# Survival after breast cancer in women with type 2 diabetes using antidiabetic medication and statins: A retrospective cohort study

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# Survival after breast cancer in women with type 2 diabetes using antidiabetic medication and statins: A retrospective cohort study


## Abstract

**Background:** We assessed survival of breast cancer in women with type 2 diabetes (T2D) treated with metformin, other types of antidiabetic medication (ADM) and statins.

**Materials and Methods:** The study cohort consisted of women with T2D and diagnosed with breast cancer in Finland in 1998─2011. Mortality rates from breast cancer and other causes were analysed by Cox models, and adjusted hazard ratios (HRs) with 95% confidence intervals (Cls) were estimated in relation to the use of different types of medication.

**Results:** The final cohort consisted of 3,533 women. No clear evidence was found for breast cancer mortality being different in metformin users (HR 0.86, 95% Cl 0.63–1.17), but their other-cause mortality appeared to be lower (HR 0.73, 95% Cl 0.55–0.97) in comparison with women using other types of oral ADM. Other-cause mortality was higher among insulin users (HR 1.45, 95% Cl 1.16–1.80) compared with users of other oral ADMs, other than metformin. Prediagnostic statin use was observed to be associated with decreased mortality from both breast cancer (HR 0.76, 95% Cl 0.63–0.92) and other causes (HR 0.75, 95% Cl 0.64–0.87).

**Conclusions:** We did not find any association between ADM use and disease-specific mortality among women with T2D diagnosed with breast cancer. However, interestingly, prediagnostic statin use was observed to predict reduced mortality from breast cancer and other causes. We hypothesize that treating treatment practices of T2D or hypercholesterolemia of breast cancer patients might affect overall prognosis of women diagnosed with breast cancer and T2D.



**Keywords:** Breast cancer, Type 2 diabetes, Cohort study, Metformin, Statins, Mortality

## Introduction

Breast cancer is the most commonly diagnosed cancer and a leading cause of death among the female population worldwide [1]. The risk of breast cancer is increased by approximately 20% in women with T2D [2]. Furthermore, several studies have suggested that breast cancer patients with type 2 diabetes (T2D) have a higher mortality rate when compared with patients without it [3-5].

Metformin is a widely prescribed type of oral antidiabetic medication (ADM) used as first-line therapy for patients with T2D [6]. There is growing interest in metformin because of its potential to favourably affect the prognosis of breast cancer. In vitro, metformin seems to have oxidative stress-mediated effects on cell-cycle arrest and apoptosis in breast cancer cells [7]. In addition, in vitro, metformin seems to enhance cytotoxicity when combined with chemotherapy and increase the radiosensitivity of tumour cells [8] . Increased circulating insulin or C-peptide levels have earlier been observed to be associated with higher mortality from breast cancer [9, 10].

The results of previous epidemiological studies on the association between metformin and survival of breast cancer patients with T2D are variable. Some studies have reported better prognosis among metformin users [11-14] , while others have not found such an association [15-17].

Statins, which are 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) inhibitors,

are the most widely prescribed lipid-modifying agents for preventing or treating cardiovascular diseases. Similar to metformin, statins have been studied in relation to their potential anticancer role. However, while preclinical studies have shown that statins can suppress tumour growth [18-20], findings in epidemiological studies on the survival of breast cancer patients who use statins, are variable [21-28].

Given the variable results in the relevant literature, further research is apparently necessary to explore the relationship between the use of ADM and statins with survival in cases of breast cancer. To provide further evidence, in this register-based cohort study we analysed the association between the use of metformin, other types of ADM, and statins, with the prognosis of breast cancer in women with T2D.

## Patients and methods

In this article, we followed the guidelines proposed in "Strengthening the Reporting of Observational Studies in Epidemiology" [29].

### *Study population and design*

The data on women with T2D were collected from the 'Diabetes in Finland' database (FinDM), which combines data from multiple nationwide registers, such as the Special Refund Entitlement Register and the Prescription Register from the Social Insurance Institution, the Care Register for Health Care and the Hospital Discharge Register from the National Institute for Health and Welfare, and the Causes of Death Register from Statistics Finland [30].

The FinDM database includes over 240,000 women with T2D. A person is entered into the FinDM database if she has a diagnosis of diabetes or reimbursement for ADM in any of the registers [30] . Data on diagnoses in hospital records have been available since 1969 for inpatients and since 1998 for outpatients [30]. Data from the Special Refund Entitlement Register have been available since 1964. Classification of patients in the register to type 1 and type 2 diabetes is mainly based on the ADM used as the first-line treatment. FinDM records have shown good coverage of persons with diabetes when compared with local diabetes registers [31]. Data on the incidence of cancers, including information on stage since 1953, were obtained by record linkage of the FinDM cohort with the files of the Finnish Cancer Registry (FCR) [32].

We identified 13,804 women with T2D who had also been diagnosed with breast cancer (Figure 1). The study cohort included women (1) whose breast cancer was diagnosed between 1 January 1998 and 31 December 2011, (2) who were at least 40 years old when T2D was diagnosed and (3) in whom the estimated duration of T2D was at least 180 days before breast-cancer diagnosis. Women with a prior cancer diagnosis (other than non-melanoma skin cancer) or whose breast cancers were diagnosed at autopsy were excluded. The final study cohort contained 3,533 women with T2D and breast cancer (Figure 1).

