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CANCER MORTALITY AND USE OF ANTIDIABETIC DRUGS

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Background: Several studies have explored the association between use of antidiabetic medication (ADM) such as metformin and insulin on risk of different cancer types, but few have analyzed cancer mortality or been able to take into account simultaneous use of different ADMs.

Materials and methods: Our study cohort included 15,892 diabetic men with either a recorded diagnosis of diabetes mellitus during 1996-2015 or recorded ADM use during the same period. The source population was 78,615 men originally identified for the Finnish Randomized Study of Screening for Prostate Cancer. Information on causes of death was obtained from national death certificate registry of Statistics Finland. The data included dates for death and primary, underlying and contributing causes as ICD-10 codes. Follow-up for deaths started at FinRSPC randomization and extended until the end of 2015.

Information on ADM purchases during 1995-2015 was obtained from national prescription database. Overall cancer mortality and mortality from specific cancer types was analyzed using Cox proportional hazards regression model with adjustment for age and co-morbidities. ADM usage was analyzed as time-dependent variable to avoid immortal time bias. Simultaneous use of different ADM classes was estimated by forming time-dependent variable for each class (biguanides, insulin secretagogues (sulphonylureas, glinides), thiazolidinediones, insulins and DPP-4 inhibitors). Lag-time analyses were used to estimate long-term risk associations.

Results: Insulin use (HR 2.16, 95%CI 1.95-2.39) and use of insulin secretagogues (HR 1.40, 95%CI 1.26-1.56) were associated with elevated cancer mortality compared to non-users. A modest risk increase was observed also in users of metformin (HR 1.13, 95%CI 1.00-1.28). The mortality increase among users of insulin and insulin secretagogues was attenuated, but remained elevated compared to non-users after allowing for a latency of 1-3 years.

Conclusion: Increased cancer mortality among users of insulin and insulin secretagogues in a cohort of diabetic men supports the role of hyperinsulinemia as a risk factor for cancer death. However, the risk increase attenuated in long-term use, suggesting that the underlying diabetes necessitating insulin use may be the cause of the risk association.

Avainsanat: diabetes, syöpäkuolleisuus, metformiini, insuliini

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2. Introduction

The relationship between diabetes mellitus and cancer has been investigated extensively. Diabetes has been associated with increased cancer incidence and mortality[1,2]. On the other hand, antidiabetic medications (ADMs) may affect cancer risk and mortality in patients with diabetes[3]. Some ADMs, such as metformin and thiazolidinediones are associated with a decreased cancer risk, while others such as insulin and sulphonylureas with an increased cancer risk[3-7].

Previous studies have reported reduced cancer risk among metformin users[8]. The research on cancer mortality has tended to focus on certain ADMs and cancer types. Most previous studies have not been able to take into account simultaneous use of different ADMs, which may be problematic as these drugs are often used in combination, and the drug choice changes during the course of the condition.

To our knowledge, comprehensive evaluation of cancer mortality among ADM users in general and among users of specific ADM groups has not been performed before. Therefore, we evaluated overall cancer mortality and risk of death due to most common cancer types by ADM use in a population-based cohort of diabetic men from the Finnish Randomized Study for Prostate Cancer Screening.

4. Materials and methods

3.1 Study cohort

FinRSPC is a randomized trial evaluating effects of prostate specific antigen (PSA)-based prostate cancer screening. All 55-67 year old men residing in the metropolitan areas of Helsinki or Tampere, Finland in 1996-1999 (80,456 men) were identified from the Finnish Population Register Centre. Prevalent prostate cancer cases were excluded and the remaining 80,144 men were randomized either to be invited to attend PSA screening at four-year intervals (31,866 men), or no intervention (48,278 men). Both groups were followed through the Finnish Cancer Registry.[9]

To evaluate effects of antidiabetic drugs among men with diabetes, we limited the study population to include only men with either a recorded diagnosis of diabetes (E10 or E11) during the follow-up (1996-2013) or any recorded antidiabetic drug use during that time, resulting in a cohort of 15,892 diabetic men.

Information on diabetes diagnoses were obtained from the Care Registers for Social Welfare and Health Care (HILMO) maintained by the National Institute for Health and Welfare. This registry records all diagnoses from in- and outpatient hospital visits in Finnish health care units. HILMO data was also used to obtain information on co-morbidities to calculate Charlson co-morbidity index according to 2011 criteria.[10] No information on severity of liver insufficiency was available from HILMO, thus all participants with this diagnosis were assumed to have mild liver insufficiency when calculating Charlson index. The data from different sources were combined using deterministic record linkage using the unique personal identification number as the key.

Information on dates and causes of deaths was obtained from the Statistics Finland, which registers all deaths in Finland. The registry has used the 10th revision of the International Classification of Diseases (ICD-10) since 1996. The data included dates for deaths and immediate, underlying and contributing causes as ICD-10 codes.

