Risk of cause-specific death in individuals with cancer – modifying role diabetes, statins, and metformin

Jari Haukka

University of Helsinki, PO Box 20, FI-00014 University of Helsinki, Finland. Email: jari.haukka@helsinki.fi; Tel. +358 504155314

Leo Niskanen, MD, Endocrinology and Diabetology, Abdominal Center, Helsinki University Hospital and Universities of Helsinki and Eastern Finland

Anssi Auvinen, University of Tampere, Faculty of Social Sciences/Health Sciences, FI-33014 Tampere

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Novelty and Impact

This cohort study (N=39,900) of mortality in incident cancer patients sheds light on how statin and/or metformin usage is associated with all-cause and cause-specific mortality. An association between baseline statin usage and lower all-cause, cancer, and cardiovascular mortality was modified by cancer type. The effect of statin use was largest for breast and colorectal cancer. The association between metformin usage and lower mortality was strongest for liver, colorectal, and breast cancer.

Abstract

Both diabetes mellitus (DM) and cancer are common diseases and they frequently occur in the same patients. We investigated the all-cause and cause-specific mortality dynamics in relation to baseline DM, statin use, and metformin use. The study population consisted of 39,900 incident cancer cases from Finland, 19,822 patients were free of DM at the start of follow-up, and 20,078 had DM. Mortality from all causes, and cancer, cardiovascular (CVD) and other causes was analysed using Poisson regression model with the following variables: sex, age, DM, statin and metformin usage in baseline, cancer type and stage, and calendar period. Statin usage was associated with a reduced cancer-specific mortality with incidence rate ratio (IRR) 0.72 (95% confidence interval 0.69-0.74), IRR for CVD mortality was 0.95 (0.88-1.02), and for other causes 0.64 (0.56-0.74). In a sub-population of DM patients, IRR for metformin in all-cause mortality was 0.74 (0.71-0.78), in cancer mortality 0.75 (0.72-0.79), in CVD mortality 0.75 (0.68-0.83), and other causes 0.68 (0.60-0.78). In conclusion, our register-based study of survival after cancer diagnosis showed that patients with diabetes had substantially poorer outcome in all measures. An association between baseline statin usage and lower all-cause, cancer, and cardiovascular mortality was modified by cancer type. The effect of statin use was largest for breast and colorectal cancer. Metformin usage in a subpopulation of oral antidiabetic users was in general associated with lower mortality, but this association was modified by cancer type. The association was strongest for liver, colorectal, and breast cancer.

Introduction

Both diabetes mellitus (DM) and cancer are common diseases and they frequently occur in the same patients. It has been estimated that overall about 35% of population will develop diabetes in their lifetime and 44% cancer[1], and about 15% both according to study of Danish population between 1995 and 2012. The overwhelmingly dominant cause of death for general population and diabetics is due to cardiovascular disease [2]. The association between diabetes and cancer is well established in terms of both cancer incidence and mortality[3–5]. According to a comprehensive meta-analysis (N=110,489), cancer patients with pre-existing diabetes have higher mortality (hazard rate (HR) 1.41; 95% confidence interval 1.28-1.55) compared to those without diabetes[6]. Highest risks of cancer death in relation to diabetes were in endometrial (HR 1.76; 1.34-2.31), breast (HR, 1.61; 1.46-1.78), and colorectal cancer (HR, 1.32; 1.24-1.41). In a pooled meta-analysis of incidence , population risk ratios for overall cancer mortality (RR) 0.97 (0.75-1.25) for men and 1.29 (1.16-1.44) for women was reported[7]. In a meta-analysis of 274,677 prostate cancer patients, cancer-specific mortality (RR 1.29; 1.22-1.38), and all-cause mortality (RR 1.37; 129-1.45) were increased in patients with diabetes.

Prognostic factors in concurrent diabetes and cancer are numerous: the diabetes-associated co-morbidities like cardiovascular disease or renal impairment may affect the therapeutic arsenal, antihyperglycemic therapy like metformin may decrease and insulin may increase the risk of cancer-progression, diabetic hyperglycemia may increase the infectious complications and cancer treatment may impair metabolic control of diabetes, thus further impairing the prognosis[8]. Due to increased risk of complications, diabetic

cancer patients may be treated less aggressively than those without diabetes, which may contribute to worse survival[9].

Statin therapy is frequently used in diabetic patients for the prevention of cardiovascular complications, but a recent large meta-analysis showed that statin therapy was associated with reduced cancer-specific mortality as well (HR 0.60, 0.47-0.77)[10]. On the other hand, recently some observational studies[11] and clinical trials[12,13] have not detected any effect on survival. Thus, the prognosis in diabetic patient with cancer is driven by several factors and cardiovascular and cancer-specific causes being the main competing causes.

We investigated the all-cause and cause-specific mortality dynamics in relation to baseline DM, usage of statins, and baseline usage of metformin. Our focus is on association between mortality and statin and antidiabetic medication in a large population with incident cancer.

Material and methods

Study population

The study population was constructed based on the CARING Project [14] in Finland (Figure 1). The initial population consisted of two groups: 1) Individuals in the insulin group had purchased and received reimbursement for at least one insulin prescription (ATC code A10A) [15] between 01-01-1997 and 31-12-2010; 2) The oral antidiabetic (OAD) group consisted of a 50% random sample of the people who had purchased and been reimbursed for at least one prescription of oral antidiabetic medication (A10B) in the same period. Initially, there were 170,052 individuals in the insulin group and 145,339 in the OAD group. Because of missing information (due to e.g. emigration), the final study population consisted of 314,353 people (insulin and OAD groups). The proportion of participants with missing information was low (0.32%), and thus, it is not probable that results are very much affected. The date of the first purchase (insulin or OAD) was defined as the index date for an individual. One control subject with same sex, same birth year, and same hospital district and who was alive at the index date was selected for each exposed study subject. In the final study population, there were 169,398 individuals with insulin and 144,955 people with OAD, and the same number of controls for both groups. Insulin users may have been using OAD at the start of follow-up. The data of purchased and reimbursed medications were obtained for both groups from the Finnish Prescription Register and Finnish Registry for Reimbursed Medication maintained by the Social Insurance Institution of Finland (KELA).

Follow-up and endpoint events

For the above mentioned study population, information on cancer diagnoses was obtained from the Finnish Cancer Registry (FCR)[16]. The data contained all cancer diagnoses starting from the year 1953. Stage was classified as local, regional, metastatic or unknown. In the construction of the study population for cancer survival, the inclusion criterion was having the first cancer diagnosis between 01-01-1996 and 31-12-2010. The following exclusion criteria were used: 1) any cancer diagnosed before the index date of the participant; 2) any cancer diagnosis before 01-01-1996. Non-melanoma skin cancers were not included in the cancer data. The criterion 1) was applied in order to avoid immortal time bias.

Follow-up for survival started at the diagnosis date of the first cancer, and ended at death or the common censoring date (31-12-2012), whichever occurred first (Appendix).

The following data were available for the study population: date of birth, sex, the date of the first cancer diagnosis, cancer diagnosis according to the ICD-O-3 coding [17], date of death, cause of death (ICD-10 code), and information of prescriptions (date, ATC code, amount purchased) between 01-01-1996 and 31-12-2010 for insulins, OAD, and statins (C10A). We formed the following four categories for diabetes, based on prescribed medication at the start of follow-up: no diabetes; on oral antidiabetics (OAD) only; using both OAD and insulin; and on insulin only.

The cancer types included were: pancreas (ICD-O-3 topography code C25), lung (C33, C34), skin melanoma (C44), colorectal (C18, C19, C20), liver (C22), bladder (C67), breast (C50), corpus uteri (C54), prostate (C61), Non-Hodgkin lymphoma (morphological codes M959, M960- M964, M967- M969, M970- M972) (NHL), and other. Medication use (no/yes) was determined for the date of diagnosis i.e. start of follow-up using prescription information.

