys buvo tarpusavyje susieti. Tolesni tyrimai rėmėsi anoniminiais duomenimis.

2.3. Tiriamųjų populiacija

Siekiant nustatyti 2 tipo CD sergančių pacientų vėžio riziką buvo identifikuoti visi vyrai ir moterys, kuriems per numatytą stebėjimo laikotarpį pagal SVEIDRA pateiktus duomenis buvo pirmą kartą diagnozuotas 2 tipo CD (TLK-10-AM kodas E11). 2 tipo CD diagnozę į duomenų bazę paprastai įrašo sveikatos priežiūros specialistai, todėl siekiant užtikrinti 2 tipo CD atvejų specifiškumą, į tyrimą buvo įtraukti tik tie pacientai, kuriems liga buvo diagnozuota sulaukus 40 metų ar vyresniame amžiuje ir kuriems buvo paskirti kompensuojamieji gliukozės kiekį mažinantys vaistai.

Pacientai, kuriems onkologinė liga buvo nustatyta anksčiau, nei patvirtinta 2 tipo CD diagnozė, nebuvo įtraukti į tiriamųjų imtį. II–IV publikacijose aprašyti ir kiti specifiniai neįtraukimo į kohortą kriterijai. Stebėjimas buvo nutraukiamas mirties ar emigracijos atveju arba stebėjimo laikotarpio pabaigoje.

V publikacijos tiriamųjų imtį sudarė visi žmonės, sirgę 2 tipo CD 2010 metų sausio pirmąją. Į kohortą nepateko pacientai, kurių ligos diagnozė sutapo su mirties data, ir pacientai, apie kurių mirties priežastį nebuvo informacijos.

Onkologinėmis ligomis sergančių pacientų išgyvenamumo tyrimams kohorta sudaryta iš pacientų, kuriems, Vėžio registro pateiktais duomenimis, tyrimo laikotarpiu pirmą kartą buvo diagnozuotas prostatos (VI), kolorektalinis (VII) arba skrandžio vėžys (VIII). Informacija apie 2 tipo CD diagnozę ir diabeto gydymą buvo gauta iš SVEIDRA duomenų bazės.

2.4. Antrojo tipo cukrinio diabeto gydymas Lietuvoje

Remiantis Lietuvos cukrinio diabeto kompensuojamo gydymo rekomendacijomis, metforminas yra pradinis geriamasis gliukozės kiekį mažinantis vaistas, skiriamas 2 tipo CD gydyti. Jei yra kontraindikacijų gydyti metforminu, pasireiškia šalutinis poveikis arba jį vartojant nepasiekiamas tikslinis glikemijos lygis (HbA1c mažiau nei 7 %), gydymui skiriamas dviejų vaistų derinys, paprastai pridedant sulfonilkarbamidų. Trečiame etape gali būti taikomas sudėtinis gydymas, kai skiriama daugiau nei dviejų rūšių gliukozės kiekį mažinančių vaistų (papildomai skiriama tiazolidinedionų, GLP-1 receptorių agonistų arba dipeltidipeptidazės-4 inhibitorių). Jei sudėtinis gydymas yra nesėkmingas arba bet kuriuo kitu metu, priklausomai nuo klinikinės paciento būklės, gali būti pradėtas gydymas insulinu. Pradėjus gydymą insulinu, gydymas metforminu paprastai nenutraukiamas (16).

2.5. Poveikio apibrėžimas

Gliukozės kiekį mažinančių vaistų įtaka analizuota II–VIII tyrimuose. Šeši mėnesiai buvo nustatytas kaip trumpiausias laikotarpis, būtinas, kad pasireikštų vaistų poveikis.

II ir III tyrimuose įvertintas ryšys tarp metformino vartojimo, kumuliacinės dozės ir rizikos susirgti prostatos bei kolorektaliniu vėžiu. Tiriamieji buvo suskirstyti į vartojusiųjų metforminą ir niekada jo nevartojusiųjų grupes. Šiuo būdu, pagal metformino vartojimą, į grupes suskirstyti 2 tipo CD sergantys pacientai VI bei VII publikacijose, kuriose analizuotas prostatos (VI) ir kolorektalinio vėžio (VI) ligonių išgyvenamumas, palyginti su kontroline grupe – pacientais, kuriems 2 tipo CD diagnozuotas nebuvo.

IV ir VIII tyrimuose visi kohortos tiriamieji pagal gydymo būdą buvo suskirstyti į keturias grupes: vartojančių metforminą ir kitus vaistus (išskyrus insuliną); gydomų insulinu ir kitais vaistais (išskyrus metforminą); vartojančių metforminą ir insuliną; vartojančių sulfonilkarbamidus, ir kontrolinę grupę – pacientų, kuriems nebuvo diagnozuotas 2 tipo CD.

V publikacijoje siekiant įvertinti mirtingumo riziką kohortos nariai pagal gydymo pobūdį buvo suskirstyti į tris grupes: gydomų geriamaisiais vaistais; insulinu ir geriamaisiais vaistais; ir tik insulinu. Siekiant nustatyti kohortos narių mirtingumo nuo specifinės priežasties riziką, įprastinės mirties priežastys buvo suskirstytos į dešimt pagrindinių kategorijų pagal TLK-10-

AM. Laikotarpis nuo diabeto diagnozės taip pat buvo suskirstytas į tris grupes (1–5, 6 –10 ir >10 metų).

2.6. Statistinė analizė

Siekiant įvertinti onkologinių ligų riziką (I–IV) buvo apskaičiuotas standartizuotas sergamumo santykis (SSS), išvedus vėžio atvejų tarp 2 tipo CD sergančių pacientų ir numatomų vėžio atvejų visos Lietuvos populiacijoje santykį.

Numatomi vėžio atvejai apskaičiuoti padauginus tikslų stebimų individo metų skaičių kohortoje pagal lytį iš kalendorinių metų ir amžiaus grupei, suskirstytai kas 5 metus, būdingo nacionalinio sergamumo rodiklių (185). Stebėjimo trukmė asmeniui buvo apskaičiuota nuo pirmo 2 tipo CD diagnozės įrašo SVEIDRA duomenų bazėje iki stebėjimo baigties datos. Analizuojant prostatos, kolorektalinio ir skrandžio vėžio riziką, buvo apskaičiuotas SSS pagal lytį, diabeto trukmę ir gliukozės kiekį mažinančių vaistų vartojimą.

Mirtingumo rizikos analizei (V) standartizuoto mirtingumo santykis (SMS) pagal lytį, amžių ir kalendorinį laikotarpį apskaičiuotas sergančių 2 tipo CD asmenų mirties atvejų skaičių dalijant iš numatomo mirties atvejų skaičiaus bendrojoje Lietuvos populiacijoje (186).

Siekiant nustatyti mirtingumo rizikos skirtumus tarp skirtingų diabetu sergančių pacientų grupių, suskirstytų pagal amžių ir diabeto trukmę, buvo taikomas chi kvadratų kriterijus.

SSS ir SMS 95 % pasikliautinieji intervalai (PI) buvo apskaičiuoti darant prielaidą, kad stebėtų atvejų skaičius pasiskirstęs pagal normalųjį skirstinį.

Atliekant išgyvenamumo analizę pacientai buvo suskirstyti į grupes pagal lytį, amžių, kada jiems buvo diagnozuota onkologinė liga, ir ligos stadiją (TNM klasifikacija). Chi kvadratų nepriklausomumo kriterijus naudotas siekiant palyginti demografinius ir klinikinius tiriamų grupių duomenis. Pasitelkus Kaplano-Mejerio metodą buvo sudarytos sergančiųjų vėžiu išgyvenamumo kreivės. Jos palygintos taikant logaritminio rango kriterijų.