All deaths with ICD-10 codes C00-D48 registered as the primary cause of death were considered to be cancer deaths. Similarly, deaths due to lung cancer (C34), colorectal cancer (C18-C20), gastric cancer (C16), pancreatic cancer (C25), liver cancer (C22), non-Hodgkin lymphoma (C82, C83 and C85), renal cell cancer (C64-C66), bladder cancer (C67) and tumors of the brain or the central nervous system (C70-C72) were determined separately.

BMI values were collected through surveys sent with FinRSPC screening invitations.[11] Data on BMI was available for 2,352 men. Data on fasting blood glucose was available for 4037 men and glycosylated hemoglobin A1c (HbA1c) for 3991 men from the database of Fimlab, the leading provider of laboratory services in the Pirkanmaa region.

3.2 Information on antidiabetic medication use

The study cohort was linked to the national prescription database maintained by the Social Insurance Institution (SII) of Finland to obtain information on ADM purchases during the years 1995-2014. SII is a governmental agency providing reimbursements for physician-prescribed medications as a part of the national health insurance. All Finnish citizens are entitled to the reimbursement for every purchase of a prescription drug approved by the SII. All reimbursed purchases are registered by the prescription database. The recorded information for each purchase includes the date, ATC code, product number and number of packages. Over-the-counter purchases or drugs used during hospital inpatient periods are not re-imbursed nor recorded by the database.

Drug strength and number of pills were determined for each purchase. The database covers ADMs comprehensively because they are available almost exclusively by prescription and approved by the SII.

Amount of drug use was standardized between different ADMs by calculating the drug-specific mg or IU quantity purchased annually and dividing it with the mg/IU amount corresponding to drug-specific Defined Daily Dose (DDDs).[12] Duration of drug use was calculated as years with any recorded drug purchases, regardless of the purchased amount. Average dose per year (intensity of use) was calculated by dividing the overall DDD quantity with years of drug use.

3.3 Statistical analysis

Overall risk of cancer death and risk of death from specific cancer types was analyzed using Cox proportional hazards regression model to calculate hazard ratios (HRs) and 95% CI intervals (95% CI). Follow-up started at the date of the screening trial randomization in 1996-1999 and was continued until death, emigration from Finland or January 1, 2015 whichever came first.

In statistical analysis, every ADM subgroup (metformin, sulphonylureas, thiazolidinediones, insulines and others including gliptins and glinides) was treated as a separate variable to evaluate independent effects and also to model simultaneous use of ADMs.

We used age-adjusted and multivariable adjusted models. The multivariable-adjusted model included use of statins, antihypertensive drugs and use of aspirin or other NSAIDs.

Status of ADM drug use as well as quantity, duration and average yearly dose were time-dependent variables, updated prospectively for each follow-up year according to registered drug purchases.

Latency in effects of ADM use was examined in lag-time analyses, in which the exposure was lagged 1-3 years forward in the follow-up; for example, drug purchases in 2004 were analyzed on 2005 in one-year lag-time analysis.

5. Results

4.1 Population characteristics

The study population included 15,892 diabetic men, of whom 12,440 (78.3%) had ever used metformin, 6,270 (39.5%) insulin, 8,226 (51.1%) insulin secretagogues and 1,819 (11.4%) thiazolidinediones. Numbers of men who had used more than one drug group are shown in **Figure 1**. During median follow-up of 17 years, there were 1,688 cancer deaths (1,062/10,000; 10.6% of the cohort), of which 1,232 (990/10,000) occurred in metformin users, 775 in users of insulins (1236/10,000), 1,007 in users of insulin secretagogues (1224/10,000) and 165 in users of thiazolidinediones (907/10,000).