Causes of death data were retrieved from Statistics Finland, where the vital status is collected for all Finnish citizens into the Finnish Causes of Death Register (FCDR)—irrespective of whether they die in Finland or abroad[18]. The cause of death data contained information about underlying and other causes of death.

The primary outcome was death after cancer diagnosis. Secondary outcomes included death from cancer (ICD10 C00-C97), from cardiovascular diseases (CVD) (F01, G45, I00-I99, Q20, Q28, R96), or other causes. Deaths were classified by underlying cause.

Statistical methods

We modelled all-cause and cause-specific (CS) mortalities using Poisson regression models with sex, age, calendar year at start of follow-up, diabetes group, statin usage, metformin usage, stage, and cancer type as independent variables. Modelling CS is suited for addressing etiologic questions, as discussed by Austin et al.[19]. Incidence rate ratios (IRR) were calculated using a log link function. Interactions were tested with likelihood ratio test. Poisson regression was chosen as statistical model, because it does not require an assumption of proportional hazards that is necessary with Cox's proportional hazards model. As sensitivity analyses we carried out Poisson regression analyses with inverse probability treatment weights (IPTW) for statins[20]. Weights were calculated with sex, age, diabetes, and calendar period in denominator, and with intercept in numerator.

We controlled for confounding using background variables as model covariates. All data-analyses were carried out using R language[21] with package Epi[22] and timereg[23].

Results

The study population consisted of 39,900 individuals. During the follow-up, 125,376 person-years were cumulated with a mean follow-up time of 3.1 years and a median 2.0 years. The number of deaths was 23,620. About half of the study population were men (57 %) (Table 1). Of the subjects, 24% were on oral antidiabetic medication (OAD), 15% on OAD and insulin, and 11% used only insulin at the date of diagnosis (start of follow-up). More than half (61%) were over 70 years of age, 28% used a statin, and 25% metformin at baseline. The most frequently used statins were simvastatin (63% of the users) and atorvastatin (18%). There were 23,498 subjects without statin and metformin treatment, 6376 with statin but not metformin, 5242 with metformin but not statin, and 4784 on both statin and metformin.

All-cause mortality was highest in pancreas (165 per 100 person-years, 95% confidence interval 158-172) and liver (116, 95% CI 109-125) cancers. The lowest all-cause mortality was in breast (7.3, 95% CI 6.9-7.6) and prostate cancer (8.4, 95% CI 8.1-8.7). Cancer was the predominant cause of death (contributing at least half of the total mortality) in all cancer types, except skin melanoma and prostate cancer. The cancer types with the highest cancer-specific mortality had also the highest all-cause mortality, and vice versa (Table 2, Appendix Table 5).

It was also evident and expected that non-diabetic people had considerably lower all-cause and cause-specific mortality (Appendix Figure 2). However, because the use of the Kaplan-Meier survival function results in estimates of incidence that are biased upward[19], we estimated also cumulative mortality functions. Cumulative mortality functions showed clearly that cancer was the leading cause of death in all study groups defined by diabetes (Appendix Figures 3). Considerable differences in unadjusted sub-distribution mortality functions according to cancer types were observed when cancer, CVD, and other causes of death were analyzed (Figure 2). Pancreas, lung, and liver cancers showed the highest cancer mortalities, but the lowest CVD mortalities. Melanoma, bladder, and prostate cancers were associated with the highest CVD mortality rates.

Analyses of all-cause mortality revealed that all diabetic groups had poorer survival compared to non-diabetic subjects (Table 2). However, among people with DM, there was no differences between OAD only, combined OAD and insulin, and insulin only groups. Statin use at the start of follow-up was associated with a lower all all-cause mortality (IRR 0.73, 0.71-0.75). Hormone-related cancers, breast and prostate, showed the lowest all-cause mortalities.

Statin usage and mortality

In the cause-specific analysis (Poisson regression) of cancer mortality, statin usage was associated with a reduced cancer-specific mortality (IRR 0.72, 0.69-0.74), for CVD mortality IRR was 0.95 (0.88-1.02), and for other causes 0.64 (0.56-0.74) (Table 3).

Cardiovascular disease (CVD) mortality was more than twice as high for the diabetic group compared to the non-diabetic subjects. IRR for insulin-only diabetic patients was as high as 2.99 (2.71-3.27). Statin usage at the start of the follow-up was not associated with CVD mortality in the cause-specific model.

We observed a significant interaction between cancer type and statin for all-cause (χ^2=27.372, df=10, p=0.0022), cancer (χ^2=20.834, df=10, p=0.02228), and CVD mortality (χ^2=21.728, df=10, p=0.01655) (Figure 3A, Appendix Table 1). Results of the interaction model were quite similar to the stratified analyses (Table 2). In all-cause mortality, statin use was associated with lower mortality for pancreas, lung, colorectal, breast, and other cancers. In cancer mortality for pancreas, colorectal, and other cancers, lower mortality was detected for statin users. In CVD mortality, lower risk for statin users were found in breast cancer (IRR 0.35, 0.18-0.68) and cancer of corpus uteri (0.48, 0.23-0.99). We tested for an interaction between diabetes and statin usage, but no interaction was detected for all-cause, or cause-specific mortalities. Thus, diabetes did not modify the effect of statin use. We also checked interactions between statin usage and stage, and no interactions were detected for all-cause, or cause-specific mortalities. IPTW analyses did not change results materially (Appendix Table 4).

In more detailed analyses of cause-specific mortality by type of statin, atorvastatin and lovastatin were associated with the lowest cancer mortality, though the differences between the agents were not large (Appendix Table 2).

Metformin usage and mortality in diabetic subpopulation

We analyzed the association between mortality and the use of metformin at the start of the follow-up including only subjects with any oral antidiabetic medication ("OAD only "and "OAD and insulin" groups). The IRR for metformin in all-cause mortality was 0.74 (0.71-0.78), for cancer mortality 0.75 (0.72-0.79), for CVD mortality 0.75 (0.68-0.83), and other causes 0.68 (0.60-0.78). Significant interactions between cancer type and statin were detected for these end-points [All-cause (χ^2= 25.893, df=10, p= 0.003887), cancer mortality (χ^2= 25.328, df=10, p= 0.004758) (Figure 3B, Appendix Table 3)].

Discussion

The aim of our study was to investigate the survival dynamics in diabetic patients with different glucose-lowering treatments after cancer diagnosis as compared to non-diabetic subjects, and the modifying effects of statin and metformin usage. We focused our analyses on all-cause mortality, examining also separately competing causes of death including cancer, cardiovascular diseases, and other causes.

Our results confirm the earlier observations that diabetes is associated with a poorer survival after cancer diagnosis [4–7]. In patients with diabetes, both types of analyses yielded a consistent pattern of results: cancer patients with a pre-existing diabetes have poorer outcome, with generally the largest effects among the patients on insulin only.

The main findings associate statin usage to lower mortality in nearly all models, and this association was not modified by diabetes. Our results are in line with a population-based (N=3638) study of lung cancer survival reporting a hazard ratio (HR) 0.91 (0.80-1.02, P=0.10) for all-cause mortality[24]. In contrast, in colorectal cancer no association between statin use and survival was detected[25]. In a nationwide cohort study of cancer patients, HR for statin users, as compared with patients who had never used statins, was 0.85 (0.83-0.87) for all-cause mortality[26]. The study reported also cancer mortality for 27 cancer types, of which 13 showed a reduced mortality in statin users. The HR for death from cancer among statin users ranged from 0.64 (0.46-0.88) for cervical cancer to 0.89 (0.81 -0.98) for pancreatic cancer. In a clinical trial of simvastatin combined with FOLFIRI/XELIRi for patients with metastatic colorectal cancer, no mortality reduction was detected[12]. A similar result was also observed in an observational study in stage III colon cancer[11]. This raises a question if the observed effect of statin use in this study is at least partly due to confounding. In a trial of pravastatin added to first-line standard chemotherapy in small-cell lung cancer, no effect on overall survival was detected[13]. In subpopulation of our study subpopulation analyses with 445 small cell lung cancers cases likewise gave similar result, no association between statin usage and all-cause mortality was observed. These discrepancies between observational and clinical studies raises the question if the observed effect (s) of statin in this and previous studies are at least partly explained by residual confounding factors, that are difficult to capture in these kind of settings.