***Assessment of exposure and covariates***

The women were categorised into mutually exclusive groups according to the ADM used during the three years before breast cancer diagnosis: (1) metformin only, (2) other oral ADM only, (3) metformin and other oral ADM, (4) insulin at any time and (5) no history of regular ADM use. Furthermore, the use of statins was assessed in two groups: users and non-users. Exposure to all

forms of medication within the three-year period was defined as starting no earlier than 180 days after the date of the first purchase. Thus, a patient who first purchased an oral ADM less than 180 days before breast-cancer diagnosis was classified into the group 'no history of regular ADM use'. However, even one purchase of insulin within the three-year period was sufficient to classify a patient into the insulin group. A patient who first purchased a statin ≥ 180 days before breast-cancer diagnosis was classified into the statin-users' group. The cumulative use of ADMS (metformin only, other oral ADM, only insulin) and statins was estimated by defined daily doses purchased within three years preceding breast-cancer diagnosis.

***Outcome ascertainment***

Follow-up of the cohort started at the date of breast cancer diagnosis, and it ended at the time of death, emigration, or the close of follow-up (31 December 2013), whichever occurred first. The follow-up data were obtained from the FCR. Their records are annually matched through computerised linkage, based on personal identity codes, with the Cause of Death Register maintained by Statistics Finland so that the dates and causes of death (including non-cancerous causes, and both underlying and contributory causes of death) are added to the records of the Cancer Registry. In FCR records, the official cause of death of each cancer patient is based on all data available, and judgement is made on whether the patient died from that cancer or from something else. Classification of deaths into the two main categories in this study, deaths from breast cancer and deaths from other causes, was based on that judgement [32]. Deaths resulting from other causes were analysed in three subgroups: deaths from other cancers, deaths from cardiovascular diseases and deaths from other causes. FCR records are also regularly linked to data in the Central Population Register of Finland, where the correctness of personal identity codes is checked, and complete names, vital status, possible date of death or emigration, as well as the official place of residence prior to the date of diagnosis, are obtained.

### *Statistical analysis*

The cumulative mortality rate from breast cancer and from other causes was assessed by using the Aalen–Johansen estimator of cumulative incidence function for competing risks in the different medication groups [33, 34]. Cox's proportional hazards model was fitted for the two causes of death separately to adjust for the effects of the calendar year, age, duration of T2D and stage of breast cancer. Hazard ratios (HRs, with accompanying 95% confidence intervals [Cls]) of the two causes of death in the medication groups were estimated from the adjusted Cox models. Possible interaction between ADM and statins was evaluated by adding pertinent product terms in the model. In the supplementary analysis, the medication group membership indicators in the Cox models were replaced with cubic spline terms for the total amount of defined daily doses of each type of medication purchased separately. This allowed for the estimation of potentially non-linear dose-dependent effects of the medications on mortality from breast cancer. Plots of scaled Schoenfeld residuals were visually inspected [35], but no evidence of a violation of the proportional hazards assumption was observed that might have had an impact on the inference. R environment, version 3.5.1, was used throughout for data preparation, statistical analysis and Cox models. The assumptions were checked against functions provided in the 'survival' package [36, 37].

## Results

Our final study cohort consisted of 3,533 eligible women with T2D who were diagnosed with breast cancer between 1998 and 2011, at least 180 days after the diagnosis of T2D. The age range in the final cohort was wide, 41 to 100 years, at the time of breast cancer diagnosis. The median follow-up period was 4.6 years (interquartile range: 2.6 to 7.7 years).

Based on the reimbursement records during the preceding three years before the diagnosis of breast cancer, 19% of the patients were classified as metformin users, 13% were users of other types of oral ADM, 21% were users of metformin and other types of ADM, 19% used insulin and 28% did not have any history of regular ADM use. The majority of other oral ADM users were sulphonylurea users (84%) (Supplementary Table 1). Metformin users, on average, were younger than women in the other groups. Patients in the insulin group had the longest duration of T2D, while the metformin group had the shortest duration of T2D before breast-cancer diagnosis (Table 1). Statins were used by 40% of the women. The most commonly used statins were simvastatin (79%) and atorvastatin (43%). Patients who used statins tended to use different types over a long time period. This fact led to the result that overall the total percentage figure for the most widely used statins came to more than 100% (Supplementary Table 1). There was no difference in age distribution, duration of T2D or breast-cancer stage between statin users and non-users. In total, 1,533 patients died during the follow-up period, mostly from causes other than breast cancer.

The unadjusted 10-year cumulative mortality from breast cancer was, on average, 20%, with little variability across the various ADM groups. However, statin users had somewhat lower mortality than non-users (Figure 2). The 10-year mortality from causes other than breast cancer varied from 22% to 46% across the different ADM groups, appearing to be lower in the metformin group compared with all the other groups, and it was 30% among statin users and 37% in non-users of statins.