Kokso proporcingos rizikos modeliais buvo remiamasi siekiant įvertinti paciento išgyvenamumą priklausomai nuo daugybinių rizikos veiksnių. Vienaveiksniais Kokso rizikos modeliais buvo siekiama nustatyti mirties rizikas (MR) bei jų 95 % PI ir palyginti bendrojo bei specifinio išgyvenamumo sergant vėžiu skirtumus, įvertinus skirtingus rizikos veiksnius: lytį, paciento amžių diagnozės nustatymo metu, diagnozės stadiją bei vartotus vaistus. Daugiaveiksniai Kokso rizikos modeliai buvo taikomi

siekiant įvertinti bendrąjį ir specifinį išgyvenamumą sergant vėžiu, įtraukiant tuos rizikos veiksnius, kurie, atlikus analizę, turėjo didžiausią įtaką išgyvenamumui (MR p reikšmė <0,2). Daugiaveiksniai Kokso rizikos modeliai, į analizę įtraukiant paciento amžių, diagnozės stadiją ir naviko histologiją, jei tokie duomenys prieinami, buvo naudojami siekiant nustatyti 2 tipo CD įtaką vėžiu sergančių ligonių išgyvenamumui, atsižvelgiant į atskirų tiriamųjų grupių skirtumus.

Rezultatai laikyti statistiškai reikšmingais, kai p reikšmė <0,05.

Duomenys apdoroti naudojant statistinės duomenų analizės programą STATA 11 arba 15 (11.0 ir 15.0 leidimai, College Station, TX, JAV).

2.7. Tyrimo privalumai ir apribojimai

Didžiausias šios disertacijos privalumas – atlikti tyrimai yra paremti realių Lietuvos gyventojų duomenimis, gautais iš patikimų registrų. Tyrimai apėmė visą Lietuvos populiaciją, rėmėsi didele imtimi ir ilgu stebėjimo laikotarpiu, tuo, ko pasiekti vykdant perspektyviuosius tyrimus paprastai nepavyksta. Taip išvengta atrankos poslinkio, o tiriamųjų populiaciją buvo galima palyginti su visos šalies populiacija. Be to, 2 tipo CD diagnozė buvo aiškiai apibrėžta, o duomenų rinkimas nebuvo paremtas savarankiškais pranešimais.

Lyginant ne vieno registrų centro duomenis buvo galima rasti informacijos apie visus pacientus, kuriems 2 tipo CD buvo gydomas farmakologiškai, kas buvo pažymėta ir V straipsnyje, todėl visi pacientai, kurie į Mirčių atvejų ir jų priežasčių registro ataskaitą galėjo būti neįtraukti arba Mirties liudijime cukrinis diabetas buvo nepateiktas kaip pagrindinė mirties priežastis, pateko į šio mokslinio darbo tyrimus.

Buvo ištirtas ne tik ryšys tarp vėžio ir 2 tipo CD, bet ir tarp atskirų CD gydymo būdų, o keliuose tyrimuose buvo įvertinta ir metformino kumuliacinės dozės įtaka vėžio rizikai bei vėžio išgyvenamumui.

Šios mokslinės disertacijos trūkumai būdingi retrospektyviesiems tyrimams. Pirma, trūko klinikinių duomenų, tarkim, apie glikemijos kontrolę ar atsparumą insulinui, bei informacijos apie tarpusavyje glaudžiai susijusius veiksnius, galinčius daryti įtaką cukrinio diabeto ir vėžio sąsajoms, tarkim, kūno masės indeksą, gretutines ligas, fizinį aktyvumą, rūkymą ir kitus. Be to, į tyrimus nebuvo įtraukta informacija apie kitus paciento vartojamus vaistus ar vėžio gydymą.

Reikia pažymėti ir tai, kad 2 tipo CD įtaka onkologinių ligų rizikai galėjo būti nepakankamai įvertinta, nes SSS rėmėsi visa populiacija, todėl

bendrojoje populiacijoje galėjo būti ir asmenų, kuriems 2 tipo CD dar nebuvo diagnozuotas, arba tų, kurie buvo gydomi ne Privalomojo sveikatos draudimo lėšomis. Net atliekant mirtingumo tyrimą (V publikacija) tikroji santykinė mirtingumo rizika galėjo būti nepakankamai įvertinta palyginti dažnai pasitaikančioms ligoms (187).

Kita vertus, asmenys, sergantys 2 tipo CD, paprastai dažniau lankosi pas gydytojus, todėl tikėtina, kad dažniau dalyvauja vėžio profilaktinės programose ir atlieka diagnostinius tyrimus. Siekiant sumažinti tokią galimybę ir atlikti kuo tikslesnius rizikos vertinimus, prostatos vėžio atvejai per pirmus metus nuo diabeto diagnozės, kaip ir skrandžio bei kolorektalinio vėžio atvejai per pirmus šešis mėnesius, nebuvo įtraukti į II, III ir IV tyrimus. Be to, VI ir VIII publikacijose pateiktų tyrimų galia) dėl santykinai nedidelio skaičiaus 2 tipo CD sergančių asmenų, kuriems diagnozuota ir onkologinė liga, buvo mažesnė, nei tikėtasi.

Galiausiai, CD gydymo bei vėžio rizikos ir išgyvenamumo rezultatų interpretacija yra sudėtingas uždavinys, nes pacientų grupės yra heterogeniškos dėl skirtingų gydymo paskirtais vaistais indikacijų, skirtingos gydymo trukmės, paskirtų vaistų dozių ir skirtingų vaistų cukriniam diabetui gydyti derinių.

3. REZULTATAI

3.1. I – 2 tipo CD ir įvairių lokalizacijų vėžio rizika

Šio tyrimo kohorta – 127 290 asmenų, sergančių 2 tipo CD, – yra didžiausia. Per 12 stebėjimo metų vėžio atvejai diagnozuoti 5 959 vyrams ir 6 661 moteriai.

Statistiškai reikšmingai didesnė rizika susirgti visų lokalizacijų vėžiu nustatyta moterims (SSS = 1,16), bet ne vyrams (SSS = 1,00). Vyrai, sirgę 2 tipo CD, turėjo didesnę riziką susirgti kepenų (SSS = 2,11), kasos (SSS = 1,77), inkstų (SSS = 1,46) ir skydliaukės (SSS = 1,83) vėžiu. Kolorektalinio vėžio (SSS = 1,23), odos melanomos (SSS = 1,40), nemelanominio odos vėžio (SSS = 1,14), vyriškųjų lyties organų (SSS = 1,86) bei kitų endokrininių organų (SSS = 1,96) vėžio rizika taip pat buvo padidėjusi.

Moterims, kurioms diagnozuotas 2 tipo CD, panašiai kaip ir vyrams, buvo nustatyta didesnė rizika susirgti kepenų (SSS = 1,45), kasos (SSS = 1,74), inkstų (SSS = 1,43), skydliaukės (SSS = 1,40), taip pat krūties (SSS = 1,24) ir gimdos (SSS = 2, 07) vėžiu.

Buvo pastebėta ir atvirkštinė CD asociacija su kelių rūšių vėžio rizika. Vyrams nustatyta mažesnė burnos (SSS = 0,49), stemplės (SSS = 0,50), gerklų (SSS = 0,57), plaučių ir trachėjos vėžio (SSS = 0,53), o moterims – melanomos (SSS = 0,74) ir leukemijos (SSS = 0,81) rizika.