Our population-level findings of statins are supported by recent results from a cell biological experiment, where administration of atorvastatin or rosuvastatin significantly reduced tumor growth in mice[27]. The results were obtained with doses, which were only slightly higher than the prescribed clinical dosage in humans.

We checked the effect of metformin usage on all-cause and cause-specific mortality in the subpopulation of oral antidiabetic users. It turned out that metformin usage was associated with a lower mortality in all-cause and cause specific mortality compared to no metformin usage. However, the association was modified by cancer type. The largest effect was detected for liver, colorectal, and breast cancer in all-cause mortality. As metformin is the recommended primary medication for new-onset type 2 diabetes in all major treatment guidelines [28], these patients likely had a shorter duration of diabetes and fewer complications

than those on insulin. Type 2 diabetic patients not treated with metformin may have characteristics that somehow associate also with impaired survival, which may have caused selection bias or confounding by indication. These complications may be gastrointestinal disturbances and renal impairment, which are the most common reasons for discontinuing metformin treatment. It is also possible that metformin has tumor suppressive effects that may be based on its metabolic effects [29,3031 32]. In the Women's Health Initiative study, long-term metformin use was associated with a lower risk of cancer death compared to other antidiabetic medication [33] in accordance with our results.

The key limitation of this study is the lack of information about major prognostic factors for cancer survival including treatment, grade of differentiation and other comorbidities, which may result in residual confounding. The register data did not allow us to separate type 1 and type 2 diabetes in detail: those treated with oral drugs only or oral drugs and insulin were assumed to represent type 2 diabetes, whereas among those treated with insulin only the distinction was not possible. However, the large majority of the cases in the older age groups have type 2 diabetes. Because we did not use medication use as a time-dependent predictor, it is possible that use of statin and metformin may have changed during the follow-up. We did not have data of socio-economic status or education that have shown to have effect on cancer survival[34–37]. However, at least in case of breast cancer no differences were detected in recent study of European countries[38]. Our Finnish study population is racially and ethnically fairly homogeneous, which may limit the generalizability of the results.

The relatively large size of the study population, long follow-up period, and inclusion of both non-diabetic and diabetic individuals in the unselected, nationwide cohort are the strengths of our study.

In conclusion, our register-based study of survival after cancer diagnosis showed that patients with diabetes had substantially poorer outcome according to all measures. An association between baseline statin usage and lower all-cause, cancer, and cardiovascular mortality was modified by cancer type. The effect of statin use was largest for breast and colorectal cancer. Metformin usage in a subpopulation of oral antidiabetic users was in general associated with a lower mortality, but this association was modified by cancer type. The association was strongest for liver, colorectal, and breast cancer.

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Table 1 Basic characteristics of the study population at start of follow-up. Number of participants, percentage by diabetes group in parentheses. OAD: oral antidiabetics

		All	no	OAD only	OAD and insulin	insulin only
All cancers	**All**	39900	19822	9700	5824	4554
Sex	male	22773	11339 (57.2%)	5503 (56.7%)	3287 (56.4%)	2644 (58.1%)
	female	17127	8483 (42.8%)	4197 (43.3%)	2537 (43.6%)	1910 (41.9%)
Age	50 or under	1163	591 (3.0%)	140 (1.4%)	71 (1.2%)	361 (7.9%)
	50-60	4015	1908 (9.6%)	838 (8.6%)	600 (10.3%)	669 (14.7%)
	60-70	10277	4905 (24.7%)	2496 (25.7%)	1759 (30.2%)	1117 (24.5%)
	Over 70	24445	12418 (62.6%)	6226 (64.2%)	3394 (58.3%)	2407 (52.9%)
Statin	no	28740	16280 (82.1%)	6127 (63.2%)	3319 (57.0%)	3014 (66.2%)
	yes	11160	3542 (17.9%)	3573 (36.8%)	2505 (43.0%)	1540 (33.8%)
Metformin	no	29874	19822 (100.0%)	3485 (35.9%)	2013 (34.6%)	4554 (100.0%)
	yes	10026	0 (0.0%)	6215 (64.1%)	3811 (65.4%)	0 (0.0%)
Stage	unknown	8195	3975 (20.1%)	2002 (20.6%)	1226 (21.1%)	992 (21.8%)
	localized	14643	7576 (38.2%)	3360 (34.6%)	2030 (34.9%)	1677 (36.8%)
	Non-localized	17062	8271 (41.7%)	4338 (44.7%)	2568 (44.1%)	1885 (41.4%)
Pancreas						
Sex	male	1078	343 (47.2%)	314 (51.2%)	251 (50.7%)	170 (56.1%)
	female	1059	383 (52.8%)	299 (48.8%)	244 (49.3%)	133 (43.9%)
Age	50 or under	29	5 (0.7%)	9 (1.5%)	4 (0.8%)	11 (3.6%)
	50-60	207	55 (7.6%)	47 (7.7%)	55 (11.1%)	50 (16.5%)
	60-70	520	152 (20.9%)	151 (24.6%)	140 (28.3%)	77 (25.4%)
	Over 70	1381	514 (70.8%)	406 (66.2%)	296 (59.8%)	165 (54.5%)
Statin	no	1649	634 (87.3%)	447 (72.9%)	335 (67.7%)	233 (76.9%)
	yes	488	92 (12.7%)	166 (27.1%)	160 (32.3%)	70 (23.1%)
Metformin	no	1480	726 (100.0%)	246 (40.1%)	205 (41.4%)	303 (100.0%)

	yes	657	0 (0.0%)	367 (59.9%)	290 (58.6%)	0 (0.0%)
Stage	unknown	440	136 (18.7%)	136 (22.2%)	95 (19.2%)	73 (24.1%)
	localized	172	56 (7.7%)	49 (8.0%)	40 (8.1%)	27 (8.9%)
	Non-localized	1525	534 (73.6%)	428 (69.8%)	360 (72.7%)	203 (67.0%)
Lung						
Sex	male	2803	1433 (77.2%)	672 (75.5%)	387 (75.0%)	311 (77.9%)
	female	858	423 (22.8%)	218 (24.5%)	129 (25.0%)	88 (22.1%)
Age	50 or under	42	16 (0.9%)	5 (0.6%)	6 (1.2%)	15 (3.8%)
	50-60	340	146 (7.9%)	78 (8.8%)	52 (10.1%)	64 (16.0%)
	60-70	1072	523 (28.2%)	254 (28.5%)	170 (32.9%)	125 (31.3%)
	Over 70	2207	1171 (63.1%)	553 (62.1%)	288 (55.8%)	195 (48.9%)
Statin	no	2697	1576 (84.9%)	571 (64.2%)	291 (56.4%)	259 (64.9%)
	yes	964	280 (15.1%)	319 (35.8%)	225 (43.6%)	140 (35.1%)
Metformin	no	2782	1856 (100.0%)	348 (39.1%)	179 (34.7%)	399 (100.0%)
	yes	879	0 (0.0%)	542 (60.9%)	337 (65.3%)	0 (0.0%)
Stage	unknown	725	359 (19.3%)	179 (20.1%)	100 (19.4%)	87 (21.8%)
	localized	510	242 (13.0%)	120 (13.5%)	81 (15.7%)	67 (16.8%)
	Non-localized	2426	1255 (67.6%)	591 (66.4%)	335 (64.9%)	245 (61.4%)
Melanoma						
Sex	male	1567	802 (50.6%)	370 (55.3%)	226 (56.1%)	169 (58.1%)
	female	1381	783 (49.4%)	299 (44.7%)	177 (43.9%)	122 (41.9%)
Age	50 or under	99	54 (3.4%)	11 (1.6%)	7 (1.7%)	27 (9.3%)
	50-60	216	110 (6.9%)	31 (4.6%)	39 (9.7%)	36 (12.4%)
	60-70	508	257 (16.2%)	126 (18.8%)	80 (19.9%)	45 (15.5%)
	Over 70	2125	1164 (73.4%)	501 (74.9%)	277 (68.7%)	183 (62.9%)
Statin	no	2008	1238 (78.1%)	392 (58.6%)	200 (49.6%)	178 (61.2%)
	yes	940	347 (21.9%)	277 (41.4%)	203 (50.4%)	113 (38.8%)
Metformin	no	2248	1585 (100.0%)	233 (34.8%)	139 (34.5%)	291 (100.0%)