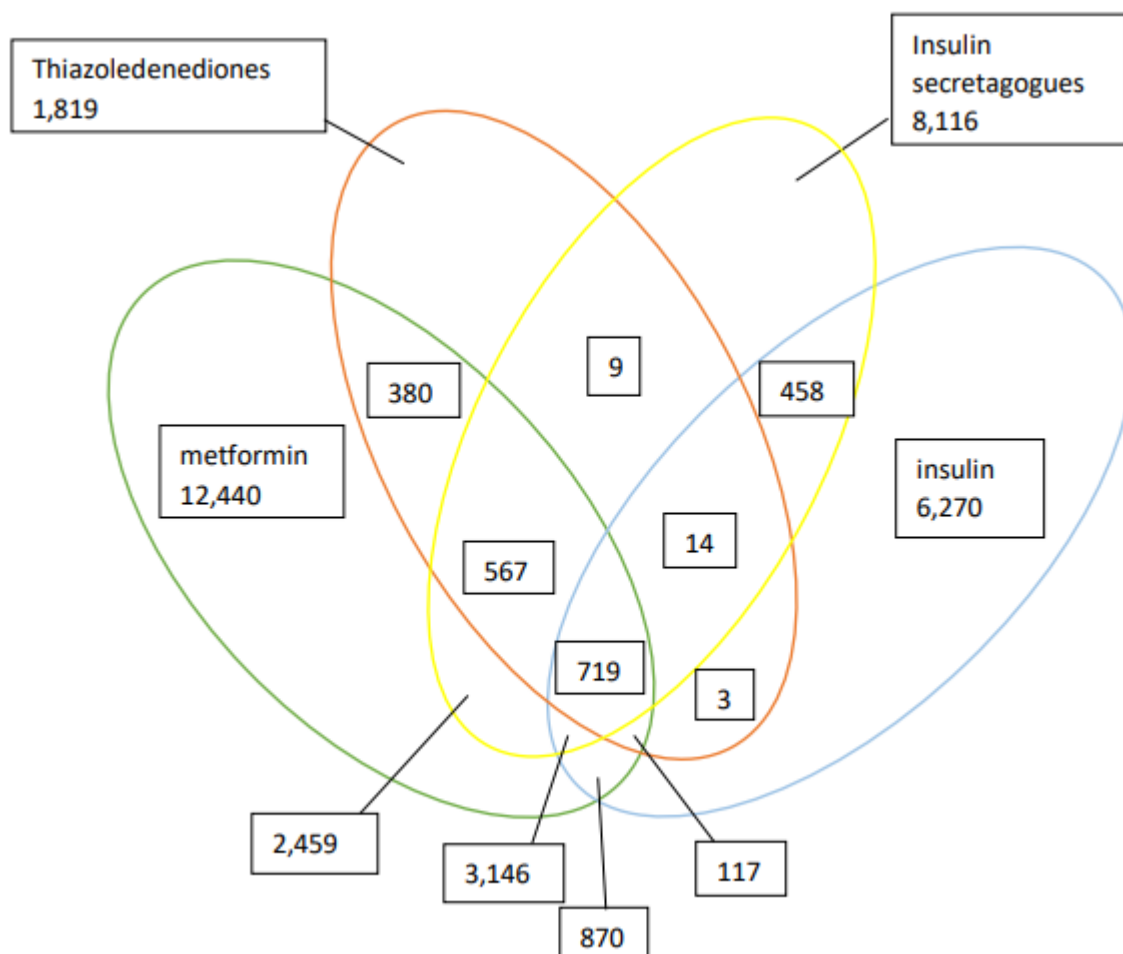


Figure 1. Numbers of users of each antidiabetic drug group. Study population of 15,892 diabetic men from the Finnish Randomized Study of Screening for Prostate Cancer

The median age at baseline did not differ between users of different drug groups. The median BMI was higher among users of metformin or thiazolidinediones compared to users of insulin or insulin secretagogues, and they had more often used also statins and NSAIDs (Table 1). Nevertheless, the median Charlson co-morbidity score was higher among users of insulin and insulin secretagogues.

Table 1. Population characteristics. Study population of 15,892 diabetic men from the Finnish Randomized Study of Screening for Prostate Cancer

	Total	Users of			
		Metformin	Thiazolidinediones	Insulin secretagogues	Insulins
N of men	15,892	12,440	1,819	8,116	6,270
Median (IQR) age at baseline	59 (55-63)	59 (55-63)	59 (55-63)	59 (55-63)	59 (55-63)
Median (IQR) follow-up after baseline	17.0 (13.0-19.0)	17.2 (14.8-19.0)	18.0 (17.0-19.0)	17.0 (11.3-18.7)	17.0 (11.9-18.7)
Median (IQR) BMI	28.4 (25.9-31.3)	28.7 (26.2-31.6)**	28.8 (26.3-32.1)**	28.4 (26.0-31.5)	28.4 (25.8-31.5)
N of deaths overall	6,613 (43.4%)	4,761 (38.3%)	475 (26.1%)	4,112 (50.7%)	3,192 (50.9%)
N of cancer deaths overall	1,688 (11.1%)	1,232 (9.9%)	165 (9.1%)	1,007 (12.4%)	775 (12.4%)
Lung cancer deaths	355 (2.3%)	255 (2.0%)	36 (2.0%)	199 (2.5%)	148 (2.4%)
Colorectal cancer deaths	152 (1.0%)	114 (0.9%)	20 (1.1%)	87 (1.1%)	49 (0.8%)
Pancreatic cancer deaths	238 (1.6%)	165 (1.3%)	25 (1.4%)	143 (1.8%)	138 (2.2%)