3.2. II – 2 tipo CD ir prostatos vėžio rizika

Į galutinę kohortą įtraukta 64 000 vyrų, kuriems 2 tipo CD diagnozuotas laikotarpiu nuo 2000 metų iki 2016 metų. Stebėjimo trukmė apėmė 49 0187 individo metus. Tyrimo laikotarpiu buvo nustatytas 2 751 prostatos vėžio atvejis, kai numatomas atvejų skaičius pagal bendrąjį populiacijos sergamumą buvo 3 106,5. Apskaičiuota 11 % mažesnė prostatos vėžio rizika, SSS = 0, 89 (95 % PI = 0,85; 0,92).

Buvo nustatyta reikšmingai mažesnė prostatos vėžio rizika tarp įvairių amžiaus grupių vyrų, sirgusių 2 tipo CD. Prostatos vėžio rizika nebuvo susijusi su 2 tipo CD trukme. Reikšmingai mažesnė prostatos vėžio rizika nustatyta abiejų grupių pacientams: tiek vartojantiems metforminą, tiek niekada jo nevartojusiems, tačiau metformino vartotojams vėžio rizika buvo mažesnė (SSS = 0, 71, 95 % PI = 0,68; 0,75), palyginti su nevartojusiųjų grupe (SSS = 0,88, 95 % PI = 0,80; 0,96). Aiškios tendencijos tarp kumuliacinės metformino dozės ir vėžio rizikos mažėjimo nebuvo nustatyta.

3.3. III – 2 tipo CD ir kolorektalinio vėžio rizika

Į galutinę kohortą įtraukta 111 109 asmenų, sirgusių 2 tipo CD. Per stebėjimo laikotarpį kolorektalinis vėžys buvo nustatytas 1 213 pacientų, o numatomas atvejų skaičius pagal bendrąjį populiacijos sergamumą buvo 954,9 atvejo. Apskaičiuotas SSS = 1,27 (95 % PI = 1,20; 1,34).

Reikšmingai didesnė rizika susirgti kolorektaliniu vėžiu nustatyta visų amžiaus grupių tiek vyrams (SSS = 1,44, 95 % PI = 1,33; 1,57), tiek moterims (SSS = 1,15, 95 % PI = 1,06; 1,24). Šiai tiriamųjų populiacijai buvo didesnė rizika susirgti tiek gaubtinės žarnos (SSS = 1,36, 95 % PI = 1,27; 1,46), tiek tiesiosios žarnos vėžiu (SSS = 1,11, 95 % PI = 1,01; 1,20).

Vėžio rizika buvo padidėjusi nepriklausomai nuo CD trukmės. Be to, rizika susirgti kolorektaliniu vėžiu buvo padidėjusi tiek metformino vartotojams, tiek šio vaisto nevartojusiems asmenims. Tačiau kolorektalinio vėžio rizika buvo mažesnė tarp metformino vartotojų (SSS = 1,47, 95 % PI = 1,36; 1,58), palyginti su niekada metformino nevartojusiais asmenimis,

kuriems rizika buvo dvigubai didesnė, palyginti su bendrąja populiacija (SSS = 2,14, 95% PI = 1,95; 2,35). Be to, kolorektalinio vėžio rizika reikšmingai mažėjo didėjant kumuliacinei metformino dozei (p <0,001).

3.4. IV – 2 tipo CD ir skrandžio vėžio rizika

Iš 99 992 į tyrimą įtrauktų asmenų, sirgusių 2 tipo CD, stebėjimo laikotarpiu diagnozuoti 337 skrandžio vėžio atvejai, o numatomas atvejų skaičius pagal bendrąjį populiacijos sergamumą buvo 400,5. Apskaičiuota 16 % mažesnė skrandžio vėžio rizika (SSS = 0,84, 95 % PI = 0,76; 0,94). Mažesnė skrandžio vėžio rizika nustatyta ir vyrams, ir moterims, tačiau tik vyrams ši rizika buvo statistiškai reikšmingai mažesnė.

Antrojo tipo CD gydymui skirtų vaistų analizė parodė didesnę skrandžio vėžio riziką vartojusiems sulfonilkarbamidus (SSS = 1,31, 95 % PI = 1,04; 1,65), taip pat insuliną ir kitus vaistus (SSS = 1,16, 95 % PI = 0,73; 1,84), nors pastarasis rezultatas nebuvo statistiškai reikšmingas. Metformino vartotojams nustatyta mažesnė rizika, palyginti su bendrąja populiacija (SSS = 0,75, 95 % PI = 0,66; 0,86), o metformino ir insulino vartotojams – statistiškai nereikšmingai mažesnė rizika (SSS = 0,67, 95 % PI = 0,40; 1,11).

3.5. V – 2 tipo CD ir mirtingumo rizika

Į mirtingumo rizikos analizę buvo įtraukta 2 tipo CD sirgusių 89 512 asmenų, kurių 63,6 % sudarė moterys. Vidutinis pacientų, kuriems buvo diagnozuotas 2 tipo CD, amžius – 61,3 metų, o vidutinė stebėjimo trukmė – 12,1 metų. Tiriamojoje populiacijoje buvo nustatyta 35 % didesnė mirtingumo rizika. Ši rizika buvo reikšmingai didesnė ir vyrams, ir moterims, SMS atitinkamai 1,24 (PI = 1,22; 1,27) ir 1,43 (PI = 1,41; 1,45).

Didžiausia mirtingumo rizika nustatyta tiems, kuriems 2 tipo CD buvo diagnozuotas jauniausiame amžiuje (SMS = 1,68, 95 % PI = 1,60; 1,76), ir itin didelė – tiems pacientams, kurie mirė nesulaukę 50-ies (SMS = 22,04, 95 % PI = 18,82; 25,81). Pacientų amžiui didėjant, SMS mažėjo, bet išliko didesnis net ir tarp vyresnio amžiaus pacientų (SMS = 1,22). Didesnė mirtingumo dėl visų priežasčių rizika buvo nustatyta moterims, ypač jaunesnio amžiaus tiriamųjų grupėje.

Mirtingumo rizika didėjo priklausomai nuo CD trukmės: SMS = 1,09, 1,23 ir 1,36 atitinkamai 1–5 metų, 6–10 metų ir >10 metų laikotarpiu po diagnozės nustatymo (p < 0, 001).

Vertinant grupes pagal gydymą gliukozės kiekį mažinančiais vaistais (geriamieji vaistai, geriamieji vaistai ir insulinas, tik insulinas), mirtingumas visose tiriamųjų grupėse buvo nustatytas didesnis, nei buvo tikėtasi visos populiacijos mastu. Mirtingumo rizika kito priklausomai nuo CD gydymo – ji buvo padidėjusi 23 % (95 % PI = 1,22; 1,25) gydytiems tik geriamaisiais vaistais ir beveik 2,5 karto didesnė gydytiems tik insulinu.

Dažniausios 2 tipo CD ligonių mirties priežastys buvo susijusios su ŠKL (65,2 %), piktybiniais navikais (15,3 %), endokrininėmis ir medžiagų apykaitos ligomis (6,2 %, daugiausia dėl 2 tipo CD – 5,2 %) ir virškinimo sistemos ligomis (4,3 %).