In the Cox regression analysis, older age and advanced stage of breast cancer were strongly associated with increased mortality from breast cancer, as expected. However, there were no clear differences between the different groups according to the prediagnostic use of ADM. The estimated HR for prediagnostic metformin users was 0.86 (95% Cl 0.63–1.17) compared with users of other types of oral ADM (Table 2). Mortality from various causes of death during the follow up in different medication groups are shown in Supplementary Table 2. Mortality resulting from other causes appeared to be somewhat lower in prediagnostic metformin users (HR 0.73, 95% Cl 0.55–0.97) and higher in prediagnostic insulin users (HR 1.45, 95% Cl 1.16–1.80) compared with users of other types of oral ADM. Prediagnostic use of statins was observed to predict decreased mortality from both breast cancer (HR 0.76, 95% Cl 0.63–0.92) and other causes (HR 0.75, 95% Cl 0.64–0.87) compared with no use of statins. Furthermore, concerning all-cause mortality, prediagnostic use of metformin (HR 0.79, 95% Cl 0.65–0.97) and statin (HR 0.75, 95% Cl 0.67-0.85) seemed both to associated with reduced all-cause mortality (Table 2). However, no clear evidence was found that the cumulative use of either metformin or statins would be associated with mortality from breast cancer (Supplementary Figure 1). No evidence of any interaction between ADM and statins was discerned either (data not shown).

## Discussion

In our large cohort study, we found no statistically discernible differences in mortality from breast cancer between the groups of women with T2D using different types of ADM. However, prediagnostic use of metformin appeared to be associated with a lower mortality rate from other causes. On the other hand, the mortality rate resulting from causes other than breast cancer was found to be higher in prediagnostic insulin users. Furthermore, prediagnostic use of statins was observed to be associated with a decreased rate of mortality rate from both breast cancer as well

as other causes.

The results of preclinical studies have suggested that metformin may suppress breast cancer cell growth indirectly by reducing circulating insulin, or directly via the activation of adenosine monophosphate-activated protein kinase [38, 39]. In two meta-analyses, metformin use was associated with 45% [40], and 47% [41] reduced all-cause mortality in breast cancer patients with T2D. In our study, we found also similar result as mortality from all causes was found to be lower in prediagnostic metformin users (HR 0.79, 95% Cl 0.65–0.97) compared with users of other types of oral ADM. Therefore, based on their meta-analysis and our result, it is becoming clearer that metformin use leads to reduce the risk of death from all-cause mortality in breast cancer patients [40]. In contrast to our findings, some previous epidemiological studies have reported an inversely related association between metformin use and breast cancer-specific mortality and all-cause mortality in women with T2D diagnosed with breast cancer [11-13]. Another study found a decreased rate of mortality from breast cancer, but only in long-term metformin users [42]. Similar to our findings, some investigators have observed a better overall survival among metformin users [43, 44], while others have not found any association between metformin use and the prognosis of breast cancer patients [15-17]. The major difference between previous studies and ours is the selection of the reference group. In all previous studies, the reference group for metformin users has been made up of non-users of metformin [11, 12, 15, 42, 43], while in our study, metformin users were compared with users of other forms of oral ADM. In another study women without T2D were included in the reference group [14].

Statin use reduces cardiovascular mortality by decreasing levels of low-density lipoprotein cholesterol [45-47]. In addition, it has been observed that statins reduce the risk of cardiovascular

disease events in patients with T2D, even without a prior history of coronary disease [48, 49]. The reduction of levels of mevalonate with the use of statins is associated with enhanced apoptosis of cancer cells [50, 51]. Ahern et al. suggested a better prognosis on breast cancer in statin-treated patients [52], and furthermore, the same author has described that simvastatin was associated with a reduced risk of breast cancer recurrence among breast cancer patients [53]. However, some previous studies have not observed an association between statin use and mortality from breast cancer and other causes [23-25, 54]. However, similar to our study, some other studies have reported lower mortality from both breast cancer and from other causes, although the study populations in these investigations have not been limited to women with T2D [22, 26, 53]. Only two studies have reported an association between statin use and the prognosis of breast cancer patients in women with T2D, and the results of these studies suggest better breast-cancer prognosis in statin users, similar to our findings [27, 28].

A major strength of our study is the availability of comprehensive national registers. Data quality is considered to be high in Finnish national registers such as the Hospital Discharge Register [55]. Furthermore, the Finnish Cause of Death Register practices and procedures seem to answer the coding of causes of death for mortality statistics appropriately [56]. In addition, the Finnish Cancer Registry (FCR) includes data on almost all cancer cases in Finland, and 93% of cases are microscopically verified. All Nordic Cancer Registries have shown a high-quality standard with regards to completeness and accuracy of the registered data, and the causes of death of patients are received from the national cause-of-death registries in all Nordic cancer registries [32]. Compared to the other cancer registries, the Finnish Cancer Registry reassesses cancer deaths along with incidence data from the registry [32]. Data on the duration of diabetes is known fairly accurately because it is based on the first diabetes diagnosis recorded in any of the user registers,

or the first purchase of any form of ADM. In addition, over-the-counter purchase of ADM and statins is not allowed in Finland and permitted the purchase of these types of medication is reimbursed by the Social Insurance Institute. The duration of medication use is known for a longer period of time than in the majority of previous studies, and time-related use has been calculated in order to avoid time-related bias. As far as we know, this is the largest cohort study involving women with T2D and concerning statin use and survival after breast cancer. In addition, our study has one of the largest sample sizes as regards metformin use and survival after breast cancer in women with T2D.