Stomach cancer deaths	64 (0.4%)	46 (0.4%)	8 (0.4%)	45 (0.6%)	27 (0.4%)
Liver cancer deaths	181 (1.2%)	147 (1.2%)	17 (0.9%)	130 (1.6%)	86 (1.4%)
Non-Hodgkin lymphoma deaths	48 (0.3%)	32 (0.3%)	1 (0.1%)	28 (0.3%)	23 (0.4%)
Kidney cancer deaths	53 (0.3%)	39 (0.3%)	6 (0.3%)	29 (0.4%)	26 (0.4%)
Urinary bladder cancer deaths	36 (0.2%)	28 (0.2%)	3 (0.2%)	24 (0.3%)	17 (0.3%)
CNS cancer deaths	27 (0.2%)	19 (0.2%)	5 (0.3%)	16 (0.2%)	17 (0.3%)
<i>Use of other drug; n (%):)</i>					
Statins*	11,323 (74.3%))	9,708 (78.0%)	1,576 (86.6%)	5,918 (72.9%)	4,725 (75.4%)
Antihypertensive drugs*	14,253 (93.5%))	11,750 (94.5%)	1,733 (95.3%)	7,670 (94.5%)	5,987 (95.5%)
NSAIDs*	13,546 (88.9%))	11,268 (90.6%)	1,691 (93.0%)	7,111 (87.6%)	5,569 (88.8%)
Aspirin*	3,663 (24.0%))	3,111 (25.0%)	476 (26.2%)	1,986 (24.5%)	1,611 (25.7%)
Anticoagulant drugs*	8,231 (54.0%))	6,896 (55.4%)	994 (54.6%)	4,459 (54.9%)	3,727 (59.4%)

Median Charlson comorbidity score*	0 (0-2)	0 (0-2)	0 (0-1)	1 (0-2)	1 (0 - 2)
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*P < 0.05 for difference between users of different drug groups
 ** p for difference < 0.001 for metformin users compared to other
 drug groups; p = 0.003 for thiazolenedione users compared to
 other drug groups

4.2 Risk of cancer death by antidiabetic drug use

Cancer mortality among metformin ever users was 8.2 deaths/ 1,000 person years, while among never users it was 16.4/1,000 person years. Use of metformin was not associated with the risk of cancer death in age-adjusted analysis (HR 1.00, 95%CI 0.88-1.14), but in the multivariable-adjusted analysis, an increased risk compared to non-users was observed (HR 1.13, 95%CI 1.00-1.28, Table 2). Similarly, users of insulin secretagogues and insulins also had an elevated risk of cancer death compared to non-users.

Table 2. Cancer mortality by antidiabetic drug use. Cohort of 15,244 diabetic men in the Finnish Randomized Study of Screening for Prostate Cancer

	Mortality from										
	Cancer overall		Lung cancer	Colorectal ca	Pancreatic ca	Stomach ca	Liver ca	Non-Hodgkin lymphoma	Renal cancer	Bladder cancer	Brain and CNS ca
	Age-adjusted analysis	Multi-variable adjusted	Multi-variable adjusted	Multi-variable adjusted	Multi-variable adjusted	Multi-variable adjusted	Multi-variable adjusted	Multi-variable adjusted	Multi-variable adjusted	Multi-variable adjusted	Multi-variable adjusted
Antidiabetic medication use	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

Metformin	1.00 (0.88- 1.14)	1.13 (1.00- 1.28)	1.05 (0.80- 1.38)	1.25 (0.82- 1.91)	1.01 (0.73- 1.40)	1.05 (0.56- 1.97)	1.87 (1.23- 2.83)	0.70 (0.35- 1.37)	1.50 (0.74- 3.06)	1.54 (0.62- 3.82)	1.21 (0.44- 3.31)
Thiazolidin ediones	0.88 (0.75- 1.04)	0.95 (0.81- 1.12)	0.98 (0.68- 1.40)	1.38 (0.85- 2.26)	1.13 (0.74- 1.74)	1.27 (0.59- 2.76)	0.82 (0.49- 1.37)	0.17 (0.02- 1.27)	1.32 (0.55- 3.21)	0.74 (0.22- 2.49)	2.48 (0.87- 7.11)
Insulin secretagog ues	1.42 (1.27- 1.59)	1.40 (1.26- 1.56)	1.29 (1.02- 1.63)	1.43 (1.01- 2.04)	1.29 (0.96- 1.74)	2.53 (1.40- 4.56)	2.28 (1.60- 3.26)	1.56 (0.83- 2.95)	0.96 (0.52- 1.78)	1.85 (0.85- 4.02)	1.02 (0.42- 2.50)
Insulin	2.04 (1.84- 2.27)	2.16 (1.95- 2.39)	1.86 (1.49- 2.34)	1.13 (0.79- 1.63)	3.86 (2.93- 5.07)	1.70 (1.01- 2.86)	2.03 (1.49- 2.76)	2.18 (1.19- 3.98)	2.80 (1.57- 5.00)	2.01 (1.00- 4.07)	5.31 (2.31- 12.23)

In a separate analysis by cancer type, the risk increase among metformin users was significant only for liver cancer. Risk increase by insulin was observed for all cancer types, and risk increase by use of insulin secretagogues was similarly observed for all cancer types with the exception of renal cancer and tumors of the brain and the central nervous system.