Sergantiems 2 tipo CD asmenims, lyginant su bendrąja populiaciją, didžiausia mirties rizika, neskaitant dėl 2 tipo CD, buvo dėl infekcinių ligų (SMS = 1,44), ypač sepsio (SMS = 1,78), kraujotakos sistemos ligų (SMS = 1,42), ypač išeminės širdies ligos (SMS = 1,46) bei smegenų kraujagyslių ligų (SMS = 1,38). Tiesa, mirtingumo dėl piktybinių navikų rizika buvo padidėjusi tik moterims, sergančioms 2 tipo CD (SMS = 1, 13), bet ne vyrams (SMS = 0,93), o mirtingumo dėl išorinių priežasčių ir su alkoholio vartojimu susijusių ligų rizika 2 tipo CD sergantiems pacientams buvo netgi mažesnė, nei bendrojoje populiacijoje, vyrų grupėje šis skirtumas buvo statistiškai reikšmingas.

3.6. VI – 2 tipo CD ir išgyvenamumas segant prostatos vėžiu

254 (3,8 %) kohortos pacientams, kuriems buvo nustatytas prostatos vėžys, jau anksčiau buvo diagnozuotas 2 tipo CD. Per visą stebėjimo trukmę iš 4 807 mirties atvejų 2 084 pacientai mirė nuo prostatos vėžio.

Nustatant prostatos vėžio diagnozę tarp CD nesergančių vyrų buvo daugiau išplitusio vėžio ir mažiau lokalaus vėžio atvejų. Koregavus tiriamųjų grupes pagal amžių ir vėžio stadiją, prostatos vėžiu sergančių pacientų mirties rizika buvo 19 % mažesnė tarp vyrų, kuriems buvo diagnozuotas 2 tipo CD, nors skirtumas nebuvo statistiškai reikšmingas (MR = 0,81, 95 % PI = 0,62; 1,06). Palyginus tiriamųjų, kuriems skirtas skirtingas CD gydymas, grupes nustatyta, kad specifinio prostatos vėžio mirties rizika buvo 26 % mažesnė tarp cukriniu diabetu sergančių vyrų, kuriems buvo paskirtas gydymas metforminu (MR = 0,74, 95 % PI = 0,54; 1,02), nei tarp pacientų, nesergančių CD, tačiau skirtumas nebuvo statistiškai reikšmingas. Prostatos vėžiu sergančių asmenų, nevartojusių metformino, mirties rizika labai nesiskyrė nuo tų, kuriems diabetas nebuvo nustatytas (MR = 1,03, 95 % PI = 0, 64; 1,66).

Koreguotas bendrasis prostatos vėžiu sirgusių asmenų išgyvenamumas buvo statistiškai reikšmingai mažesnis (MR = 1,24, 95 % PI = 1,07; 1,43) tarp vyrų, sirgusių 2 tipo CD. Didžiausia mirties rizika nustatyta metformino nevartojusiems vyrams (MR = 1,63, 95 % PI = 1,27; 2,10), o CD nesirgusių pacientų ir metformino vartotojų mirties rizika buvo panaši (MR = 1,12, PI = 0,94; 1,33).

3.7. VII – 2 tipo CD ir išgyvenamumas sergant kolorektaliniu vėžiu

Kolorektaliniu vėžiu sirgę 1 094 (7,27 %) pacientai, įtraukti į tyrimo populiaciją, iki diagnozuojant vėžį sirgo ir 2 tipo CD. Per visą stebėjimo laikotarpį buvo nustatyta 10 927 mirties atvejų, iš kurių 8 559 – nuo kolorektalinio vėžio.

Taikant daugiaveiksnę analizę koregavus grupes pagal amžių ir diagnozės stadiją paaiškėjo, kad CD sirgusieji turėjo 13 % mažesnę specifinę mirties nuo kolorektalinio vėžio riziką (MR = 0,87, 95 % PI = 0,80; 0,94), o bendrojo išgyvenamumo skirtumo šiose grupėse nepastebėta.

Palyginus CD sergančius pacientus pagal jiems skirtą gydymą nuo diabeto ir rodiklį koregavus pagal amžių bei diagnozės stadiją, buvo nustatytas 23 % didesnis specifinis kolorektalinio vėžio išgyvenamumas (MR = 0,77, 95 % PI = 0,64; 0,93) ir 25 % (MR = 0,75, 95 % PI = 0,64; 0,87) didesnis bendrasis išgyvenamumas metformino vartotojų grupėje.

3.8. VIII – 2 tipo CD ir išgyvenamumas sergant skrandžio vėžiu

Į tyrimą įtrauktiems skrandžio vėžiu sirgusiems 555 (6,59 %) pacientams anksčiau buvo nustatyta 2 tipo CD diagnozė. Per stebėjimo laikotarpį buvo 7 199 mirties atvejai, iš kurių 6 111 – nuo skrandžio vėžio.

Daugiaveiksnėje analizėje atlikus koregavimą pagal lytį, amžių ir ligos stadiją, reikšmingo CD ligonių skrandžio vėžio išgyvenamumo (MR = 0,93, 95 % PI = 0,84; 1,03) ir bendrojo išgyvenamumo (MR = 0,97, 95 % CI = 0,88; 1,06) skirtumo, palyginti su tiriamaisiais, kuriems CD nebuvo diagnozuotas, nebuvo.

Be to, nebuvo ir reikšmingo skrandžio vėžio ligonių ir bendrojo išgyvenamumo skirtumo nagrinėjant grupes pagal vaistų nuo diabeto vartojimą. Tiesa, mažiausias išgyvenamumas buvo tų, kuriems buvo skirtas

gydymas sulfonilkarbamidais (vėžio mirtingumo, lyginant su metformino vartotojais, MR = 1,09, bendrojo mirtingumo MR = 1,02).

4. REZULTATŲ APTARIMAS

Šioje daktaro disertacijoje nagrinėjama tema – pirmoji tokios apimties ir tokį ilgą laikotarpį apimanti analizė, kurioje nagrinėjama visos Lietuvos asmenų, sergančių CD, populiacija bei 2 tipo CD ir jo gydymo sąsajos su vėžio rizika ir išgyvenamumu bei mirtingumo nuo įvairių priežasčių rizika. Moksliniame darbe buvo atskleista, kad asmenys, kuriems diagnozuotas 2 tipo CD, turi reikšmingai didesnę mirtingumo riziką, palyginti su bendrąja populiacija. Jie dažniau miršta nuo širdies ir kraujagyslių ligų, infekcinių, virškinimo bei šlapimo ir lyties organų ligų, o moterys – ir nuo onkologinių bei kvėpavimo sistemos ligų. Be to, moterims būdinga didesnė bendroji vėžio rizika, o tiek vyrams, tiek moterims nustatyta didesnė tam tikrų lokalizacijų vėžio rizika. Be to, neatrodo, kad CD neigiamai veiktų prostatos, kolorektalinio ir skrandžio vėžio išgyvenamumą, o metformino vartojimas, tikėtina, turi teigiamą įtaką kolorektalinio ir prostatos vėžio išgyvenamumui.

Toliau apariami kiekvieno atskiro tyrimo rezultatai.

4.1. I – 2 tipo CD ir įvairių lokalizacijų vėžio rizika

Vėžio rizikos tyrimo duomenimis, asmenys, sergantys 2 tipo CD, turi reikšmingai didesnę riziką susirgti tam tikrų lokalizacijų vėžiu. Buvo nustatyta skirtinga bendroji vėžio rizika vyrams ir moterims. Vyrų ir moterų rizikos skirtumus iš dalies lemia labiausiai paplitę moterims būdingi gimdos ir krūties navikai. Kai šie navikai nėra įtraukiami į rizikos analizę, moterų vėžio rizika sumažėja, bet vis tiek išlieka didesnė (SSS 1,06, 95 % PI 1,03–1,09). Kita vertus, vyrams nustatyta daugiau įvairių lokalizacijų, kurių vėžio rizika buvo didesnė, palyginti su moterimis, tačiau šių rūšių onkologinės ligos yra mažiau paplitusios, todėl ir nelėmė bendrosios vėžio rizikos padidėjimo.