The main weakness of our study is that we have only information available in the registers. The registers lack information on traditional prognostic factors and specific subtypes of breast cancer, including hormone receptor status. In a preclinical study by Nelson et al. [57], it was suggested that statins might be more beneficial in oestrogen receptor-positive breast cancer as a result of disruption of oestrogen synthesis via the cholesterol-lowering mechanism. However, previous epidemiological studies have not observed any interaction between statin use and oestrogen receptor status as regards the prognosis of breast cancer patients [25, 26]. The used registers also lack data on body mass index. The results of some studies have suggested that obese women have a poorer prognosis of breast cancer compared with normal-weight women [58, 59], although other studies with opposite findings have also been published [60, 61]. Furthermore, the registers lack data on laboratory examinations, socioeconomic situation and aspects of lifestyle. Comorbidities are not recorded in the FinDM database adequately enough and were therefore not included in our study. The FCR includes some information on cancer treatment given, but the data are not complete enough to be included in our study. Challenges of confounding by indication are present in observational studies, including our study, which contains endpoints that

have not yet been studied in randomised controlled trials [62]. As various types of medication are initiated to treat conditions other than the one in the focus of an observational study, differences in participants can have an impact on the results. Thus, it is known that insulin is required in T2D treatment in later phases of the disease due to the fact that insulin secretion decreases over time in patients with T2D [63]. In addition, insulin might be a third treatment option, and initiating insulin means a failure of earlier treatment or contraindication to other types of medication, which can be interpreted as a generally ill-health condition [64]. Therefore, different characteristics of particular medication users might lead to unintentional selection bias in observational studies [65]. However, the selection of the reference group as other ADM users reduces this bias.

Nowadays, the prognosis of breast cancer is excellent as the average 5-year and 10-year relative survival ratios are 87-90% and 73-83% in the Nordic countries [66]. However, after 12 years of follow-up, older women diagnosed with breast cancer were equally likely to die from breast cancer as they were to die as a result of cardiovascular disease [67]. Treating and considering other existing diseases, such as diabetes and hypercholesterolemia might lead to a better survival of women diagnosed with breast cancer.

## Conclusion

Our findings are inconclusive regarding an association between metformin and disease-specific mortality among breast-cancer patients with T2D. However, we observed a lower rate of mortality from other causes in users of metformin compared with those using other types of oral

ADM. Furthermore, we found some evidence that prediagnostic statin use reduced mortality from breast cancer and from other causes in women with breast cancer and T2D. Considering the whole evidence, treating diabetes or hypercholesterolemia at the same time when treating breast cancer might yield a better prognosis of women diagnosed with breast cancer and T2D.

## Notes

**Acknowledgements:** Not applicable

**Authors' contributions:** MH and EU drafted the paper. EL supervised the statistical analyses. AH analysed the data, and MM helped to gather accurate data of the medication. MA and RS provided the FinDM data. AH, MM, MA, RS, AA, UP, PK, AJ and EL reviewed and edited the manuscript. All authors read and approved the final manuscript.

**Availability of data and material:** The data that support the findings of this study are available from the National Institute for Health and Welfare, but restrictions apply to the availability of these data and so they are not publicly available. Data are, however, available upon reasonable request and with the permission of the National Institute for Health and Welfare, the Social Insurance Institution and Statistics Finland.

## Legends of figures and tables

Figure 1: Flowchart showing how the cohort was formed.