4.3 Risk trends by cumulative antidiabetic drug use

Cancer mortality decreased in inverse association with years of metformin use. However, when analyzed by cancer type, this was driven mainly by pancreatic cancer: HR for pancreatic cancer death was 0.48 (0.28-0.84) among men who had used metformin for eight years or longer (Table 3). No significant risk lowering by years of metformin use were observed for other cancer types (Table 4).

Table 3. Cancer mortality by duration of antidiabetic drug use.

	Mortality from				
	Cancer overall	Lung cancer	Colorectal ca	Pancreatic ca	Stomach ca
Duration of use	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Metformin					
1-7 yrs	1.23 (1.08-1.39)	1.14 (0.87-1.49)	1.25 (0.81-1.93)	1.21 (0.88-1.66)	1.08 (0.57-2.03)
8-10 yrs	0.92 (0.77-1.11)	0.83 (0.56-1.24)	1.41 (0.80-2.49)	0.48 (0.28-0.84)	1.03 (0.41-2.55)
11 yrs or longer	0.73 (0.60-0.88)	0.70 (0.46-1.07)	0.91 (0.47-1.74)	0.47 (0.27-0.79)	0.74 (0.27-2.03)
Intensity of use, DDD/year					
1-91	1.37 (1.13-1.66)	1.04 (0.66-1.64)	1.43 (0.76-2.71)	2.06 (1.33-3.19)	1.20 (0.44-3.33)
91-200	1.35 (1.16-1.56)	1.22 (0.88-1.69)	1.33 (0.80-2.21)	1.22 (0.82-1.81)	1.01 (0.45-2.28)
200 or more	0.97 (0.85-1.11)	0.97 (0.72-1.30)	1.15 (0.72-1.83)	0.71 (0.49-1.02)	1.03 (0.52-2.05)

Duration of use					
Insulin secretagogues					
1-4 yrs	1.64 (1.45-1.87)	1.65 (1.25-2.16)	1.30 (0.82-2.05)	1.86 (1.34-2.56)	2.52 (1.27-4.99)
5-9 yrs	1.32 (1.15-1.52)	1.04 (0.75-1.43)	1.60 (1.02-2.49)	0.83 (0.55-1.26)	3.09 (1.56-6.13)
10 yrs or longer	1.10 (0.93-1.30)	1.06 (0.74-1.51)	1.44 (0.86-2.40)	0.96 (0.61-1.51)	1.60 (0.63-4.10)
Intensity of use					
1-261	1.75 (1.53-1.99)	1.78 (1.35-2.33)	1.60 (1.03-2.46)	1.82 (1.29-2.56)	2.73 (1.37-5.44)
261-487	1.28 (1.11-1.48)	1.06 (0.77-1.47)	1.36 (0.84-2.18)	1.27 (0.87-1.83)	2.31 (1.10-4.87)
487 or more	1.10 (0.94-1.27)	0.92 (0.66-1.29)	1.29 (0.78-2.11)	0.77 (0.50-1.17)	2.46 (1.16-5.22)
Duration of use					
Insulins					
1-4 yr	3.18 (2.82-3.59)	2.54 (1.93-3.34)	1.34 (0.84-2.14)	7.03 (5.23-9.45)	2.30 (1.23-4.30)

5-10 yrs	1.62 (1.39-1.89)	1.45 (1.03-2.05)	1.10 (0.65-1.87)	1.87 (1.19-2.94)	1.46 (0.69-3.08)
11 yrs or longer	1.31 (1.08-1.60)	1.39 (0.93-2.10)	0.84 (0.41-1.70)	1.51 (0.85-2.70)	0.90 (0.27-3.03)
Intensity of use					
1-203	2.67 (2.38-3.01)	2.39 (1.84-3.11)	1.15 (0.73-1.80)	5.00 (3.70-6.77)	2.86 (1.13-5.00)
203-408	1.67 (1.42-1.97)	1.49 (1.03-2.16)	1.16 (0.67-2.03)	2.62 (1.70-4.02)	0.60 (0.18-1.97)
408 or more	1.28 (1.02-1.60)	1.11 (0.66-1.85)	0.69 (0.28-1.70)	1.61 (0.86-3.01)	0.34 (0.05-2.50)

Table 4. Cancer mortality by duration of antidiabetic drug use.