Tyrimo metu apskaičiuotas asmenų, sirgusių 2 tipo CD, bendrasis vėžio SSS panašus į ankstesniuose Europoje atliktuose kohortiniuose tyrimuose gautus rezultatus (117–119) bei Ohkuma ir kt. atliktos 121 kohortos metaanalizės duomenis, nors pastarosios metaanalizės apskaičiuota santykinė rizika buvo kiek didesnė nei mūsų ir reikšmingai padidėjusi tiek vyrams, tiek moterims (120).

Vertinant atskirų vėžio lokalizacijų SSS, mūsų rezultatai palyginami su anksčiau atliktų metaanalizių rezultatais (58, 121–130). Pavyzdžiui, panašiai kaip Song ir kt. atliktoje metaanalizėje, ir vyrams, ir moterims, kuriems diagnozuotas 2 tipo CD, nustatyta daugiau nei 75 % didesnė kasos vėžio rizika (122). Nors šiuo atveju gali būti įtariamas atvirkštinis priežastinis ryšys, nuolat pastebima didesnė kasos vėžio rizika ir po ilgesnio stebėjimo rodo, kad tai abejotina (63, 122).

Vyrų, sergančių 2 tipo CD sergamumo kepenų vėžiu rizika buvo dvigubai didesnė, o moterų – 45 %, palyginti su bendrąja populiacija. Šie rezultatai yra panašūs į nustatytus Wang ir kt. 2012 m. bei 2016 m. metaanalizėse (58, 121). Naujausioje metaanalizėje apskaičiuota, kad 2 tipo CD ir kepenų vėžio sąsajoms turi įtakos rūkymas ir kūno masės indeksas (58). Šiame tyrime nustatyta 23 % didesnė kolorektalinio vėžio rizika vyrams ir 7 % – moterims, nors pastarasis skirtumas buvo statistiškai nereikšmingas. Kelios kohortinių bei atvejų ir kontrolės tyrimų metaanalizės parodė didesnę kolorektalinio vėžio riziką ir vyrams, ir moterims, sergantiems 2 tipo CD (125–127). Antojo tipo CD ir kolorektaliniam vėžiui būdingi tie patys rizikos veiksniai – nutukimas ir rūkymas, bet net ir atsižvelgus į šiuos veiksnius ryšys tarp šių ligų išlieka (127). Panašiai nustatėme 40 % didesnę inkstų vėžio riziką vyrams ir moterims. Šis rezultatas panašus į Bao ir kt. atliktos metaanalizės, kurioje apskaičiuota, kad inkstų vėžio rizika, susijusi su 2 tipo CD, nepriklauso nuo alkoholio vartojimo, KMI, nutukimo ir rūkymo (123).

Taigi kai kurių vėžio lokalizacijų riziką gali paveikti svarbūs klinikiniai veiksniai, kurie skirtingose populiacijose gali būti nevienodi. Deja, klinikinių veiksnių analizė daugelyje retrospektyviųjų tyrimų, taip pat ir mūsų, neįmanoma, nes registruose trūksta tokio tipo duomenų.

Mūsų tyrime moterims, sergančioms 2 tipo CD, skydliaukės vėžio rizika buvo 40 %, vyrams – 80 % didesnė, nors vyrams tai išliko reta vėžio forma. Ankstesnių tyrimų rezultatai nenuoseklūs (124, 131). Didesnė rizika nustatyta moterims, gyvenančioms vietovėse, kuriose skydliaukės vėžys santykinai plačiau paplitęs (124). Spėjame, kad Lietuvoje didesnis skydliaukės vėžio atvejų skaičius tarp sergančiųjų 2 tipo CD, ypač vyrų, yra nustatomas todėl, kad Lietuvoje pacientams, besilankantiems pas endokrinologus, paprastai atliekamas skydliaukės ultragarsinis tyrimas, o prireikus – ir aspiracinė punkcinė biopsija, tokiu būdu anksti aptinkamos ir mikrokarcinomos (188).

Šiame tyrime vyrų, kuriems diagnozuotas 2 tipo CD, prostatos vėžio rizika nesiskyrė nuo bendrosios populiacijos, priešingai nei neseniai atliktoje metaanalizėje, kur prostatos vėžio rizika buvo 14 % mažesnė sergantiems CD vyrams (189). Lietuvoje 2006 metais šalies mastu pradėjo veikti

ankstyvos stadijos prostatos vėžio nustatymo programa, todėl apskritai padaugėjo prostatos vėžio atvejų (190). Taigi mūsų rezultatų nukrypimą galima iš dalies paaiškinti sustiprinta CD sergančiųjų stebėsena, papildomų medicininių tyrimų atlikimu, tarp kurių ir prostatos specifinio antigeno (PSA) testas, kuriuo aptinkami ir ankstyvos stadijos besimptomiai navikai (138).

Be to, buvo nustatyta ne tik didesnė kai kurių lokalizacijų, bet ir mažesnė plaučių, trachėjos, stemplės, burnos ir gerklų vėžio rizika CD sergantiems vyrams. Palyginimui, trylikos tyrimų metaanalizė rado, kad CD didina stemplės vėžio riziką, tačiau nebuvo klinikinių veiksnių duomenų (192). Burnos ertmės, ryklės, stemplės, gerklų, trachėjos bei plaučių navikai paprastai siejami su rūkymu ir piktnaudžiavimu alkoholiu (193). Mažesnę kai kurių rūšių vėžio riziką mūsų tyrime galima paaiškinti skirtingu žinomų rizikos veiksnių paplitimu CD sergančių žmonių grupėje ir bendrojoje populiacijoje.

4.2. II straipsnis – 2 tipo CD ir prostatos vėžio rizika

Siekdami atsižvelgti į galimą stebėsenos poslinkį, kurį įtarėme I tyrime, ir ištirti galimą ilgalaikio gydymo metforminu poveikį, į šią analizę įtraukėme vyrus, kuriems 2 tipo CD buvo diagnozuotas daugiau nei prieš vienerius metus. Palyginti su bendrąja populiacija, jiems nustatyta 11 % mažesnė prostatos vėžio rizika. Mūsų gauti rezultatai atitiko Bansal ir kt. metaanalizės rezultatus (189). Be to, panašiai kaip Turner ir kt. ar Xu ir kt. tyrimuose, neradome sąsajų tarp 2 tipo CD trukmės ir prostatos vėžio rizikos (145, 146).

Dar viena įdomi įžvalga: jaunesnio amžiaus asmenims, sergantiems CD, būdinga mažesnė prostatos vėžio rizika. Dviejų tyrimų duomenimis, pacientai, kuriems CD diagnozuotas jaunesniems nei 30-ies metų, turėjo santykinai mažesnę prostatos vėžio riziką, nei tie, kurie CD susirgo vyresni (148, 194). Tiesa, į šiuos tyrimus buvo įtraukti visų tipų CD sirgę ir jauni pacientai, todėl, kadangi prostatos vėžys yra vyresnio amžiaus pacientų liga, gali būti, kad jaunesnių tiriamųjų įtraukimas ir trumpesnis stebėjimo laikotarpis gali turėti įtakos tyrimo rezultatams. Mūsų tiriamųjų kohortoje mažesnė prostatos vėžio rizika pastebėta visose amžiaus grupėse, pradedant nuo 40-ies.