	yes	700	0 (0.0%)	436 (65.2%)	264 (65.5%)	0 (0.0%)
Stage	unknown	1130	614 (38.7%)	247 (36.9%)	161 (40.0%)	108 (37.1%)
	localized	1571	834 (52.6%)	369 (55.2%)	205 (50.9%)	163 (56.0%)
	Non-localized	247	137 (8.6%)	53 (7.9%)	37 (9.2%)	20 (6.9%)
Colorectal						
Sex	male	2191	1015 (52.7%)	554 (55.6%)	325 (55.9%)	297 (59.0%)
	female	1817	912 (47.3%)	443 (44.4%)	256 (44.1%)	206 (41.0%)
Age	50 or under	80	44 (2.3%)	9 (0.9%)	8 (1.4%)	19 (3.8%)
	50-60	351	150 (7.8%)	78 (7.8%)	55 (9.5%)	68 (13.5%)
	60-70	945	420 (21.8%)	236 (23.7%)	165 (28.4%)	124 (24.7%)
	Over 70	2632	1313 (68.1%)	674 (67.6%)	353 (60.8%)	292 (58.1%)
Statin	no	2835	1579 (81.9%)	637 (63.9%)	310 (53.4%)	309 (61.4%)
	yes	1173	348 (18.1%)	360 (36.1%)	271 (46.6%)	194 (38.6%)
Metformin	no	2972	1927 (100.0%)	351 (35.2%)	191 (32.9%)	503 (100.0%)
	yes	1036	0 (0.0%)	646 (64.8%)	390 (67.1%)	0 (0.0%)
Stage	unknown	607	268 (13.9%)	171 (17.2%)	88 (15.1%)	80 (15.9%)
	localized	1201	595 (30.9%)	274 (27.5%)	161 (27.7%)	171 (34.0%)
	Non-localized	2200	1064 (55.2%)	552 (55.4%)	332 (57.1%)	252 (50.1%)
Liver						
Sex	male	644	136 (58.6%)	208 (69.6%)	182 (71.7%)	118 (69.8%)
	female	310	96 (41.4%)	91 (30.4%)	72 (28.3%)	51 (30.2%)
Age	50 or under	11	4 (1.7%)	0 (0.0%)	2 (0.8%)	5 (3.0%)
	50-60	93	16 (6.9%)	21 (7.0%)	29 (11.4%)	27 (16.0%)
	60-70	273	49 (21.1%)	84 (28.1%)	82 (32.3%)	58 (34.3%)
	Over 70	577	163 (70.3%)	194 (64.9%)	141 (55.5%)	79 (46.7%)
Statin	no	725	202 (87.1%)	229 (76.6%)	162 (63.8%)	132 (78.1%)
	yes	229	30 (12.9%)	70 (23.4%)	92 (36.2%)	37 (21.9%)

Metformin	no	632	232 (100.0%)	119 (39.8%)	112 (44.1%)	169 (100.0%)
	yes	322	0 (0.0%)	180 (60.2%)	142 (55.9%)	0 (0.0%)
Stage	unknown	368	75 (32.3%)	123 (41.1%)	98 (38.6%)	72 (42.6%)
	localized	235	48 (20.7%)	74 (24.7%)	69 (27.2%)	44 (26.0%)
	Non-localized	351	109 (47.0%)	102 (34.1%)	87 (34.3%)	53 (31.4%)
Bladder						
Sex	male	1240	588 (79.7%)	310 (79.3%)	198 (79.5%)	144 (82.3%)
	female	313	150 (20.3%)	81 (20.7%)	51 (20.5%)	31 (17.7%)
Age	50 or under	23	10 (1.4%)	5 (1.3%)	0 (0.0%)	8 (4.6%)
	50-60	109	44 (6.0%)	29 (7.4%)	16 (6.4%)	20 (11.4%)
	60-70	379	178 (24.1%)	91 (23.3%)	74 (29.7%)	36 (20.6%)
	Over 70	1042	506 (68.6%)	266 (68.0%)	159 (63.9%)	111 (63.4%)
Statin	no	1055	580 (78.6%)	224 (57.3%)	140 (56.2%)	111 (63.4%)
	yes	498	158 (21.4%)	167 (42.7%)	109 (43.8%)	64 (36.6%)
Metformin	no	1163	738 (100.0%)	147 (37.6%)	103 (41.4%)	175 (100.0%)
	yes	390	0 (0.0%)	244 (62.4%)	146 (58.6%)	0 (0.0%)
Stage	unknown	316	141 (19.1%)	82 (21.0%)	54 (21.7%)	39 (22.3%)
	localized	1054	505 (68.4%)	262 (67.0%)	168 (67.5%)	119 (68.0%)
	Non-localized	183	92 (12.5%)	47 (12.0%)	27 (10.8%)	17 (9.7%)
Breast						
Sex	male	33	15 (0.6%)	5 (0.5%)	7 (1.3%)	6 (1.2%)
	female	4255	2309 (99.4%)	952 (99.5%)	516 (98.7%)	478 (98.8%)
Age	50 or under	260	150 (6.5%)	22 (2.3%)	10 (1.9%)	78 (16.1%)
	50-60	708	409 (17.6%)	126 (13.2%)	81 (15.5%)	92 (19.0%)
	60-70	1173	650 (28.0%)	252 (26.3%)	158 (30.2%)	113 (23.3%)
	Over 70	2147	1115 (48.0%)	557 (58.2%)	274 (52.4%)	201 (41.5%)
Statin	no	3146	1951 (84.0%)	584 (61.0%)	286 (54.7%)	325 (67.1%)

