# Breast cancer extent and survival among diabetic women in a Finnish nationwide cohort study

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ABSTRACT

Breast cancer (BC) and diabetes are major health problems. We examined the association between diabetes and BC stage at diagnosis and subsequent survival in a Finnish cohort of female BC patients. All BC cases (N = 73,170) diagnosed in 1995-2013 with dates and causes of death were identified from the Finnish Cancer Registry. Participation in organized mammography screening was obtained from Mass Inspection Registry. Information on diabetes diagnoses and background conditions recorded during 1995-2013 were obtained from national Care Register for Health Care and merged to data on medication use from the national Prescription Register. Logistic regression with adjustment for mammography screening and age at BC diagnosis was used to evaluate the risk of advanced stage BC at diagnosis. Cox regression was used to evaluate overall and BC survival. Analyses were adjusted for age, background conditions and mammography screening. Survival analyses were further adjusted for tumor extent, histology and primary treatment. Of the cohort 11,676 (16.0 %) had diabetes. Screening participation did not differ by diabetes. Compared to non-diabetic women, diabetics had more often locally advanced (OR 1.18; 95% CI 1.10-1.26) or metastatic BC at diagnosis (OR 1.30; 95% CI 1.18-1.43). During a median follow-up of 5.8 years after BC diagnosis 10,900 (14.9 %) women died of BC. Risk of BC death was higher among diabetic compared to non-

diabetic women (HR 1.36, 95% CI 1.27-1.46). Risk of BC death increased with duration of diabetes. This supports diabetes as a risk factor for fatal breast cancer.

# INTRODUCTION

Breast cancer (BC) and diabetes mellitus (DM) are two major health problems for women. Incidence of both conditions rises after middle-age. BC is the most common cancer among women worldwide (1). It is the leading cause of cancer death among women in less developed countries, and the second most frequent cause of cancer death in developed regions (1). Age-standardized BC incidence has been increasing steadily worldwide whilst mortality has been decreasing since the 1990s (1). Around the world number of diabetics has risen from 108 million in 1980 to 422 million in 2014 (2). Global prevalence in DM among adults over 18 years of age is estimated to be 8,5% in 2014 (2).

Several previous studies have evaluated the association between use of antidiabetic drug metformin and BC risk and survival; many studies have reported a risk reducing effect for metformin (3). However, role of the underlying DM is unclear. Previous studies (4, 5, 6, 7) have explored the association between BC risk and DM *per se* especially among postmenopausal women with type 2 DM (7,8). It has been shown that BC patients with DM have also higher BC mortality (4, 5) and overall mortality. DM is often closely associated with obesity, hyperinsulinemia and hyperglycemia, inflammation which in turn may affect risk of BC progression (5,8). Few studies have been able to estimate simultaneously the risk associations with closely correlated conditions obesity, DM, hypertension and hypercholesterolemia. Further, the role of timing of DM diagnosis in BC prognosis is unclear.

We compared the association between DM (defined as recorded diagnosis of DM or antidiabetic drug use) and BC stage and survival in a large nationwide cohort of BC cases from Finland with simultaneous evaluation of background hypertension, hypercholesterolemia, cardiovascular disease and obesity.

## MATERIALS AND METHODS

### *Study cohort*

The study population included all newly diagnosed BC cases among women in Finland from 1995 to 2013. In total 78,023 cases were identified from the Finnish cancer registry which covers over 99% of cancer cases in Finland (9). The registry collects data by mandatory cancer diagnosis reports from all Finnish health care units and pathology laboratories. ICD-codes C50.1-C50.9 were used to identify BC cases. Information included diagnosis date, patient age, tumor extent (available for 85.6% of cases, categorized into three groups localized, locally advanced (axillary lymph node involvement) and metastatic, histology (99.9%) and primary treatment (99.6%) as well as the date and causes of death. Information on deaths was available up to the end of 2013. Deaths with ICD-10 codes C50.1-C50.9 registered as the primary cause of death were considered BC deaths. Hormone receptor status or tumor grade are not recorded by the registry, thus not available at this time. From the original study population, we excluded 349 men with BC and 4,504 women who were diagnosed with carcinoma in situ only or the date of later diagnosis of invasive cancer was missing. Thus, after exclusion of 4,853 BC cases due to missing information the final study cohort included 73,170 women.