Vyrų, kuriems nustatytas hipogonadizmas, ir pakaitinės hormonų terapijos tyrimai rodo, kad testosteronas atlieka svarbų vaidmenį vystantis prostatos vėžiui (195, 196). Testosterono lygio įvertinimas nustatant diabeto

diagnozę ir gydant būtų naudingas norint įvertinti papildomus prostatos vėžio vystymosi veiksnius.

Šiame tyrime nustatėme, kad metformino vartotojų prostatos vėžio rizika yra reikšmingai mažesnė, palyginti su niekada nevartojusiais, – atitinkamai 29 % ir 12 %. Taivane atliktas tyrimas taip pat parodė galimą metformino naudą: tyrėjai apskaičiavo, kad kuo didesnė kumuliatyvinė metformino dozė, tuo mažesnė prostatos vėžio rizika (197). Tačiau panašiame Švedijoje atliktame tyrime vyrams, sergantiems 2 tipo CD, metformino vartojimas vėžio rizikos labiau nesumažino, palyginti su iš viso vaistų nuo diabeto nevartojusiais vyrais (198).

Kad diabeto, metformino vartojimo ir prostatos vėžio ryšys gali būti priežastinis, galima įtarti remiantis tuo, kad prostatos vėžio rizika mažėja ilgėjant diabeto trukmei ir ilgėjant metformino vartojimo trukmei arba didėjant kumuliacinei metformino dozei, tačiau mūsų tyrimas neparodė ryšio tarp cukrinio diabeto trukmės ar kumuliacinės metformino dozės.

4.3. III – 2 tipo CD ir kolorektalinio vėžio rizika

Kolorektalinis vėžys yra siejamas su atsparumu insulinui ir 2 tipo CD, o metforminas, atrodo, pasižymi poveikiu per literatūros apžvalgoje aptartus tam tikrus mechanizmus slopinti naviko vystymąsi. Šiame tyrime, kuriame kohorta stebėta 10 metų, nustatyta, kad 2 tipo CD susijęs su didesne kolorektalinio vėžio rizika abiejų lyčių bei įvairaus amžiaus asmenims. Kita vertus, metformino vartojimas didėjant kumuliacinei dozei buvo susijęs su mažėjančia kolorektalinio vėžio rizika, kas palaiko priešvėžinio metformino poveikio hipotezę.

Šie rezultatai yra panašūs į Danijoje, Kinijoje ir Airijoje atliktų tyrimų rezultatus (132–134), tačiau kituose tyrimuose iš Kanados, JK ar Vokietijos, taip pat atsitiktinių imčių kontroliuojamuose klinikiniuose tyrimuose ADOPT ir RECORD apsauginio metformino poveikio nenustatyta (136–139).

Su laiku susijęs poslinkis, kurio sunku išvengti retrospektyviuosiuose tyrimuose, gali paaiškinti kai kuriuos tyrimo rezultatų skirtumus (98). Neseniai atliktas kohortinis tyrimas, kuriame naudoti metodai šiam poslinkiui sumažinti, parodė, kad ilgalaikis metformino vartojimas yra susijęs su mažesne kolorektalinio vėžio rizika. Be to, vietoj sulfonilkarbamidų paskyrus metforminą arba pridėjus metforminą pastarajame tyrime pastebėtas kolorektalinio vėžio rizikos sumažėjimas (199).

4.4. IV – 2 tipo CD ir skrandžio vėžio rizika

Šiame tyrime buvo tirtas ne tik metformino, bet keleto gliukozės kiekį mažinančio gydymo derinių, siekiant nustatyti galimas sąsajas su diabeto gydymu ir vėžio rizika. Rezultatai atskleidė, kad 2 tipo CD nėra susijęs su padidėjusia skrandžio vėžio rizika, priešingai, 2 tipo CD sirgusieji turėjo mažesnę skrandžio vėžio riziką, nors moterims šis skirtumas nebuvo statistiškai reikšmingas.

Be to, buvo reikšmingų vėžio rizikos skirtumų atskirose grupėse pagal diabetui skirtų vaistų vartojimą. Šiame tyrime vartojusieji metforminą kartu su kitais geriamaisiais gliukozės kiekį mažinančiais vaistais turėjo 25 % mažesnę, o vartojusieji sulfonilkarbamidus – 31 % didesnę skrandžio vėžio riziką. Daugelis skrandžio vėžio rizikos epidemiologinių tyrimų buvo atlikti Taivane, iš jų vienų tyrimų rezultatai buvo panašūs, o kitų skyrėsi (140–143). Dėl skirtingų tyrimo populiacijų, tyrimų struktūros bei stebėjimo bei gydymo trukmės, taip pat dėl įvairių gliukozės kiekį mažinančių vaistų derinių skyrimo sunku tiesiogiai palyginti tyrimus ir daryti galutines išvadas.

Tačiau dvi naujausios metaanalizės gavo rezultatus, panašius į mūsų (200, 201). Miao ir kt. atlikta 22 tyrimų metaanalizė parodė, kad asmenų, sergančių CD, skrandžio vėžio rizika ar mirštamumas nuo skrandžio vėžio skyrėsi mažai arba nesiskyrė (200). Zhou ir kt. atliktoje metaanalizėje, apimančioje septynis tyrimus, nustatyta, kad metformino terapija, palyginti su kitokia terapija, buvo susijusi su mažesne skrandžio vėžio rizika ligoniams, sergantiems 2 tipo CD (201).

4.5. V – 2 tipo CD ir mirtingumo rizika

Asmenims, sergantiems 2 tipo CD, nustatyta 35 % didesnė mirtingumo nuo visų priežasčių rizika, o moterims ši rizika buvo dar didesnė, ypač jauniausio amžiaus grupėje. Perteklinis mirtingumas, susijęs su 2 tipo CD, buvo ypač didesnis tiems, kuriems 2 tipo CD diagnozuotas jaunesniame amžiuje, kurie mirė jaunesni, CD sirgo ilgiausiai, ir tiems, kuriems reikėjo gydymo insulinu.

Šiame nacionaliniame tyrime dalyvavo daugiau nei 89 tūkst. 2 tipo CD sergančių asmenų, stebėjimo laikotarpiu išanalizuota daugiau nei 30 tūkst. mirties atvejų. Esant didelei kohortai buvo galima ištirti įvairias mirtingumo priežastis ir gautus rezultatus palyginti su visos populiacijos rezultatais.

Tyrimas parodė, kad 2 tipo CD sirgę vyrai ir moterys turėjo ne tik didesnę riziką mirti nuo paties diabeto ar nuo širdies ir kraujagyslių ligų

(ŠKL), bet ir daug didesnę riziką mirti nuo infekcinių, virškinimo ir urogenitalinių ligų. Tačiau mirtingumas nuo vėžio buvo reikšmingai padidėjęs tik CD sergančioms moterims, bet ne vyrams, tikriausiai dėl didesnio sergamumo gimdos kūno ir krūties vėžiu, kurį nustatėme moterims, sergančioms 2 tipo CD (I). Be to, didesnė rizika mirti nuo kvėpavimo takų ligų taip pat buvo nustatyta moterims.