	yes	1142	373 (16.0%)	373 (39.0%)	237 (45.3%)	159 (32.9%)
Metformin	no	3250	2324 (100.0%)	284 (29.7%)	158 (30.2%)	484 (100.0%)
	yes	1038	0 (0.0%)	673 (70.3%)	365 (69.8%)	0 (0.0%)
Stage	unknown	299	168 (7.2%)	51 (5.3%)	40 (7.6%)	40 (8.3%)
	localized	2157	1211 (52.1%)	459 (48.0%)	248 (47.4%)	239 (49.4%)
	Non-localized	1832	945 (40.7%)	447 (46.7%)	235 (44.9%)	205 (42.4%)
Corpus uteri						
Sex	female	1211	497 (100.0%)	358 (100.0%)	240 (100.0%)	116 (100.0%)
Age	50 or under	23	9 (1.8%)	6 (1.7%)	4 (1.7%)	4 (3.4%)
	50-60	138	49 (9.9%)	41 (11.5%)	35 (14.6%)	13 (11.2%)
	60-70	336	139 (28.0%)	84 (23.5%)	79 (32.9%)	34 (29.3%)
	Over 70	714	300 (60.4%)	227 (63.4%)	122 (50.8%)	65 (56.0%)
Statin	no	803	397 (79.9%)	214 (59.8%)	129 (53.8%)	63 (54.3%)
	yes	408	100 (20.1%)	144 (40.2%)	111 (46.3%)	53 (45.7%)
Metformin	no	764	497 (100.0%)	99 (27.7%)	52 (21.7%)	116 (100.0%)
	yes	447	0 (0.0%)	259 (72.3%)	188 (78.3%)	0 (0.0%)
Stage	unknown	278	113 (22.7%)	84 (23.5%)	52 (21.7%)	29 (25.0%)
	localized	688	292 (58.8%)	182 (50.8%)	140 (58.3%)	74 (63.8%)
	Non-localized	245	92 (18.5%)	92 (25.7%)	48 (20.0%)	13 (11.2%)
Prostate						
Sex	male	7533	4276 (100.0%)	1679 (100.0%)	888 (100.0%)	690 (100.0%)
Age	50 or under	26	11 (0.3%)	8 (0.5%)	1 (0.1%)	6 (0.9%)
	50-60	568	331 (7.7%)	107 (6.4%)	67 (7.5%)	63 (9.1%)
	60-70	2411	1345 (31.5%)	550 (32.8%)	313 (35.2%)	203 (29.4%)
	Over 70	4528	2589 (60.5%)	1014 (60.4%)	507 (57.1%)	418 (60.6%)
Statin	no	5088	3343 (78.2%)	908 (54.1%)	446 (50.2%)	391 (56.7%)
	yes	2445	933 (21.8%)	771 (45.9%)	442 (49.8%)	299 (43.3%)

Metformin	no	5741	4276 (100.0%)	515 (30.7%)	260 (29.3%)	690 (100.0%)
	yes	1792	0 (0.0%)	1164 (69.3%)	628 (70.7%)	0 (0.0%)
Stage	unknown	1839	1019 (23.8%)	379 (22.6%)	244 (27.5%)	197 (28.6%)
	localized	4039	2314 (54.1%)	923 (55.0%)	462 (52.0%)	340 (49.3%)
	Non-localized	1655	943 (22.1%)	377 (22.5%)	182 (20.5%)	153 (22.2%)
NHL						
Sex	male	60	24 (49.0%)	12 (60.0%)	15 (65.2%)	9 (52.9%)
	female	49	25 (51.0%)	8 (40.0%)	8 (34.8%)	8 (47.1%)
Age	50 or under	2	1 (2.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
	50-60	11	3 (6.1%)	2 (10.0%)	2 (8.7%)	4 (23.5%)
	60-70	22	9 (18.4%)	3 (15.0%)	6 (26.1%)	4 (23.5%)
	Over 70	74	36 (73.5%)	14 (70.0%)	15 (65.2%)	9 (52.9%)
Statin	no	72	38 (77.6%)	13 (65.0%)	9 (39.1%)	12 (70.6%)
	yes	37	11 (22.4%)	7 (35.0%)	14 (60.9%)	5 (29.4%)
Metformin	no	87	49 (100.0%)	14 (70.0%)	7 (30.4%)	17 (100.0%)
	yes	22	0 (0.0%)	6 (30.0%)	16 (69.6%)	0 (0.0%)
Stage	unknown	55	27 (55.1%)	11 (55.0%)	10 (43.5%)	7 (41.2%)
	localized	26	11 (22.4%)	5 (25.0%)	7 (30.4%)	3 (17.6%)
	Non-localized	28	11 (22.4%)	4 (20.0%)	6 (26.1%)	7 (41.2%)
Other						
Sex	male	5624	2707 (48.2%)	1379 (48.8%)	808 (48.9%)	730 (51.9%)
	female	5874	2905 (51.8%)	1448 (51.2%)	844 (51.1%)	677 (48.1%)
Age	50 or under	568	287 (5.1%)	64 (2.3%)	29 (1.8%)	188 (13.4%)
	50-60	1274	595 (10.6%)	278 (9.8%)	169 (10.2%)	232 (16.5%)
	60-70	2638	1183 (21.1%)	665 (23.5%)	492 (29.8%)	298 (21.2%)
	Over 70	7018	3547 (63.2%)	1820 (64.4%)	962 (58.2%)	689 (49.0%)
Statin	no	8662	4742 (84.5%)	1908 (67.5%)	1011 (61.2%)	1001 (71.1%)

	yes	2836	870 (15.5%)	919 (32.5%)	641 (38.8%)	406 (28.9%)
Metformin	no	8755	5612 (100.0%)	1129 (39.9%)	607 (36.7%)	1407 (100.0%)
	yes	2743	0 (0.0%)	1698 (60.1%)	1045 (63.3%)	0 (0.0%)
Stage	unknown	2138	1055 (18.8%)	539 (19.1%)	284 (17.2%)	260 (18.5%)
	localized	2990	1468 (26.2%)	643 (22.7%)	449 (27.2%)	430 (30.6%)
	Non-localized	6370	3089 (55.0%)	1645 (58.2%)	919 (55.6%)	717 (51.0%)

Table 2 All-cause and cause-specific mortality rate ratios. Stratified analyses by cancer type. All analyses are adjusted for sex, age, diabetes (DM), statin medication, stage, and calendar period using multivariate Poisson model. NA=not available.

Pancreas		**All-cause mortality**	**Cancer mortality**	**CVD mortality**	**Other mortality**
Sex (ref. male)	female	0.94 (0.86 - 1.03)	0.96 (0.88 - 1.06)	0.38 (0.20 - 0.71)	0.85 (0.46 - 1.56)
Age	(per 1 year)	1.04 (1.04 - 1.05)	1.04 (1.04 - 1.05)	1.10 (1.07 - 1.15)	1.08 (1.04 - 1.11)
DM (ref. no DM)	OAD only	1.14 (1.02 - 1.27)	1.15 (1.03 - 1.29)	0.94 (0.42 - 2.11)	0.96 (0.44 - 2.12)
	OAD and insulin	1.20 (1.07 - 1.35)	1.18 (1.04 - 1.33)	2.48 (1.19 - 5.16)	1.25 (0.56 - 2.81)
	insulin only	1.29 (1.12 - 1.48)	1.26 (1.09 - 1.45)	1.27 (0.45 - 3.62)	2.45 (1.13 - 5.31)
Statin (ref. no)	yes	0.85 (0.76 - 0.94)	0.83 (0.74 - 0.92)	2.16 (1.09 - 4.27)	0.93 (0.45 - 1.92)
Stage (ref. unknown)	localized	0.56 (0.47 - 0.67)	0.55 (0.45 - 0.67)	0.81 (0.35 - 1.90)	0.69 (0.32 - 1.51)
	non-localized	1.29 (1.15 - 1.44)	1.37 (1.22 - 1.54)	0.54 (0.28 - 1.05)	0.29 (0.15 - 0.56)
Lung		**All-cause mortality**	**Cancer mortality**	**CVD mortality**	**Other mortality**
Sex (ref. male)	female	0.86 (0.79 - 0.93)	0.89 (0.82 - 0.97)	0.54 (0.38 - 0.77)	0.87 (0.58 - 1.32)
Age	(per 1 year)	1.04 (1.04 - 1.04)	1.04 (1.03 - 1.04)	1.07 (1.05 - 1.09)	1.07 (1.04 - 1.09)
DM (ref. no DM)	OAD only	1.20 (1.10 - 1.30)	1.17 (1.07 - 1.28)	1.45 (1.03 - 2.03)	1.43 (0.93 - 2.20)
	OAD and insulin	1.10 (0.99 - 1.23)	1.07 (0.96 - 1.20)	1.50 (0.99 - 2.28)	1.43 (0.82 - 2.49)
	insulin only	1.49 (1.33 - 1.67)	1.38 (1.22 - 1.56)	3.02 (2.07 - 4.42)	1.97 (1.14 - 3.43)
Statin (ref. no)	yes	0.75 (0.69 - 0.82)	0.74 (0.68 - 0.81)	1.03 (0.75 - 1.41)	0.62 (0.39 - 0.98)
Stage (ref. unknown)	localized	0.40 (0.35 - 0.46)	0.35 (0.30 - 0.40)	0.76 (0.54 - 1.07)	0.61 (0.40 - 0.95)
	non-localized	1.63 (1.49 - 1.78)	1.83 (1.66 - 2.01)	0.71 (0.51 - 0.98)	0.46 (0.30 - 0.70)
Melanoma		**All-cause mortality**	**Cancer mortality**	**CVD mortality**	**Other mortality**
Sex (ref. male)	female	0.86 (0.77 - 0.96)	0.73 (0.60 - 0.90)	0.95 (0.81 - 1.13)	0.81 (0.64 - 1.03)
Age	(per 1 year)	1.07 (1.06 - 1.08)	1.02 (1.02 - 1.03)	1.11 (1.10 - 1.12)	1.09 (1.07 - 1.10)
DM (ref. no DM)	OAD only	1.31 (1.14 - 1.51)	1.05 (0.80 - 1.36)	1.50 (1.23 - 1.83)	1.31 (0.98 - 1.73)
	OAD and insulin	1.64 (1.39 - 1.93)	1.26 (0.93 - 1.69)	2.37 (1.88 - 2.98)	1.14 (0.76 - 1.71)
	insulin only	1.96 (1.64 - 2.35)	1.38 (0.99 - 1.92)	2.23 (1.70 - 2.92)	2.33 (1.63 - 3.31)
Statin (ref. no)	yes	0.84 (0.73 - 0.96)	0.81 (0.63 - 1.03)	1.05 (0.86 - 1.29)	0.66 (0.48 - 0.90)
Stage (ref. unknown)	localized	0.92 (0.82 - 1.04)	0.64 (0.50 - 0.82)	1.00 (0.85 - 1.19)	1.15 (0.90 - 1.46)