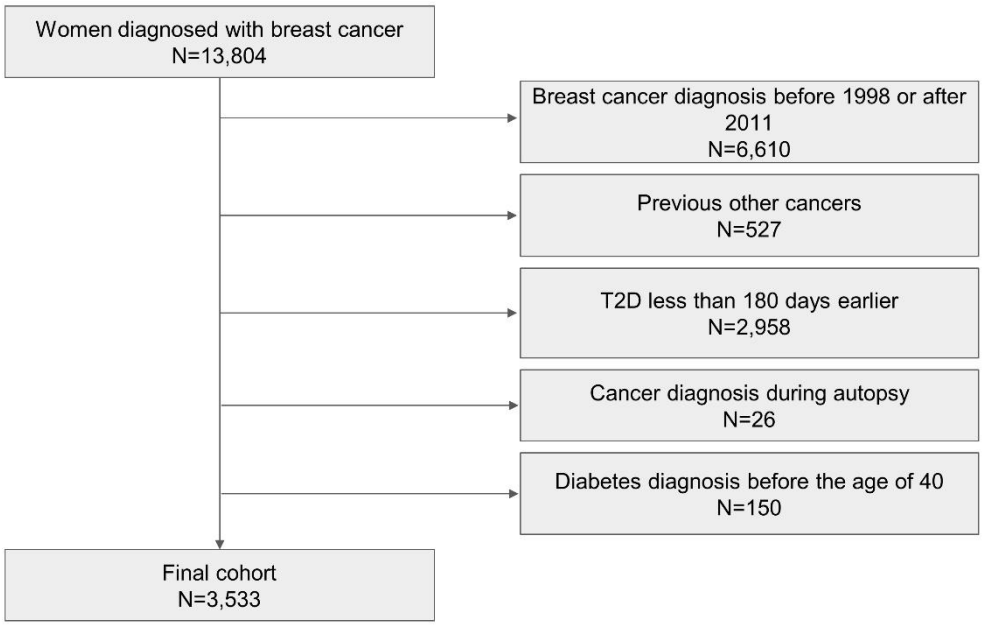
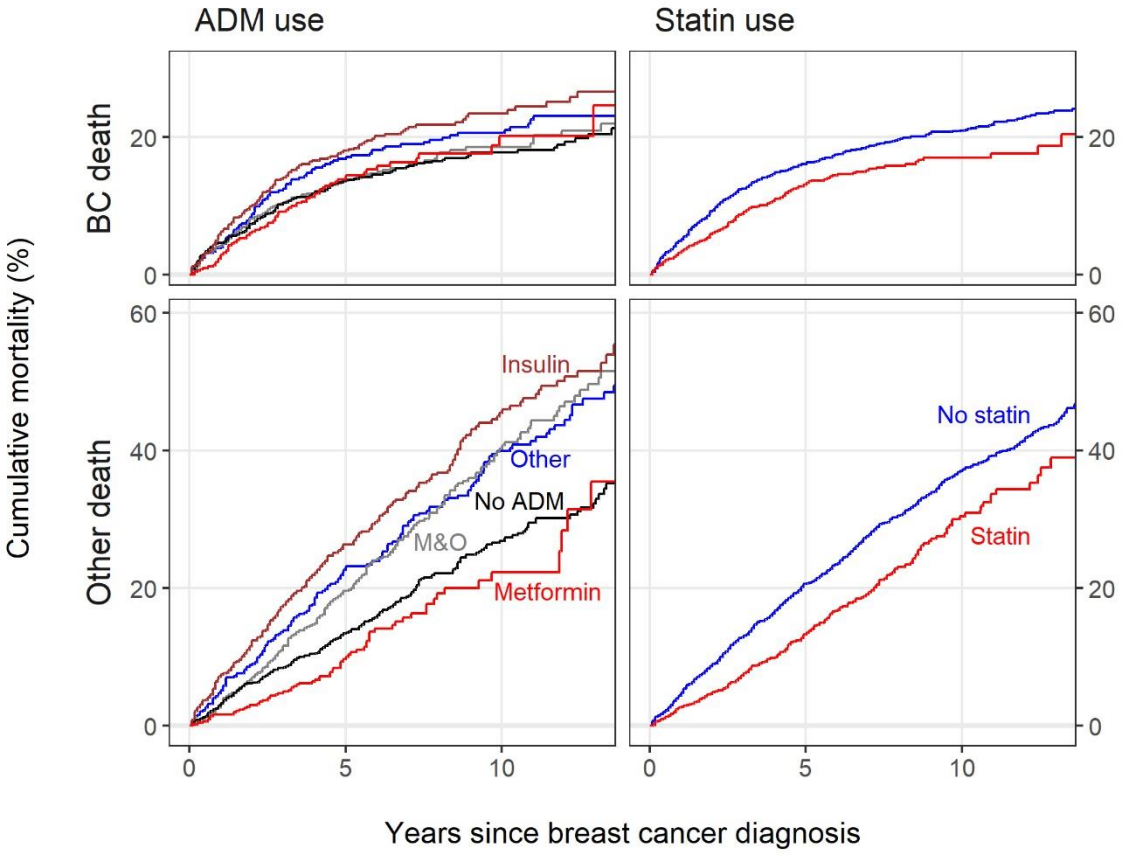


Figure 2: Cumulative mortality curves for the two causes of death in the different medication groups. ADM = antidiabetic medication, M&O = metformin and other oral ADM.



374 Table 1: Distribution of baseline characteristics and outcome status in the different medication

375 groups.

| | | Antidiabetic medication (ADM) | | | | | Use of statins | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Metformin[a] (%) | Other oral ADM[a] (%) | Metformin and other oral ADM[a] (%) | Insulin (%) | No history of regular ADM[b] (%) | Yes[a] (%) | No[b] (%) | Total (%) |
| Total | n | 658 | 444 | 752 | 686 | 993 | 1 402 | 2 131 | 3 533 |
| Age at diagnosis | Median | 68 | 77 | 73 | 74 | 70 | 71 | 74 | 72 |
| | IQR[c] | 62–77 | 68–83 | 64–80 | 66–80 | 62–79 | 64–78 | 64–81 | 64–80 |
| Diagnosis age categories | | | | | | | | | |
| | 40–59 | 113 (17) | 43 (10) | 106 (14) | 74 (11) | 187 (19) | 166 (12) | 357 (17) | 523 (15) |
| | 60–69 | 251 (38) | 95 (21) | 189 (25) | 185 (27) | 319 (32) | 499 (36) | 540 (25) | 1,039 (29) |
| | 70–79 | 209 (32) | 141 (32) | 254 (34) | 249 (36) | 275 (28) | 486 (35) | 642 (30) | 1,128 (32) |
| | 80–100 | 85 (13) | 165 (37) | 203 (27) | 178 (26) | 212 (21) | 251 (18) | 592 (28) | 843 (24) |
| Diabetes duration in years | | | | | | | | | |
| | Median | 3.4 | 4.9 | 7.3 | 11.9 | 6.5 | 7.1 | 6.1 | 6.5 |
| | IQR[c] | 2.0–5.6 | 2.7–7.7 | 4.4–11.2 | 7.9–16.0 | 2.0–10.9 | 3.5–12.0 | 2.9–10.6 | 3.1–11.2 |
| Diabetes duration categories | | | | | | | | | |
| | 0.5–< 3 | 296 (45) | 128 (29) | 96 (13) | 30 (4) | 300 (30) | 300 (21) | 550 (26) | 850 (24) |
| | 3–< 6 | 211 (32) | 159 (36) | 199 (26) | 60 (9) | 169 (17) | 296 (21) | 502 (24) | 798 (23) |
| | 6–< 12 | 118 (18) | 113 (25) | 302 (40) | 254 (37) | 327 (33) | 456 (33) | 658 (31) | 1,114 (32) |
| | 12–< 42 | 33 (5) | 44 (10) | 155 (21) | 342 (50) | 197 (20) | 350 (25) | 421 (20) | 771 (22) |
| Stage | | | | | | | | | |
| | Local | 331 (50) | 233 (52) | 348 (46) | 291 (42) | 541 (54) | 695 (50) | 1,049 (49) | 1,744 (49) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Advanced | 291 (44) | 174 (39) | 355 (47) | 322 (47) | 387 (39) | 615 (44) | 914 (43) | 1,529 (43) |
| | Unknown | 36 (5) | 37 (8) | 49 (7) | 73 (11) | 65 (7) | 92 (7) | 168 (8) | 260 (7) |
| Outcome at the end of follow-up | | | | | | | | | |
| | Breast cancer death | 88 (13) | 91 (21) | 119 (16) | 142 (21) | 160 (16) | 186 (13) | 414 (19) | 600 (17) |
| | Other death | 75 (11) | 174 (39) | 221 (29) | 242 (35) | 221 (22) | 248 (18) | 685 (32) | 933 (26) |
| | Alive | 495 (75) | 179 (40) | 412 (55) | 302 (44) | 612 (62) | 968 (69) | 1,032 (48) | 2,000 (57) |