	Mortality from				
	Liver ca	Non-Hodgkin lymphoma	Renal ca	Bladder ca	Brain and CNS ca
Duration of use	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Metformin					
1-3 yrs	1.93 (1.27-2.94)	0.73 (0.36-1.49)	1.58 (0.78-3.19)	1.60 (0.64-3.98)	1.19 (0.43-3.29)
4-6 yrs	1.50 (0.83-2.69)	0.69 (0.26-1.81)	1.37 (0.51-3.69)	1.18 (0.30-4.58)	1.63 (0.42-6.39)
7 yrs or longer	1.81 (1.01-3.26)	0.56 (0.20-1.58)	0.60 (0.16-2.16)	1.47 (0.40-5.41)	0.69 (0.13-3.54)
Intensity of use					
1-91	1.75 (0.93-3.32)	0.92 (0.30-2.84)	1.51 (0.48-4.76)	1.74 (0.44-6.87)	-
91-200	2.29 (1.42-3.69)	0.47 (0.17-1.33)	1.75 (0.75-4.08)	2.12 (0.76-5.89)	1.88 (0.59-5.95)

200 or more	1.67 (1.07- 2.61)	0.76 (0.36- 1.58)	1.36 (0.62- 2.99)	1.19 (0.44- 3.23)	1.15 (0.38- 3.45)
Duration of use					
Insulin secretagogues					
1-4 yrs	2.00 (1.30- 3.07)	2.05 (0.99- 4.25)	1.18 (0.57- 2.43)	1.04 (0.35- 3.13)	1.49 (0.56- 3.98)
5-8 yrs	2.54 (1.66- 3.87)	1.78 (0.82- 3.88)	0.84 (0.37- 1.90)	3.09 (1.28- 7.46)	0.90 (0.30- 2.73)
9yrs or longer	2.47 (1.53- 3.99)	0.54 (0.15- 1.93)	0.78 (0.29- 2.06)	1.61 (0.51- 5.11)	0.45 (0.09- 2.26)
Intensity of use					
1-261	2.29 (1.48- 3.53)	2.46 (1.23- 4.95)	1.25 (0.59- 2.66)	1.67 (0.61- 4.53)	1.79 (0.67- 4.81)
261-487	1.93 (1.23- 3.04)	1.05 (0.42- 2.61)	1.09 (0.51- 2.33)	2.25 (0.89- 5.66)	0.99 (0.33- 2.97)
487 or more	2.68 (1.74- 4.12)	0.94 (0.36- 2.43)	0.55 (0.22- 1.38)	1.63 (0.59- 4.50)	0.40 (0.10- 1.61)
Duration of use					

Insulins					
1-3 yr	2.28 (1.55-3.34)	4.09 (2.05-8.13)	5.30 (2.84-9.89)	2.38 (1.00-5.65)	8.47 (3.36-21.36)
4-8 yrs	2.06 (1.36-3.11)	1.80 (0.75-4.29)	1.09 (0.37-3.20)	1.89 (0.73-4.94)	3.18 (0.97-10.49)
9 yrs or longer	1.44 (0.78-2.64)	0.58 (0.13-2.51)	1.00 (0.23-4.40)	1.51 (0.41-5.50)	3.17 (0.63-15.87)
Intensity of use					
1-203	1.91 (1.30-2.80)	2.99 (1.50-5.94)	4.58 (2.24-8.69)	1.80 (0.72-4.47)	10.81 (4.46-26.21)
203-408	1.89 (1.20-2.98)	1.91 (0.76-4.79)	2.16 (0.86-5.38)	1.87 (0.67-5.21)	-
408 or more	2.21 (1.30-3.75)	1.04 (0.24-4.46)	0.54 (0.07-4.04)	3.02 (1.09-8.37)	3.11 (0.67-14.46)

Among users of sulphonylureas and insulins the risk of cancer death was elevated especially during the first years of usage. The risk increase attenuated in continued use, but the risk estimates remained elevated compared to men with diabetes not using these drugs (Table 3).

4.4 Lag-time analyses

In lag-time analysis, the decreased risk of pancreatic cancer death observed among metformin users disappeared. Rather, use of metformin was associated with an increased risk of cancer death for all cancer types similar to insulin and insulin secretagogues (Table 5).

Table 5. Lag-time analyses

Mortality from										
	Cancer overall	Lung cancer	Colorectal ca	Pancreatic ca	Stomach ca	Liver ca	Non-Hodgkin lymphoma	Renal ca	Bladder ca	Brain and CNS ca
Antidiabetic medication use	HR (95%)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
	None									
	1 year lag time									
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Metformin	1.26 (1.11-1.43)	1.07 (0.82-1.40)	1.48 (0.97-2.27)	1.10 (0.80-1.52)	1.05 (0.56-1.96)	2.03 (1.35-3.06)	0.92 (0.46-1.84)	1.61 (0.79-3.27)	1.83 (0.73-4.61)	1.57 (0.57-4.36)
Insulin secretagogues	1.45 (1.30-1.61)	1.41 (1.11-1.78)	1.43 (1.00-2.04)	1.38 (1.03-1.85)	2.68 (1.50-4.80)	2.33 (1.64-3.32)	1.18 (0.63-2.21)	1.15 (0.62-2.12)	1.81 (0.82-3.96)	1.02 (0.42-2.46)