	non-localized	3.80 (3.16 - 4.57)	8.31 (6.48 - 10.66)	1.14 (0.71 - 1.82)	0.82 (0.38 - 1.77)
Colorectal		**All-cause mortality**	**Cancer mortality**	**CVD mortality**	**Other mortality**
Sex (ref. male)	female	0.78 (0.72 - 0.85)	0.87 (0.78 - 0.96)	0.57 (0.47 - 0.70)	0.72 (0.56 - 0.94)
Age	(per 1 year)	1.06 (1.06 - 1.07)	1.05 (1.05 - 1.06)	1.10 (1.08 - 1.11)	1.06 (1.04 - 1.08)
DM (ref. no DM)	OAD only	1.31 (1.19 - 1.46)	1.24 (1.10 - 1.40)	1.62 (1.28 - 2.05)	1.31 (0.94 - 1.84)
	OAD and insulin	1.34 (1.18 - 1.51)	1.11 (0.95 - 1.30)	2.04 (1.56 - 2.69)	2.08 (1.45 - 3.00)
	insulin only	1.93 (1.71 - 2.19)	1.39 (1.18 - 1.63)	3.85 (2.99 - 4.95)	3.28 (2.32 - 4.64)
Statin (ref. no)	yes	0.68 (0.62 - 0.76)	0.66 (0.58 - 0.74)	0.96 (0.77 - 1.19)	0.47 (0.33 - 0.67)
Stage (ref. unknown)	localized	0.53 (0.46 - 0.60)	0.37 (0.30 - 0.44)	0.76 (0.60 - 0.95)	0.72 (0.53 - 0.99)
	non-localized	1.65 (1.47 - 1.84)	2.33 (2.01 - 2.69)	0.73 (0.57 - 0.94)	0.59 (0.42 - 0.84)
Liver		**All-cause mortality**	**Cancer mortality**	**CVD mortality**	**Other mortality**
Sex (ref. male)	female	1.11 (0.96 - 1.29)	1.20 (1.03 - 1.41)	0.62 (0.30 - 1.27)	0.48 (0.23 - 0.98)
Age	(per 1 year)	1.03 (1.02 - 1.04)	1.04 (1.03 - 1.04)	1.05 (1.02 - 1.09)	1.00 (0.97 - 1.02)
DM (ref. no DM)	OAD only	1.04 (0.86 - 1.25)	1.09 (0.90 - 1.32)	0.62 (0.27 - 1.43)	0.69 (0.33 - 1.42)
	OAD and insulin	1.06 (0.88 - 1.29)	1.11 (0.91 - 1.36)	0.55 (0.22 - 1.38)	0.90 (0.45 - 1.84)
	insulin only	1.11 (0.90 - 1.38)	1.05 (0.83 - 1.32)	1.66 (0.74 - 3.74)	1.10 (0.53 - 2.27)
Statin (ref. no)	yes	0.83 (0.70 - 0.98)	0.87 (0.73 - 1.04)	0.88 (0.40 - 1.95)	0.34 (0.15 - 0.78)
Stage (ref. unknown)	localized	0.53 (0.44 - 0.63)	0.50 (0.41 - 0.61)	0.70 (0.36 - 1.35)	0.70 (0.40 - 1.21)
	non-localized	1.68 (1.44 - 1.96)	1.86 (1.58 - 2.19)	0.62 (0.27 - 1.43)	0.65 (0.32 - 1.30)
Bladder		**All-cause mortality**	**Cancer mortality**	**CVD mortality**	**Other mortality**
Sex (ref. male)	female	0.93 (0.78 - 1.10)	1.07 (0.85 - 1.35)	0.61 (0.43 - 0.86)	1.23 (0.82 - 1.83)
Age	(per 1 year)	1.07 (1.06 - 1.08)	1.05 (1.04 - 1.06)	1.09 (1.08 - 1.11)	1.08 (1.06 - 1.10)
DM (ref. no DM)	OAD only	1.47 (1.23 - 1.76)	1.46 (1.15 - 1.86)	1.79 (1.29 - 2.49)	1.09 (0.68 - 1.75)
	OAD and insulin	1.85 (1.52 - 2.27)	1.74 (1.31 - 2.31)	2.52 (1.78 - 3.56)	1.21 (0.70 - 2.10)
	insulin only	2.18 (1.76 - 2.70)	1.39 (0.99 - 1.96)	3.07 (2.14 - 4.40)	3.15 (2.01 - 4.94)
Statin (ref. no)	yes	0.77 (0.64 - 0.92)	0.69 (0.53 - 0.88)	1.17 (0.86 - 1.58)	0.41 (0.24 - 0.70)
Stage (ref. unknown)	localized	0.61 (0.52 - 0.72)	0.57 (0.44 - 0.73)	0.65 (0.49 - 0.85)	0.65 (0.44 - 0.96)
	non-localized	3.51 (2.82 - 4.37)	6.47 (4.90 - 8.56)	0.82 (0.43 - 1.55)	0.74 (0.31 - 1.76)
Breast		**All-cause mortality**	**Cancer mortality**	**CVD mortality**	**Other mortality**
Age	(per 1 year)	1.07 (1.07 - 1.08)	1.05 (1.04 - 1.05)	1.12 (1.11 - 1.13)	1.09 (1.08 - 1.10)