Finland has a government-mandated, nationwide comprehensive mammography screening program which covers all Finnish women of age 50-69. Invitations for mammography are sent every two years. Screening program started in 1980s and has a 90.9% national coverage (9). We obtained data on the number of mammography screens for each participant by linking the study cohort to national Mass Inspection registry maintained by the National Institute of Health and Welfare.

### *Information on diabetes and other background conditions*

Data on recorded diagnoses were gathered by linking the study cohort to the Finnish Care Register for Health Care which registers diagnoses from all in- and outpatient hospital visits and treatment periods during 1995-2013. Linkage was carried out using unique personal identification number which is given to every Finnish citizen either at birth or alternatively can be applied for after receiving permission for residency for at least a year. Diagnoses of DM, hypertension, dyslipidemia, obesity and coronary artery disease were identified using respective ICD-10 coding (Supplementary table 1). The registry does not cover diagnoses from primary health care visits. Linking these diagnoses with drugs used in hypertension and hypercholesterolemia this information was more comprehensive excluding obesity which has no specific medication.

*Information on medication use*

The study cohort was linked to prescription database of the Finnish Social Insurance Institution (SII) using personal identification number to obtain information on antidiabetic, antihypertensive and cholesterol-lowering medication use during 1995-2013. As part of the national health insurance SII reimburses costs of medication purchases for drugs prescribed by a licensed physician. National health insurance and its compensation covers the whole Finnish population and all compensated medication purchases are recorded by the database. Over-the-counter purchases or drugs dispensed during hospital inpatient period are not covered by the prescription database. The information includes ATC-classification, date for each purchase, medication strength, package size and the number of refills.

Antidiabetic drugs were identified based on ATC-codes (Supplementary table 2). Additionally, we identified drugs used in management of hypertension, dyslipidemia and hormonal therapy (tamoxifen, fulvestrant and aromatase inhibitors). All drugs for the above-mentioned indications are available in Finland only through physicians' prescription, thus recorded by the prescription database.

*Statistical analysis*

Information on yearly drug purchases was combined with the information on recorded diagnoses from the Finnish Care Register for Health Care to obtain yearly status of DM, hypertension and dyslipidemia. Participant was considered to have these conditions from the first year they had a recorded diagnosis or medication purchase for the conditions.

The study population was categorized into two categories as hypertensive (recorded diagnosis of hypertension or purchase of antihypertensive drugs), dyslipidemic (recorded diagnosis of dyslipidemia or purchase of cholesterol-lowering statin drugs), obese (recorded diagnosis) or having coronary artery disease (recorded diagnosis). DM (recorded diagnosis of DM or purchase of antidiabetic drugs was categorized separately by timing in relation to BC: whether DM had been diagnosed before or after BC. Exposure time for pre-diagnostic DM was evaluated as number of years since the first DM diagnosis or purchase of anti-DM drug between 1995 and year of BC diagnosis. For post-diagnostic DM, the exposure time was defined as number of years between DM diagnosis or drug purchase and the end of follow-up. Charlson Comorbidity Index was calculated using recorded ICD-10 diagnoses from in- and outpatient hospital visits from HILMO supplemented with medication usage data from the SII prescription database. The 2011 updated version of the index was used (10).

We used logistic regression to evaluate odds ratios (ORs) and 95% confidence intervals (95% CIs) for having locally advanced or metastatic BC at diagnosis by pre-diagnostic DM. These analyses were adjusted for age and additionally for background conditions and number of mammography screening rounds attended.