[a] Duration of medication use ≥ 180 days

[b] Duration of medication use <180 days three years before breast cancer diagnosis

[c] Interquartile range

377 Table 2: Estimation results from Cox proportional hazard models of mortality from breast

378 cancer, other causes of death, and all causes.

| Variable | Value | Mortality from breast cancer Hazard ratio (95% CI) | Mortality from other causes Hazard ratio (95% CI) | Mortality from all causes Hazard ratio (95% CI) |
|---|---|---|---|---|
| Year of diagnosis | | | | |
| | 1998–2002 | 1 | 1 | **1** |
| | 2003–2007 | 0.90 (0.74–1.11) | 0.93 (0.80–1.09) | 0.92 (0.82–1.05) |
| | 2008–2011 | 0.99 (0.78–1.24) | 0.85 (0.68–1.05) | 0.92 (0.79–1.07) |
| Age at diagnosis (years) | | | | |
| | 40–59 | 0.94 (0.70–1.27) | 0.57 (0.40–0.82) | 0.77 (0.61–0.96) |
| | 60–69 | 1 | 1 | 1 |
| | 70–79 | 1.62 (1.30–2.01) | 3.03 (2.45–3.74) | 2.31 (1.99–2.69) |
| | 80–100 | 2.56 (2.02–3.25) | 8.17 (6.60–10.12) | 5.12 (4.38–5.98) |
| Duration of diabetes (years) | | | | |
| | 0.5–< 3 | 1 | 1 | 1 |
| | 3–< 6 | 0.94 (0.74–1.20) | 0.99 (0.80–1.23) | 0.96 (0.82–1.13) |
| | 6–< 12 | 1.01 (0.80–1.28) | 1.20 (0.98–1.46) | 1.12 (0.96–1.3) |
| | 12–< 42 | 1.03 (0.79–1.35) | 1.21 (0.96–1.51) | 1.13 (0.95–1.34) |
| Stage | | | | |
| | Local | 1 | 1 | 1 |
| | Advanced | 5.26 (4.28–6.46) | 1.10 (0.95–1.26) | 1.94 (1.74–2.16) |
| | Unknown | 2.35 (1.62–3.41) | 1.49 (1.20–1.85) | 1.68 (1.4–2.02) |
| Prediagnostic statin use | | | | |
| | No | 1 | 1 | 1 |
| | Yes | 0.76 (0.63–0.92) | 0.75 (0.64–0.87) | 0.75 (0.67–0.85) |
| Prediagnostic ADM group | | | | |
| | Metformin | 0.86 (0.63–1.17) | 0.73 (0.55–0.97) | 0.79 (0.65–0.97) |
| | Other[a] | 1 | 1 | 1 |
| | Metformin and other[a] | 0.80 (0.60–1.06) | 1.01 (0.82–1.24) | 0.92 (0.78–1.09) |
| | Insulin | 1.16 (0.86–1.55) | 1.45 (1.16–1.80) | 1.32 (1.11–1.57) |
| | No history of regular ADM use | 0.93 (0.71–1.21) | 0.81 (0.66–0.99) | 0.86 (0.73–1.01) |

[a] other oral antidiabetic medication

ADM = antidiabetic medication, 95% CI = 95% confidence interval

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Supplementary Table 1: ATC codes for different types of medication and percentages of other types of oral antidiabetic medication (ADM) and statins used in the medication groups where the duration of use was at least 180 days.