DM (ref. no DM)	OAD only	1.48 (1.30 - 1.69)	1.32 (1.11 - 1.58)	1.82 (1.42 - 2.34)	1.57 (1.17 - 2.10)
	OAD and insulin	1.78 (1.53 - 2.08)	1.28 (1.02 - 1.60)	2.98 (2.27 - 3.91)	1.90 (1.35 - 2.68)
	insulin only	2.00 (1.71 - 2.35)	1.40 (1.11 - 1.77)	3.43 (2.59 - 4.53)	1.95 (1.35 - 2.82)
Statin (ref. no)	yes	0.66 (0.57 - 0.76)	0.71 (0.59 - 0.86)	0.61 (0.47 - 0.80)	0.69 (0.50 - 0.95)
Stage (ref. unknown)	localized	0.47 (0.39 - 0.56)	0.30 (0.23 - 0.40)	0.76 (0.56 - 1.04)	0.56 (0.39 - 0.80)
	non-localized	1.04 (0.88 - 1.24)	1.35 (1.05 - 1.74)	0.91 (0.66 - 1.26)	0.61 (0.42 - 0.89)
Corpus uteri		**All-cause mortality**	**Cancer mortality**	**CVD mortality**	**Other mortality**
Age	(per 1 year)	1.09 (1.08 - 1.10)	1.08 (1.07 - 1.10)	1.12 (1.09 - 1.14)	1.08 (1.05 - 1.12)
DM (ref. no DM)	OAD only	1.46 (1.16 - 1.84)	1.21 (0.91 - 1.62)	1.75 (1.08 - 2.84)	2.70 (1.31 - 5.54)
	OAD and insulin	2.30 (1.80 - 2.94)	1.65 (1.19 - 2.29)	3.87 (2.44 - 6.12)	3.57 (1.68 - 7.59)
	insulin only	2.09 (1.52 - 2.86)	1.07 (0.65 - 1.76)	3.81 (2.23 - 6.51)	5.09 (2.29 - 11.32)
Statin (ref. no)	yes	0.80 (0.63 - 1.00)	0.82 (0.61 - 1.10)	0.95 (0.62 - 1.47)	0.59 (0.30 - 1.17)
Stage (ref. unknown)	localized	0.77 (0.60 - 0.97)	0.68 (0.48 - 0.96)	0.80 (0.54 - 1.18)	1.01 (0.55 - 1.86)
	non-localized	3.37 (2.61 - 4.35)	5.44 (3.91 - 7.58)	1.14 (0.63 - 2.04)	0.87 (0.31 - 2.45)
Prostate		**All-cause mortality**	**Cancer mortality**	**CVD mortality**	**Other mortality**
Age	(per 1 year)	1.08 (1.08 - 1.09)	1.06 (1.05 - 1.07)	1.10 (1.09 - 1.11)	1.10 (1.09 - 1.11)
DM (ref. no DM)	OAD only	1.47 (1.34 - 1.62)	1.18 (1.02 - 1.36)	1.77 (1.51 - 2.07)	1.73 (1.40 - 2.12)
	OAD and insulin	1.98 (1.77 - 2.21)	1.47 (1.23 - 1.75)	2.60 (2.18 - 3.10)	2.21 (1.73 - 2.83)
	insulin only	1.98 (1.76 - 2.23)	1.14 (0.93 - 1.40)	2.86 (2.38 - 3.44)	2.88 (2.26 - 3.67)
Statin (ref. no)	yes	0.84 (0.77 - 0.92)	0.82 (0.72 - 0.95)	1.02 (0.88 - 1.19)	0.61 (0.49 - 0.76)
Stage (ref. unknown)	localized	0.72 (0.66 - 0.79)	0.56 (0.48 - 0.66)	0.82 (0.71 - 0.94)	0.83 (0.69 - 1.00)
	non-localized	1.73 (1.57 - 1.90)	3.02 (2.63 - 3.47)	1.04 (0.87 - 1.24)	0.79 (0.61 - 1.02)
NHL		**All-cause mortality**	**Cancer mortality**	**CVD mortality**	**Other mortality**
Sex (ref. male)	female	0.93 (0.55 - 1.55)	1.20 (0.64 - 2.26)	0.55 (0.17 - 1.78)	0.54 (0.08 - 3.58)
Age	(per 1 year)	1.06 (1.03 - 1.09)	1.04 (1.01 - 1.08)	1.13 (1.05 - 1.22)	1.14 (0.97 - 1.34)
DM (ref. no DM)	OAD only	2.06 (1.07 - 3.97)	2.63 (1.20 - 5.76)	1.17 (0.28 - 4.92)	1.25 (0.11 - 14.83)
	OAD and insulin	0.73 (0.36 - 1.48)	0.69 (0.27 - 1.72)	0.61 (0.14 - 2.58)	2.05 (0.24 - 17.28)
	insulin only	2.56 (1.26 - 5.20)	3.32 (1.45 - 7.64)	1.76 (0.36 - 8.62)	NA
Statin (ref. no)	yes	1.27 (0.68 - 2.38)	1.00 (0.46 - 2.15)	2.80 (0.73 - 10.80)	0.48 (0.03 - 7.14)
Stage (ref. unknown)	localized	1.45 (0.76 - 2.79)	1.24 (0.54 - 2.81)	3.61 (1.04 - 12.57)	NA

	non-localized	3.46 (1.88 - 6.36)	4.29 (2.11 - 8.72)	1.37 (0.26 - 7.25)	2.39 (0.29 - 19.49)
Other		**All-cause mortality**	**Cancer mortality**	**CVD mortality**	**Other mortality**
Sex (ref. male)	female	0.85 (0.82 - 0.89)	0.90 (0.85 - 0.94)	0.71 (0.62 - 0.80)	0.70 (0.59 - 0.81)
Age	(per 1 year)	1.06 (1.06 - 1.07)	1.06 (1.06 - 1.06)	1.09 (1.08 - 1.10)	1.07 (1.06 - 1.08)
DM (ref. no DM)	OAD only	1.50 (1.42 - 1.58)	1.41 (1.33 - 1.50)	2.03 (1.74 - 2.38)	1.78 (1.46 - 2.16)
	OAD and insulin	1.47 (1.37 - 1.57)	1.32 (1.23 - 1.42)	2.54 (2.14 - 3.03)	1.70 (1.35 - 2.15)
	insulin only	1.64 (1.53 - 1.76)	1.38 (1.27 - 1.50)	3.04 (2.54 - 3.65)	2.81 (2.26 - 3.49)
Statin (ref. no)	yes	0.67 (0.63 - 0.71)	0.65 (0.61 - 0.70)	0.87 (0.75 - 1.01)	0.53 (0.43 - 0.66)
Stage (ref. unknown)	localized	0.54 (0.50 - 0.58)	0.47 (0.43 - 0.51)	0.72 (0.62 - 0.85)	0.76 (0.61 - 0.93)
	non-localized	1.81 (1.71 - 1.92)	2.18 (2.04 - 2.33)	0.80 (0.68 - 0.93)	1.04 (0.86 - 1.27)