Risk of BC death (hazard ratio, HR) was evaluated using Cox regression model adjusted for age and tumor extent at diagnosis, tumor histology, screening participation, primary treatment (surgery vs. other treatment), Charlson Comorbidity Index and for any use of statins, antihypertensive drugs or hormonal therapy during the follow-up. Time metric was years and months since BC diagnosis. The follow-up continued until death or the common closing date of Dec 31,2013, whichever came first. DM before BC diagnosis was analyzed as time-independent variable based on status and years of exposure between 1995

and year of BC diagnosis. DM post-BC diagnosis was analyzed as time-dependent variable, where DM status and cumulative years of exposure were updated separately for each follow-up year based on yearly recorded diagnoses and medication purchases.

Validity of proportional hazards assumption was tested by adding interaction term between time-independent variables and follow-up time into Cox regression model. Subgroup analyses were performed by variables for which the interaction term was statistically significant.

We used Fine and Gray competing risks regression analysis to compare risk of BC deaths with non-breast cancer deaths as the competing risk, as DM is a known risk factor for cardiovascular disease and deaths.

Analyses were done using IBM SPSS Statistics version 24 (Chicago, IL, USA). STATA 14.0 was used for competing risk regression analyses.

## RESULTS

### *Population characteristics*

During the median follow-up of 5.8 years after diagnosis a total 22,520 (30.8%) women died, of these 10,900 (14.9%) due to BC. In total 2,465 women (3.2% of the cohort) had a recorded DM diagnosis; 279 with type I DM, 2,219 with type II DM and 62 with other type of DM, including DM with complications. A total of 11,676 (16.0%) women had either a recorded DM diagnosis or purchases of anti-DM medication during the study period. Due to small number of women with DM I or other type of DM, all types of DM were analyzed as one group. Mean mammography screening participation rate was 57.9%, with no significant difference by diabetes.

Diabetic women were older at diagnosis and had more often also hypertension, hypercholesterolemia, obesity and cardiovascular disease compared to the non-diabetic group (Table 1). In the diabetic group, most of the patients (95.4%) were at postmenopausal age at diagnosis. No differences in mammography screening (median of four mammography screens before diagnosis), Charlson Comorbidity Index, tumor histology or primary treatment were observed compared to the non-diabetics. Diabetic women had slightly less hormonal therapy after BC diagnosis (34.5% vs 38.4%, p for difference < 0.001).

### *Tumor stage at diagnosis by diabetes mellitus*

Compared to non-diabetic women, BC was more often locally advanced or metastatic in diabetic women (multivariable adjusted OR 1.26; 95% CI 1.18-1.35 for locally advanced and OR 1.59; 95% CI 1.44-1.75 for metastatic cancer) (Table 2). At separate analysis, the risk association was similar among postmenopausal women. The risk association was stronger in women who had diabetes for at least five years before BC diagnosis.

*Risk of breast cancer death by diabetes mellitus*

For diabetics diagnosed before BC diagnosis, the risk of breast cancer death was higher compared to non-diabetics both in the age-adjusted (HR 1.18; 95% CI 1.10-1.27) and multivariable-adjusted analysis (HR 1.36; 95% CI 1.27-1.46) (Table 3). Also overall mortality was higher in the diabetic group (Table 3). Overall mortality, but not BC-specific mortality increased even more in participants with at least five years of DM before BC diagnosis.

Also DM after BC diagnosis was associated with increased risk of BC-specific death, albeit not as strongly as pre-diagnostic DM (HR 1.15; 95% CI 1.09-1.22) and deaths due to any cause (HR 1.32; 95% CI 1.28-1.37) (Table 3). Again, the risk increase for deaths due to any cause increased along with years of diabetes in a linear manner, whereas the risk increase for breast cancer deaths attenuated in long-term.

*Subgroup analyses*

In subgroup analyses DM both before and after BC diagnosis was associated with worse BC survival regardless of tumor extent at diagnosis (Table 4). Similarly, tumor histology did not modify the risk associations.

The risk increase for BC death by diabetes after BC diagnosis was stronger in the youngest age-group (39 or younger) (p for difference by age group < 0.001). No clear effect modification by primary treatment or background conditions were observed (Table 4).