Insulin	1.76 (1.59- 1.96)	1.49 (1.18- 1.89)	1.11 (0.77- 1.61)	2.51 (1.92- 3.30)	1.34 (0.78- 2.30)	1.78 (1.30- 2.43)	1.70 (0.91- 3.17)	1.83 (1.01- 3.31)	2.24 (1.11- 4.53)	3.13 (1.39- 7.03)
	3 years lag time									
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Metformin	1.27 (1.12- 1.43)	1.20 (0.92- 1.56)	1.79 (1.18- 2.74)	0.82 (0.60- 1.12)	1.24 (0.67- 2.30)	2.24 (1.50- 3.33)	1.05 (0.52- 2.11)	1.73 (0.87- 3.46)	1.64 (0.68- 3.96)	1.39 (0.51- 3.74)
Insulin secretagogues	1.33 (1.20- 1.49)	1.21 (0.95- 1.53)	1.27 (0.89- 1.81)	1.27 (0.95- 1.70)	2.38 (1.34- 4.23)	2.05 (1.44- 2.91)	1.10 (0.58- 2.07)	1.27 (0.68- 2.35)	1.74 (0.80- 3.78)	0.76 (0.31- 1.86)
Insulin	1.31 (1.17- 1.47)	1.24 (0.96- 1.60)	0.96 (0.65- 1.44)	1.06 (0.76- 1.46)	1.28 (0.72- 2.27)	1.88 (1.37- 2.58)	1.18 (0.59- 2.36)	1.29 (0.68- 2.46)	2.02 (0.98- 4.15)	1.31 (0.50- 3.40)

Elevated risk of cancer death among users of sulphonylureas and insulins remained for most cancer types in 1-year lag-time analysis, whereas in the 3-year lag time analysis the risk increase was no longer observed for colorectal and pancreatic cancer (Table 4).

4.5 Subgroup analyses

Use of other drugs affected the risk of cancer death mainly in users of insulin secretagogues; the risk increase among users of this drug group was ameliorated by concomitant use of aspirin (p for interaction 0.022), cholesterol-lowering statins (p for interaction 0.002) and anticoagulant drugs (p for interaction < 0.001) (**Figure 2**). Similarly, use of other drug groups slightly lowered the observed risk estimates among insulin users.

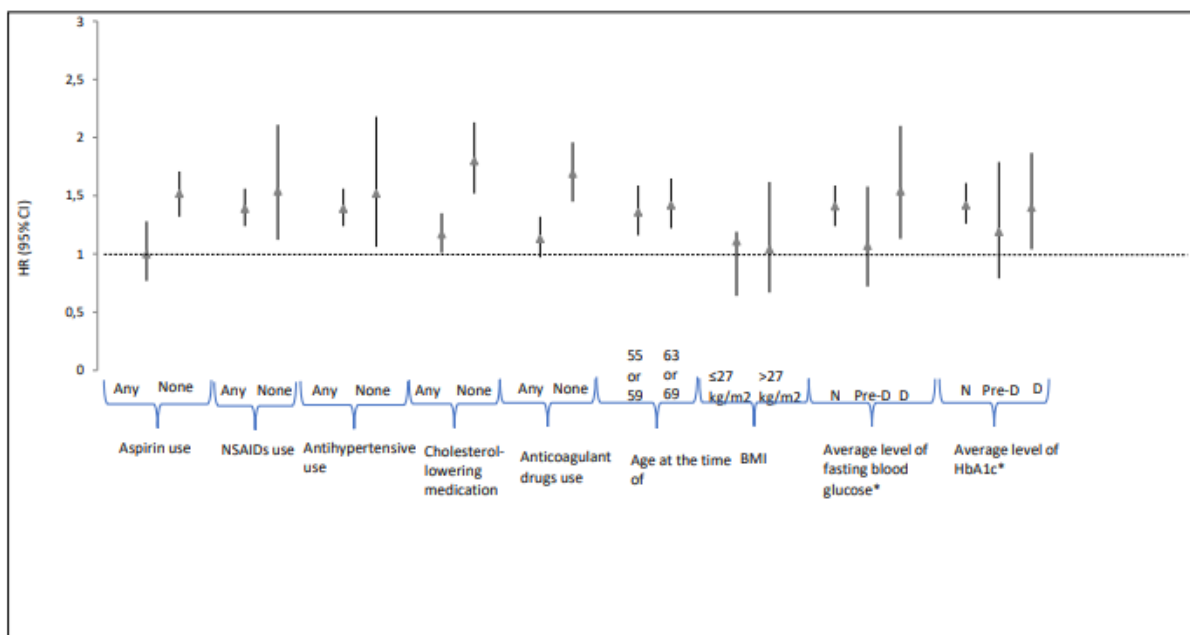


Figure 2. Cancer mortality in users of insulin secretagogues, a stratified subgroup analysis

BMI and HbA1c did not have a clear effect modification on risk association between ADM use and risk of cancer death. BMI modified the risk association only among users of glitazones; cancer mortality was increased among glitazone users compared to non-users only in the subgroup of men with BMI less than 27 kg/m² (p for interaction 0.037).