Panašūs tyrimai iš viso pasaulio, tiek ankstesni (19, 150–152), tiek naujausi (153–155, 202), nepriklausomai nuo to, kad ilgainiui tobulėjo CD gydymas, taip pat rodo, kad 2 tipo CD didina mirtingumą nuo visų priežasčių; tačiau ryšys su nekraujagyslinėmis mirties priežastimis įvairiose populiacijose šiek tiek skiriasi. Įdomu tai, kad mūsų populiacijoje mirtingumas nuo išorinių priežasčių ir su alkoholiu susijusių ligų, taip pat nervų sistemos ligų diabetu sergančių pacientų kohortoje buvo mažesnis nei bendrojoje populiacijoje. Informacijos apie šias rečiau pasitaikančias mirties priežastis kituose tyrimuose nėra daug ir ji įvairuoja, todėl mūsų duomenys papildo svarbią spragą apie mažiau ištirtas mirties priežastis.

Kai kuriuose ankstesniuose tyrimuose 2 tipo CD ligoniams nustatyta nepakitusi, palyginti su bendrąja populiacija, mirtingumo nuo išorinių priežasčių rizika (19, 150, 151), kituose – padidėjusi (152, 203); tiesa, daugelis tyrimų nenagrinėjo šių mirties priežasčių. Labiausiai tikėtina, kad šias mirties priežastis gali veikti socialiniai, ekonominiai ir kultūriniai tirtų populiacijų skirtumai.

Nors dauguma epidemiologinių tyrimų atlikta Vakarų šalyse, atrodo, kad padidėjusio mirtingumo tendencijos nelabai skiriasi ir Rytuose, kur tokia rizika yra dar didesnė. Taip pat didesnė ir rizika mirti nuo kai kurių lokalizacijų vėžio (156). Kaip ir mūsų duomenimis, didžiausias mirtingumo rizikos padidėjimas būdingas moterims ir jaunesniems asmenims (157).

Atsižvelgus į CD kontroliuoti skirtą gydymą, tyrime nustatyta, kad tie, kurie vartojo insuliną, turėjo didžiausią mirtingumo riziką, palygti su tais, kurie vartojo tik geriamuosius gliukozės kiekį mažinančius vaistus arba kuriems taikytas sudėtinis gydymas. Panašios sąsajos pastebėtos ir anksčiau paskelbtuose tyrimuose (19). Tai gali būti labiau susiję ligos sunkumu, nei su pačiu gydymu, nes paprastai insulinas yra skiriamas tada, kai ligos kontrolei nebeužtenka dietos ir geriamųjų vaistų arba kai yra kontraindikacijų skirti geriamuosius vaistus, pavyzdžiui, pacientas serga inkstų ar kepenų nepakankamumu.

4.6. VI – 2 tipo CD ir išgyvenamumas sergant prostatos vėžiu

Prostatos vėžys linkęs progresuoti lėčiau nei daugelis kitų navikų, todėl, norint gauti reikšmingų rezultatų, prostatos vėžio išgyvenamumo tyrimų trukmė turėtų būti ilga. Mūsų nacionaliniame prostatos vėžiu sergančių pacientų kohortos tyrime pacientai buvo stebimi iki 10 metų.

Tyrimas parodė, kad pacientams, sergantiems prostatos vėžiu ir 2 tipo CD, buvo didesnė bendrojo mirtingumo rizika, tačiau prostatos vėžio specifinis išgyvenamumas reikšmingai nesiskyrė, o 2 tipo CD sirgusiųjų grupėje buvo šiek tiek mažesnis. Be to, buvo aiški geresnio specifinio prostatos išgyvenamumo tendencija metformino vartotojams, palyginti su tais, kurie CD nesirgo ir kurie sirgo, bet metformino nevartojo. Be to, bendrasis CD sergančių metformino vartotojų išgyvenamumas nesiskyrė nuo diabetu nesergančių pacientų, tačiau buvo reikšmingai blogesnis diabetu sergančių pacientų, kurie metformino nevartojo. Gali būti, kad tai lėmė blogesnė metabolinė kontrolė ir bendroji padidėjusi mirtingumo rizika šioje 2 tipo CD sergančių pacientų grupėje.

Metformino poveikio ne su CD susijusioms baigtims nagrinėjimas klinikiniame moksle yra sudėtingas dėl tyrimo populiacijų ir metodų įvairovės. Literatūroje įrodymai apie teigiamą metformino poveikį prostatos vėžio išgyvenamumui yra prieštaringi (168). Kai kurie ankstyviausi retrospektyvieji klinikiniai tyrimai parodė teigiamą metformino poveikį prostatos vėžio ligonių išgyvenamumui (114, 161, 162), kiti tokio poveikio nerado (163–165). Keli perspektyvieji tyrimai taip pat neparodė gydymo metforminu naudos (166, 167), tačiau šiuos tyrimus apribojo palyginti nedidelės tiriamųjų, vartojusių metforminą, grupės.

4.7. VII – 2 tipo CD ir išgyvenamumas sergant kolorektaliniu vėžiu

Šis tyrimas yra vienas didžiausių iki šiol atliktų kohortinių kolorektalinio vėžio tyrimų, parodęs, kad bendrasis ir specifinis išgyvenamumas sergant kolorektaliniu vėžiu reikšmingai geresnis metformino vartotojų grupėje, palyginti su nevartojusiais metformino ir net nesergančiais 2 tipo CD.

Ankstesni kohortiniai tyrimai parodė, kad metformino vartojimas pagerina kolorektalinio vėžio ligonių išgyvenamumą (170–172). Tačiau šiuose tyrimuose vertintas tik bendrasis mirtingumas, o ne specifinis išgyvenamumas sergant vėžiu. Keletas mažesnių retrospektyviųjų analizių, panašiai kaip šiame tyrime, nustatė ilgesnį specifinį kolorektalinio vėžio išgyvenamumą pacientams, sirgusiems CD ir vartojusiems metforminą (134,

174), o keli kiti (175–177) reikšmingų skirtumų, susijusių su metformino vartojimu, nenustatė.

Tačiau neseniai atlikta metformino kaip papildomo kelių lokalizacijų vėžio, įskaitant kolorektalinį vėžį, gydymo būdo metaanalizė parodė, kad šio vaisto vartojimas yra naudingas visoms ankstyvosios stadijos kolorektalinio vėžio baigtims (115). Be to, metastazavusio kolorektalinio vėžio klinikinio II fazės tyrimo rezultatai parodė, kad CD sergantiems pacientams metforminas, vartojamas kartu su įprasta chemoterapija, turi teigiamą poveikį (178).

Rezultatų skirtumus literatūroje galima paaiškinti skirtinga tyrimų struktūra, nevienalytėmis tyrimų populiacijomis, skirtingais diabeto ir vėžio gydymo būdais, stebėjimo periodais ir daugeliu kitų veiksnių, turinčių įtakos studijų rezultatams.

4.8. VIII – 2 tipo CD ir išgyvenamumas sergant skrandžio vėžiu

Tyrimo rezultatai neparodė reikšmingo ryšio tarp vaistų nuo hiperglikemijos vartojimo ir skrandžio vėžio išgyvenamumo 2 tipo CD sergantiems pacientams Lietuvoje. Tačiau geresnės išgyvenamumo tendencijos buvo pastebėtos grupėse, kurių pacientams skirtas gydymas metformino ar insulino deriniais, o blogiausias išgyvenamumas (ir mažesnis nei diabetu nesergančių pacientų) – sulfonilkarbamidus vartojusiųjų grupėje.

Keletas ankstesnių tyrimų nagrinėjo CD ir skirtingų gydymo derinių įtaką bendrajam vėžio pacientų išgyvenamumui (78, 159, 160), ir tik keliuose ankstesniuose tyrimuose buvo įvertinta vaistų nuo hiperglikemijos ir išgyvenamumo sergant skrandžio vėžiu sąsaja (179–181). Jų rezultatai, panašiai kaip mūsų, buvo palankesni metformino vartotojams.