The risk increase by prediagnostic DM was stronger in women with positive mammography screen; HR 2.00; 95% CI (1.56-2.56, p for interaction = 0.004) but remained elevated also in the mammography screen negative group (table 4).

*Sensitivity analyses*

In competing risks regression analysis women with prediagnostic DM had significantly increased risk for BC death HR 1.18; 95% CI (1.09-1.28). Diabetes after BC diagnosis was not associated with increased BC death in competing risks regression analysis. However, the analysis was prone to immortal time bias as diabetes could not be analysed as time-dependent variable.

In multivariable-adjusted analysis also Charlson Comorbidity Index was independent predictor of breast cancer death in multivariable-adjusted analysis (HR 1.04; 95% CI 1.03-1.05 per 1-point increase in the index).

To account for possible bias by missing information on prevalent diabetes diagnosed before BC we performed the analysis including only cases diagnosed on year 2000 or later. This ensured that all cases had information on diabetes for a minimum of five years' time before the diagnosis. The analysis included 57,023 patients, of which 8,992 had diabetes either before or after breast cancer diagnosis. The results did not differ from the main analysis; multivariable adjusted HR for BC mortality by pre-diagnosis DM (HR 1.36, 95% CI 1.25-1.47) and BC mortality by post-diagnosis diabetes (HR 1.18, 95% CI 1.10-1.26).

## DISCUSSION

Breast cancer patients with DM had elevated risk for locally advanced and metastatic tumor extent despite identical participation to mammography screening compared to non-diabetic patients. The association got stronger in correlation with years since the first recorded DM diagnosis. Further, we found an association with increased BC mortality and overall mortality which also got stronger along with years of DM before BC diagnosis. DM after BC diagnosis was further associated with worse disease-specific survival, but the risk increase attenuated along with years of DM post-diagnosis.

Our study supports few previous studies reporting that BC patients with DM present with more advanced stage at diagnosis (11, 12). Retrospective cohort study (13) of 38,407 BC patients reported that women with DM were 14 %-21% more likely to present with Stage II-Stage IV BC after adjustment for socioeconomic factors, age, screening participation and comorbidities. Erikson et al (14) also defined DM according to HbA1C levels in a small study of 185 BC patients. BC patients with DM had more advanced cancer stage at diagnosis. None of these studies took antidiabetic medication use into account. Thus, our study adds to these previous findings as our study population was larger, and our definition of DM, hypertension and dyslipidemia also included medication usage for these indications.

Previous studies (15, 16) have been controversial on whether diabetic women participate less frequently in screening mammograms which might explain later stage cancer at diagnosis. However, in our study we observed more advanced stage BC among diabetics despite identical mammography screening history compared to non-diabetics. Thus, our findings suggest that stage difference by DM is not explained by differential screening participation. However, as diabetic patients are prone to be more obese than non-diabetics, breast self-examination via palpation may be more unreliable. This may lead to delayed diagnosis. Thus obesity remains a possible confounding factor in analyses on breast cancer extent.

Higher BC mortality has previously been reported in BC patients with DM (4, 5). We observed increased risk of BC death among diabetic women independent of tumor extent at diagnosis. Thus, our results suggest

that the survival difference is not a consequence of differing tumor stage at diagnosis between diabetic and non-diabetic women. It has also been proposed that BC patients with DM are less likely to receive chemotherapy because of higher toxicity rates (17, 18), which is a possible mechanism behind the observed risk increase

On the other hand, DM may have a direct effect on carcinogenesis and cancer progression. Hyperglycemia and hyperinsulinemia accelerate cancer cell proliferation and inhibition of apoptosis *in vitro* (5, 19). Also obesity, a condition closely associated with DM, has been linked with increased BC risk in women and worse overall prognosis (20). Obesity is associated with chronic inflammation (7), oxidative stress (21) and reduction of AMP-activated protein kinase (22). The mechanism is likely to be multifactorial.