4.6 Sensitivity analyses

We run a sensitivity analyses with new user design, where we excluded men who had recorded use of any ADMs before baseline. Results were generally similar as in the main analysis, but the risk association between insulin use and risk of cancer death became stronger for overall cancer mortality (HR 2.96, 95% CI 2.59-3.37), pancreatic cancer (HR 7.02, 95% CI 5.09-9.68) and kidney cancer (HR 4.86, 95% CI 2.25-10.48).

6. Discussion

We found that among men with diabetes, use of insulin and insulin secretagogues are linked to a higher risk of cancer death. Our results support a role of hyperinsulinemia as a risk factor for cancer death. The increased risk was associated also with metformin users, although the risk increase was smaller. This suggests that poor glycemic control or advanced diabetes, which requires extensive medication use, could be a risk factor for cancer death. The risk increase among insulin users remained in lag time analyses for up to three years after the actual usage suggesting a long-term risk connection.

An association of diabetes with cancer incidence and mortality has previously been demonstrated by many studies[1,2]. There are several explanations for the association. Diabetes and cancer have common risk factors, for example obesity, some dietary patterns and a sedentary lifestyle[13,14]. In our subgroup analysis, BMI did not show significant effect modification on the risk association between anti-DM drug use and cancer mortality, though the statistical power was limited. Other possible links may be effects of hyperglycemia[15], hyperinsulinemia, anti-diabetic medication or combination of these risk factors[14].

Our study supports hyperinsulinemia as a risk factor for cancer death, as we found that use of insulins and drugs increasing insulin secretion was connected to a higher cancer mortality compared to diabetic men not using these drugs. These medications increase circulating insulin levels, which affects cancer cell growth, proliferation and resistance to apoptosis *in vitro*[16,17]. Hyperinsulinemia may also be connected with development of more aggressive cancer types[18] and may promote development of many cancers, for example colon cancer[19,20], skin cancer[21,22], breast cancer[23], prostate cancer[24], lung cancer[25,26], liver cancer[27] and pancreatic cancer[28]. Insulin-like growth factors have also been linked to risk of cancer and cancer

death[29,30]. Diabetes decreases serum IGF-I levels and use of insulin or sulphonylureas restores them.[31]

Some studies have reported that sulphonylureas decrease growth of cancer cells *in vitro*[32]. However, epidemiological evidence suggests the contrary: sulphonylureas have been linked with an increased risk of advanced prostate cancer[7,33]. Other studies have found no difference in risk of cancer when comparing sulphonylurea users to metformin users[34,35], but the risk has been reported to be lower among users of insulin sensitizers when compared to insulin secretagogues[36]. Thus, the increase in insulin secretion during use of sulphonylureas and other insulin secretagogues may have greater importance regarding cancer mortality than any direct effects sulphonylureas may have on cancer cells.

Our results are not concordant with previous studies linking metformin use with decreased overall cancer risk and mortality[5,37-40]. Some retrospective analyses suggest that metformin increases the effectiveness of chemotherapy[6,41,42]. Metformin has been suggested to affect cancer cell growth by reducing stimulus from insulin and IGF-1, blocking of the PI3K/Akt/mTOR signaling pathway and inhibition of cell division[4]. However, we did not observe association between metformin and cancer mortality among diabetic men. One explanation to this might be that the risk-decreasing effects of metformin are masked by risk-increasing effects of diabetes. To our knowledge, this is the first study to estimate long-term risk association, as well as simultaneous use of other antidiabetic drugs and dose-dependence with metformin use.

Strengths of our study were large population-based study population, detailed, reliable information on quantity and timing of ADM use, which made it possible to evaluate effects of different ADM groups while taking into account simultaneous use of multiple drug groups.

Study weaknesses were that we did not have comprehensive information of BMI or blood glucose levels, although in subgroup analysis we had limited ability to evaluate them. These may have been confounding factors. We also did not have information

on lifestyle habits such as smoking, exercise or diet or indicators of SES such as education. These may also have been confounding factors. We did not have data on type of diabetes or total disease duration apart from medication use and recorded diagnoses. We did not have detailed data on patient characteristics to account for differences in indications of various ADMs.

In conclusion, we found that use of antidiabetic drugs in general, but especially insulins and insulin secretagogues are linked to increased risk of cancer death. The increased risk is related to beginning of usage and attenuates in long-term, supporting the notion that risk increase is greatest in the beginning of usage, i.e. likely to be caused by underlying untreated diabetes. Risk attenuation in long-term suggests that proper diabetes management may lower the oncological risks associated with untreated diabetes. Metformin's possible shielding effects were not confirmed in this analysis.

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