Apibendrinant CD įtaką skrandžio vėžiu sergančių pacientų išgyvenimui, rodos, per anksti daryti tvirtas išvadas iš turimų literatūros įrodymų. Būsimuose tyrimuose turėtų būti vertinami galimi įtaką darantys klinikiniai veiksniai, vaistų dozės, informacija apie specifines CD indikacijas ir vėžio gydymą, taip pat būtų pravartu palyginti duomenis iš įvairių tyrimų centrų ir šalių.

5. IŠVADOS

1. Bendroji vėžio rizika didesnė moterims, sergančioms 2 tipo CD, bet ne vyrams. Reikšmingai didesnė tam tikrų lokalizacijų – kepenų, kasos, inkstų ir skydliaukės vėžio rizika tiek vyrams, tiek moterims. Kolorektalinio vėžio ir odos vėžio rizika didesnė vyrams, o krūties ir gimdos vėžio rizika – moterims.

2. Prostatos vėžio rizika vyrams, kurie iki vėžio diagnozės mažiausiai vienerius metus sirgo 2 tipo CD, yra mažesnė. Metformino vartojimas siejamas su mažiausia vėžio rizika.

3. Asmenims, sirgusiems 2 tipo CD mažiausiai 6 mėnesius iki vėžio diagnozės, yra didesnė kolorektalinio vėžio rizika. Kolorektalinio vėžio rizika mažėja didėjant kumuliacinei metformino dozei.

4. Antrojo tipo CD nėra susijęs su didesne skrandžio vėžio rizika. Metformino ir kitų geriamųjų gliukozės kiekį mažinančių vaistų vartojimas siejamas su mažesne, o sulfonilkarbamidų – su didesne skrandžio vėžio rizika.

5. Lietuvoje asmenims, sergantiems 2 tipo CD, mirtingumo nuo visų priežasčių rizika didesnė. Ir vyrams, ir moterims, sergantiems 2 tipo CD, didesnė mirties nuo paties CD, širdies ir kraujagyslių, infekcinių, virškinimo ir urogenitalinių ligų rizika. Moterims taip pat yra padidėjusi mirtingumo nuo vėžio ir kvėpavimo takų ligų rizika. Didžiausias mirtingumas yra tų asmenų, kurie 2 tipo CD susirgo jaunesniame amžiuje, mirė jaunesniame amžiuje, ilgiau sirgo CD, ir tiems, kuriems skirtas gydymas insulinu. Moterų mirtingumo rizika yra didesnė nei vyrų visose grupėse pagal amžių, CD trukmę ir taikytą gydymą.

6. Ilgalaikis prostatos vėžiu sergančių vyrų išgyvenamumas yra geresnis, nors ir nereikšmingai, tiems, kurie serga 2 tipo CD ir vartoja metforminą. Bendrasis išgyvenamumas yra blogesnis sergant 2 tipo CD ir jis yra mažiausias metformino nevartojančiųjų grupėje.

7. Asmenims, sergantiems 2 tipo CD, specifinė mirties nuo kolorektalinio vėžio rizika yra mažesnė. Metformino vartotojų specifinis kolorektalinio vėžio ir bendrasis išgyvenamumas, palyginti su metformino nevartojančiais asmenimis, yra reikšmingai geresnis.

8. Išgyvenamumo skirtumų tarp skrandžio vėžio pacientų, sergančių 2 tipo CD, taip pat vartojančių skirtingus vaistų nuo diabeto derinius, nepastebima.

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COPIES OF PUBLICATIONS

LIST OF PUBLICATIONS NOT INCLUDED IN THE THESIS

1. **Linkeviciute-Ulinskiene D**, Dulskas A, Smailyte G, Zabuliene L., Urbonas V. Response to Letter to the Editor: *Metformin in colorectal cancer: a match ruled by MiR26b? Cancer Epidemiology*. 2020 Feb;64:101626. doi: 10.1016/j.canep.2019.101626. Epub 2019 Nov 16.
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2. Undzyte G, Patasius A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Stukas R, Dulskas A, Smailyte G. *Increased kidney cancer risk in diabetes mellitus patients: a population-based cohort study in Lithuania*. Aging Male. 2020 Apr 28:1-5.
https://doi.org/10.1080/13685538.2020.1755249

3. Danila E, **Linkevičiūtė-Ulinskienė D**, Zablockis R, Gruslys V, Cicėnas S, Smailytė G. *A Cohort Study of Exposure to Antihyperglycemic Therapy and Survival in Patients with Lung Cancer*. Int J Environ Res Public Health. 2020 Mar 7;17(5):1747.
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4. Dulskas A, Patasius A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Smailyte G. *Cohort Study of Antihyperglycemic Medication and Pancreatic Cancer Patients Survival*. Int J Environ Res Public Health. 2020 Aug 19;17(17):E6016.
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LIST OF PRESENTATIONS

1. **Linkeviciute-Ulinskiene D**, Patasius A, Zabuliene L, Smailyte G. *Increased risk of site-specific cancer in people with type 2 diabetes: a national cohort study*. Oral presentation. 7th EYES (European Society of Endocrinology Young Endocrinologists and Scientists) Meeting, Athens, Greece, September 13-15, 2019.

2. Patasius A, Kincius M, **Linkeviciute-Ulinskiene D**, Zabuliene L, Smailyte G. *Reduced risk of prostate cancer in a cohort of Lithuanian diabetes mellitus patients*. Journal of Clinical Oncology 37, no. 7_suppl (March 01, 2019) 130-130. DOI: 10.1200/JCO.2019.37.7_suppl.130. Poster presentation. Genitourinary Cancers Symposium, San Francisco, USA, February 13-15, 2019.

3. Undzyte G, Patasius A, Stukas R, **Linkeviciute-Ulinskiene D**, Smailyte G. *Increased risk of kidney cancer in a cohort of Lithuanian diabetes mellitus patients*. European Urology Supplements 2019;18(3):e2506, ISSN: 1569-9056; eISSN: 1569-9056; DOI: 10.1016/S1569-9056(19)32200-6. Poster presentation. 6th Baltic Meeting in conjunction with the European Association of Urology, Tallinn, Estonia, May 24-25, 2019.

4. Kincius M, Patasius A, **Linkeviciute-Ulinskiene D**, Zabuliene L, Smailyte G. *Preexisting diabetes, metformin use, and long-term survival in patients with prostate cancer*. Poster presentation. 32nd NUF Congress (Scandinavian Association of Urology) Reykjavik, Island, June 5-8, 2019.

5. Dulskas A, Patasius A, **Linkeviciute-Ulinskienė D**, Zabuliene L., Urbonas V, Smailyte G. *Metformin increases cancer specific survival in colorectal cancer patients – national cohort study*. Poster presentation. ESCP's (European Society of Coloproctology) 14th Annual Meeting, Vienna, Austria, September 25-27, 2019.

1st publication/ 1 publikacija

Increased Risk of Site-Specific Cancer in People with Type 2 Diabetes: A National Cohort Study

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2nd publication / 2 publikacija

Reduced risk of prostate cancer in a cohort of Lithuanian diabetes mellitus patients

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Positive effect of metformin treatment in colorectal cancer patients with type 2 diabetes: national cohort study

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A Cohort Study of Antihyperglycemic Medication Exposure and Gastric Cancer Risk

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Preexisting diabetes, metformin use and long-term survival in patients with prostate cancer

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Metformin increases cancer specific survival in colorectal cancer patients – national cohort study

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8th publication / 8 publikacija

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