Strengths of this study are the large nationwide cohort of 73,170 female patients with background information of background conditions, screening, treatment and maximum follow-up of 18 years. Our data on recorded diagnoses of diabetes, hypertension and hypercholesterolemia was based on hospital contacts, but was complemented by detailed data on medication use, thus covering all participants with medical treatment for the conditions. The exception was obesity, for which medication use is marginal. Detailed information on timing of medication use and diagnoses allowed us to evaluate them on a yearly basis. Thus, we were able to estimate the role of timing of DM on BC stage and prognosis.

The study limitations include missing information on hormone replacement therapy as it is not reimbursed by the SII and not recorded in the prescription registry. Hormone receptor status or tumor grade were also unavailable from the national registries. We had no direct record of BMI and it is assumed that obesity diagnosis recorded in health care registries represents the most morbid cases, underestimating true prevalence of obesity. Further, we had no information on socioeconomic status and life-style factors such as smoking, which may have caused confounding increasing the observed risk estimates. Low socioeconomic status has been associated with worse survival in many cancer types, but in BC the association is somewhat unclear (23, 24). Current smoking is associated with increased risk of breast cancer death (25).

## CONCLUSIONS

Women with DM have more often advanced stage BC and the prognosis of the disease is poorer compared to non-diabetic women even after adjustment for disease extent and screening participation. We found that these findings are strongest if DM was diagnosed before BC diagnosis which confirms the risk relationship between long-term DM exposure and fatal BC.

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Table 1. Characteristics of the study cohort of 73,170 female breast cancer (BC) patients diagnosed in Finland during 1995-2013.

| | Diabetes before BC diagnosis | | |
|---|---|---|---|
| Characteristic | Yes<br>*5,469 (7.5%)*<br><br>No. (%) | No<br>*67,701 (92.5%)*<br><br>No. (%) | Total<br>*73,170 (100%)*<br><br>No. (%) |
| **Deaths** | | | |
| BC deaths | 874 (16.0) | 10,026 (14.8) | 10,900 (14.9) |
| non-BC deaths | 1,576 (28.8) | 10,044 (14.8) | 11,620 (15.9) |
| **Age at BC diagnosis*†** | | | |
| 39 or younger | 5 (0.1) | 570 (0.8) | 575 (0.8) |
| 40-55 | 207 (3.8) | 8,311 (12.3) | 8,518 (11.6) |
| 56 and older | 5,257 (96.1) | 58,820 (86.9) | 64,077 (87.6) |
| **Mammography screening history** | | | |
| Any; n(%) | 2,560 (46.8) | 39,829 (58.8) | 42,359 (57.9) |
| **Tumor stage at diagnosis** | | | |
| Localized | 2,451 (44.8) | 34,185 (50.5) | 36,636 (50.1) |
| Locally advanced | 1,789 (32.7) | 22,254 (32.9) | 24,043 (32.9) |
| Metastatic | 641 (11.7) | 5,484 (8.1) | 6,125 (8.4) |
| Unknown | 588 (10.8) | 5,778 (8.5) | 6,366 (8.7) |
| **Tumor histology; n (%)** | | | |
| Invasive ductal | 4,075 (74.5) | 50,973 (75.3) | 55,042 (75.2) |
| Invasive lobular | 879 (16.1) | 11,367(16.8) | 12,246 (16.7) |
| Other | 504 (9.2) | 5,310 (7.8) | 5,814 (7.9) |
| Unknown | 11 (0.2) | 51 (0.1) | 62 (0.1) |
| **Primary treatment** | | | |
| Curative-intent surgery | 3,304 (60.4) | 45,527 (67.2) | 48,831 (66.7) |
| Other/unknown | 2,165 (39.6) | 22,174 (32.8) | 24,339 (33.3) |
| **Hormonal therapy*** | | | |
| n (%) | 1,660 (30.4) | 26,004 (38.4) | 27,664 (37.4) |

| **Co-morbidities** | | | |
|---|---|---|---|
| Charlson Co-morbidity Index; median (IQR)‡ | 0 (0-1) | 0 (0-0) | 0 (0-1) |
| Hypertension* | 5,124 (93.7) | 45,745 (67.6) | 50,869 (69.5) |
| Hypercholesterolemia* | 3,448 (63.0) | 21,993 (32.5) | 25,446 (34.8) |
| Obesity* | 87 (1.6) | 340 (0.5) | 427 (0.6) |
| Cardiovascular disease* | 557 (10.2) | 2,279 (3.4) | 2,836 (3.9) |

* P for difference between diabetic and non-diabetic group < 0.001. Calculated with chi-square.