| | | |
|---|---|---|
| **OTHER ORAL ANTIDIABETIC MEDICATIONS (n = 444):** | | |
| **Sulphonylureas:** | | 84 % |
| A10BB01 | Glibenclamide | |
| A10BB02 | Chlorpropamide | |
| A10BB03 | Tolbutamide | |
| A10BB07 | Glipizide | |
| A10BB12 | Glimepiride | |
| **Glitazones:** | | 6 % |
| A10BG02 | Rosiglitazone | |
| A10BG03 | Pioglitazone | |
| **DPP-4 inhibitors:** | | 7 % |
| A10BH01 | Sitagliptin | |
| A10BH02 | Vildagliptin | |
| A10BH03 | Saxagliptin | |
| A10BH05 | Linagliptin | |
| **Glinides:** | | 3 % |
| A10BX02 | Repaglinide | |
| A10BX03 | Nateglinide | |
| A10BX04 | Exenatide | |
| A10BX07 | Liraglutide | |
| **Combination medications:** | | |
| A10BD06 | Glimepiride and pioglitazone | |
| A10BD04 | Rosiglitazone and glimepiride | |
| | | |
| A10BX01 | Guar gum | 26 % |
| **METFORMIN AND OTHER ORAL ADM COMBINATIONS:** | | 4 % |
| A10BD03 | metformin and rosiglitazone | |
| A10BD05 | metformin and pioglitazone | |
| A10BD07 | metformin and sitagliptin | |
| A10BD08 | metformin and vildagliptin | |
| A10BD10 | metformin and saxagliptin | |
| A10BD11 | metformin and linagliptin | |
| **STATINS (n = 1402):** | | |
| C10AA01 | Simvastatin | } 79% |
| C10BA02 | Simvastatin and ezetimibe | |
| C10AA02 | Lovastatin | 11 % |
| C10AA03 | Pravastatin | } 12% |
| C10BA03 | Pravastastin and fenofibrate | |
| C10AA04 | Fluvastatin | 21 % |
| C10AA05 | Atorvastatin | 43 % |
| C10AA06 | Serivastatin | 1 % |

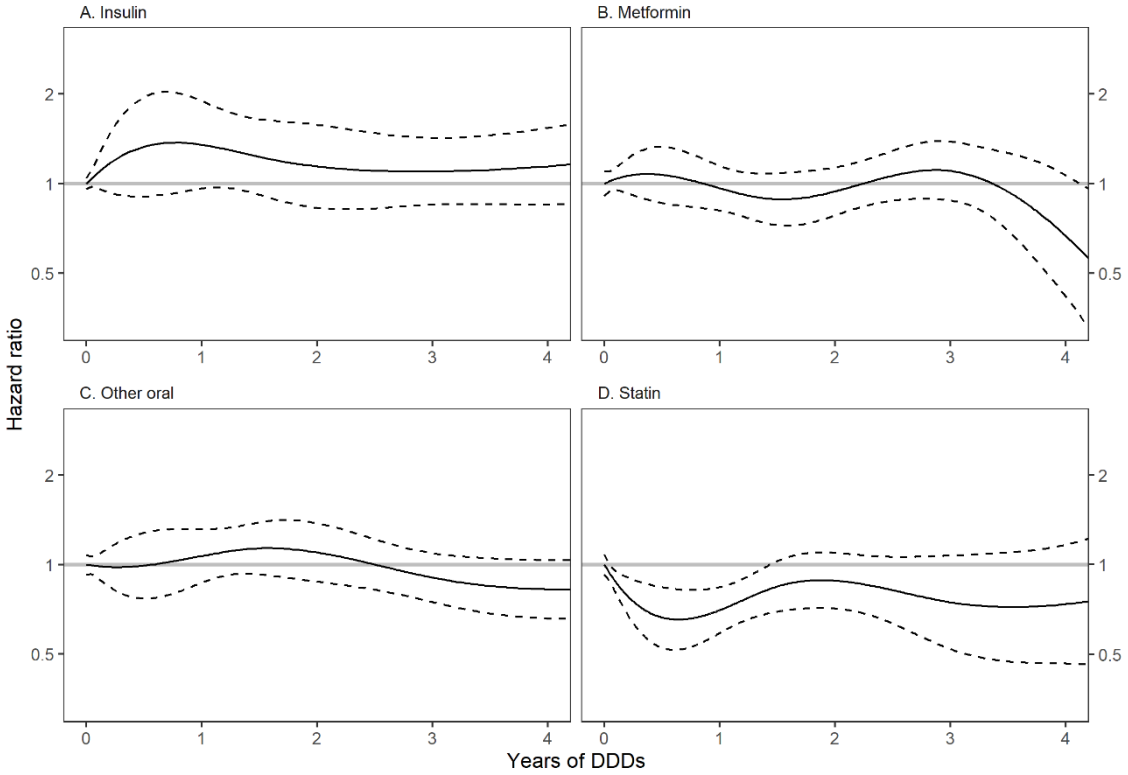
| | | |
|---|---|---|
| C10AA07 | Rosuvastatin | 14 % |
| C10AA08 | Pitavastatin | 0 % |

Supplementary Table 2: Estimation results from Cox proportional hazard models of mortality from different causes of death.