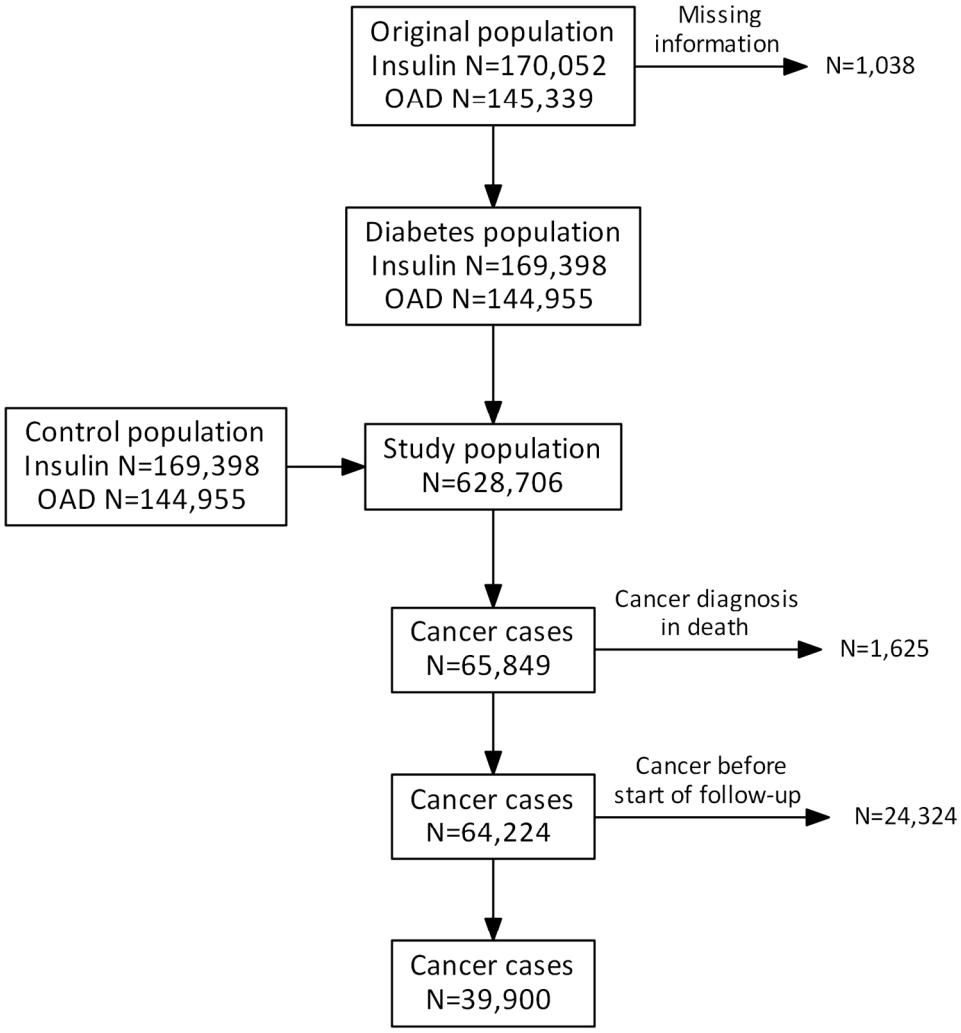


Figure 1. Construction of study population. People with at least one purchase of oral antidiabetics (OAD) (50% random sample) and all insulin users between 1996 and 2010 in Finland were included in the exposed cohort. One control for each cohort member was matched by sex, birth year, and living area.

496x513mm (96 x 96 DPI)

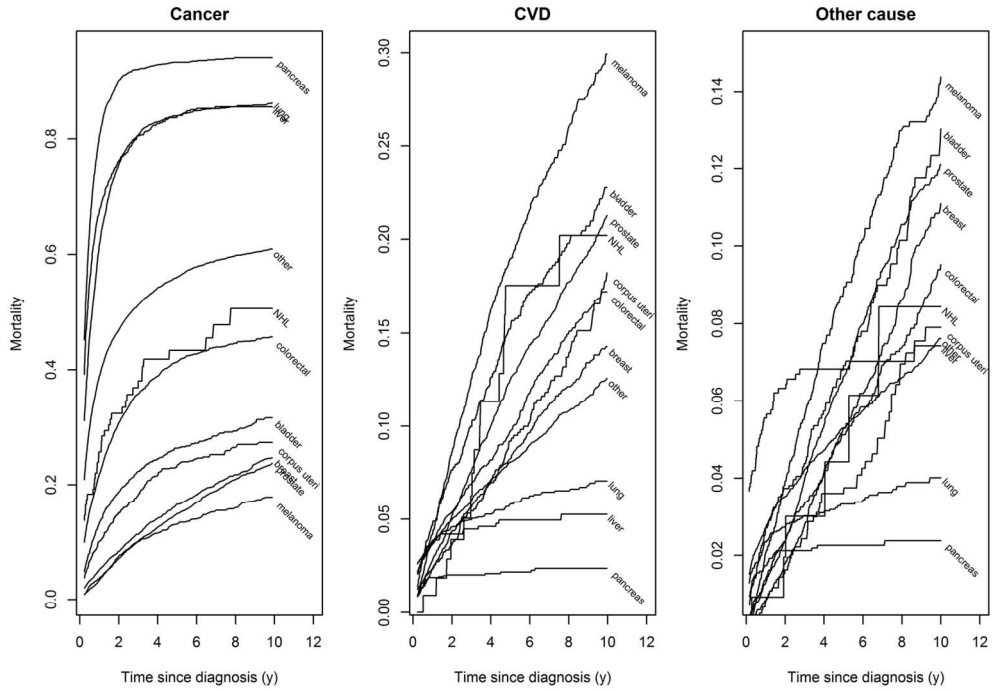
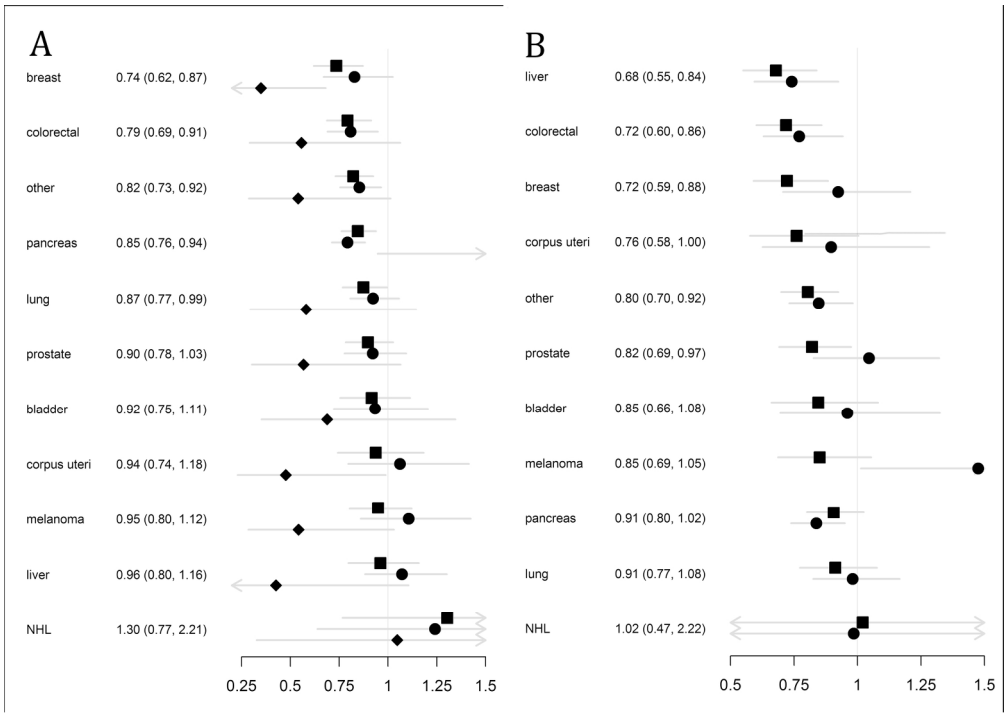


Figure 2. Cumulative mortality functions by cancer type for three competing causes of death: cancer, cardiovascular diseases (CVD), and other causes. Note different y-axis scales.

135x95mm (300 x 300 DPI)



(A) Association between baseline statin usage and all-cause and cause-specific mortality by cancer type. IRR with 95% confidence intervals for all-cause mortality. All-cause (square), cancer (bullet), and CVD mortality (diamond). All analyses are adjusted for sex, age, diabetes, stage, interaction between cancer type and statin usage, and calendar period with Poisson regression. %"%"(B) Association between baseline metformin usage and all-cause and cause-specific mortality by cancer type. Only users of oral antidiabetics included. IRR with 95% confidence intervals for all-cause mortality. All-cause (square) and cancer (bullet). All analyses are adjusted for sex, age, diabetes, stage, interaction between cancer type and metformin usage, and calendar period with Poisson regression.

192x135mm (300 x 300 DPI)