| | | Other cancer C00–C97 | | Cardiovascular I00–I99 | | Other reasons | |
|---|---|---|---|---|---|---|---|
| | | Mortaltiy from other cancer | Mortality from other causes | Mortality from cardiovascular | Mortality from other causes | Mortality from other reasons | Mortality from other causes |
| Variable | Value | Hazard ratio (95% CI) | Hazard ratio (95% CI) | Hazard ratio (95% CI) | Hazard ratio (95% CI) | Hazard ratio (95% CI) | Hazard ratio (95% CI) |
| Year of diagnosis | | | | | | | |
| | 1998–2002 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 2003–2007 | 0.77 (0.50–1.19) | 0.94 (0.83–1.07) | 0.92 (0.74–1.14) | 0.92 (0.79–1.07) | 1.02 (0.79–1.33) | 0.90 (0.78–1.03) |
| | 2008–2011 | 0.56 (0.29–1.09) | 0.95 (0.81–1.11) | 0.84 (0.63–1.12) | 0.95 (0.79–1.14) | 0.98 (0.67–1.42) | 0.90 (0.76–1.07) |
| Age at diagnosis, years | | | | | | | |
| | 40–59 | 0.96 (0.49–1.89) | 0.75 (0.59–0.95) | 0.36 (0.19–0.70) | 0.87 (0.68–1.12) | 0.62 (0.34–1.13) | 0.80 (0.63–1.03) |
| | 60–69 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 70–79 | 2.04 (1.25–3.33) | 2.34 (1.99–2.74) | 3.26 (2.40–4.42) | 2.03 (1.71–2.42) | 3.34 (2.32–4.81) | 2.12 (1.79–2.50) |
| | 80–100 | 2.72 (1.54–4.82) | 5.36 (4.55–6.30) | 9.73 (7.16–13.21) | 3.83 (3.19–4.61) | 9.32 (6.44–13.48) | 4.40 (3.70–5.22) |
| Duration of diabetes, years | | | | | | | |
| | 0.49–<3 | 1 | 1 | 1 | 1 | 1 | 1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3–<6 | 1.01 (0.57–1.79) | 0.96 (0.81–1.13) | 0.98 (0.72–1.34) | 0.96 (0.80–1.16) | 0.99 (0.70–1.41) | 0.95 (0.79–1.15) |
| | 6–<12 | 1.33 (0.77–2.30) | 1.11 (0.94–1.29) | 1.31 (0.98–1.75) | 1.05 (0.88–1.26) | 1.02 (0.73–1.42) | 1.15 (0.97–1.36) |
| | 12–<42 | 1.11 (0.58–2.15) | 1.13 (0.94–1.35) | 1.42 (1.04–1.94) | 1.01 (0.82–1.24) | 0.95 (0.65–1.39) | 1.18 (0.97–1.43) |
| Stage | | | | | | | |
| | Local | 1 | 1 | 1 | 1 | 1 | 1 |
| | Advanced | 0.90 (0.61–1.34) | 2.07 (1.85–2.32) | 1.22 (1.00–1.47) | 2.41 (2.11–2.76) | 1.01 (0.80–1.29) | 2.30 (2.04–2.60) |
| | Unknown | 0.61 (0.24–1.52) | 1.81 (1.50–2.19) | 1.74 (1.31–2.30) | 1.60 (1.25–2.05) | 1.44 (0.99–2.07) | 1.78 (1.44–2.20) |
| Prediagnostic statin use | | | | | | | |
| | No | 1 | 1 | 1 | 1 | 1 | 1 |
| | Yes | 0.98 (0.64–1.49) | 0.74 (0.65–0.84) | 0.84 (0.68–1.03) | 0.72 (0.63–0.84) | 0.55 (0.41–0.73) | 0.82 (0.71–0.93) |
| Prediagnostic ADM group | | | | | | | |
| | Metformin | 0.64 (0.30–1.34) | 0.81 (0.66–1.01) | 0.58 (0.39–0.88) | 0.88 (0.69–1.12) | 1.05 (0.66–1.67) | 0.74 (0.59–0.93) |
| | Other | 1 | 1 | 1 | 1 | 1 | 1 |
| | Metformin and other | 0.60 (0.33–1.10) | 0.96 (0.80–1.14) | 0.98 (0.74–1.29) | 0.89 (0.72–1.10) | 1.26 (0.87–1.82) | 0.85 (0.70–1.02) |
| | Insulin | 1.20 (0.66–2.19) | 1.33 (1.11–1.60) | 1.31 (0.97–1.77) | 1.33 (1.07–1.65) | 1.81 (1.22–2.68) | 1.21 (1.00–1.48) |
| | None | 0.55 (0.31–0.96) | 0.89 (0.75–1.06) | 0.72 (0.54–0.96) | 0.92 (0.76–1.12) | 1.10 (0.77–1.57) | 0.80 (0.67–0.96) |

Supplementary Figure 1: Estimated hazard ratios (with 95% CIs) of mortality from breast cancer in relation to the cumulative use of medication. DDD = defined daily doses.



## Compliance with ethical standards

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**Conflict of interest:** MM is employed by Orion Corporation. However, Orion Corporation had no role in the study design, collection, analysis and interpretation of data, the writing of the report nor the decision to submit the article for publication. EU has received grants from the Cancer Society of Finland, the Cancer Society of Northern Finland, the Finnish Association of Gynaecological Surgery, The Finnish Medical Foundation, Oulu Medical Research Foundation and The Finnish Society of Obstetrics and Gynaecology. MH, AH, MA, RS, AA, UP, PK, AJ and EL declare that they have no conflicts of interest.

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and the 1964 Declaration of Helsinki and its later amendments or with comparable ethical standards. According to Finnish legislation, no separate ethics approval is needed for studies that involve only administrative registers. However, ethics approval was obtained for the FinDM study from the research ethics committee of the National Institute of Health and Welfare (30 January 2014, meeting 1/2014, 340 §609). Permission to use data was obtained from those maintaining the original registers (National Institute for Health and Welfare, the Social Insurance Institution and Statistics Finland).

**Informed consent:** According to Finnish legislation, no separate informed consent is needed for studies that involve only administrative registers.

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