† Age group categorized as pre-menopausal (younger than forty), menopausal (40-55) and post-menopausal (56 or older)

‡ Breast cancer diagnosis excluded from the calculation of the Charlson Co-morbidity Index

Table 2. Breast cancer (BC) extent by diabetes mellitus status. Study cohort of 73,170 female breast cancer patients diagnosed in Finland during 1995-2013.

| Diabetes status | Number of BC cases | | | | OR (95% CI)* | |
|---|---|---|---|---|---|---|
| | Localized | Locally advanced | Metastatic | Unknown | Locally advanced BC | BC with distant metastases |
| **All BC cases** | 36,636 | 24,043 | 6,125 | 6,366 | | |
| Non-diabetics | 30,832 | 20,167 | 5,160 | 5,778 | Ref | Ref |
| Diabetics before BC | 2,451 | 1,789 | 641 | 588 | 1.26 (1.18-1.35) | 1.59 (1.44-1.75) |
| Years of diabetes before BC | | | | | | |
| less than 5 | 1,333 | 939 | 316 | 258 | 1.19 (1.09-1.30) | 1.41 (1.24-1.61) |
| 5 or more | 1,118 | 850 | 325 | 330 | 1.35 (1.23-1.48) | 1.81 (1.58-2.07) |
| **BC in age 56 or older** | 33,233 | 20,062 | 5,046 | 6,166 | | |
| Non-diabetics | 27,607 | 16,441 | 4,152 | 5,164 | Ref | Ref |
| Diabetics before BC | 2,382 | 1,694 | 609 | 572 | 1.24 (1.16-1.33) | 1.52 (1.37-1.68) |
| Years of diabetes before BC | | | | | | |
| less than 5 | 1,292 | 893 | 294 | 251 | 1.19 (1.09-1.30) | 1.37 (1.19-1.57) |
| 5 or more | 1,090 | 801 | 315 | 321 | 1.30 (1.19-1.43) | 1.70 (1.48-1.95) |

* Calculated using logistic regression with adjustment for age, number of mammography screening rounds attended before the BC diagnosis, hypercholesterolemia, hypertension, coronary artery disease and obesity

Table 3. Risk of breast cancer (BC) death and death due to any cause, by diabetes mellitus (DM) status. Cohort of 73,170 breast cancer patients diagnosed in Finland between 1995-2013.

| DM status | BC deaths | | | All-cause deaths | | |
|---|---|---|---|---|---|---|
| | Number of deaths | HR (95% CI) for BCdeath | | Number of deaths | HR (95% CI) for death | |
| | | Age-adjusted | Multivariable-adjusted* | | Age-adjusted | Multivariable-adjusted* |
| **DM before BC diagnosis** | | | | | | |
| No | 10,026 | Ref | Ref | 20,070 | Ref | Ref |
| Yes | 874 | 1.18 (1.10-1.27) | 1.36 (1.27-1.46) | 2,450 | 1.42 (1.36-1.48) | 1.60 (1.53-1.67) |
| Years of diabetes before BC | | | | | | |
| less than 5 | 478 | 1.15 (1.05-1.27) | 1.32 (1.20-1.45) | 1,272 | 1.33 (1.25-1.40) | 1.45 (1.40-1.57) |
| 5 or more | 396 | 1.22 (1.10-1.35) | 1.42 (1.28-1.57) | 1,178 | 1.54 (1.45-1.63) | 1.76 (1.66-1.87) |
| **DM after BC diagnosis** | | | | | | |
| No | 9,505 | Ref | Ref | 18,628 | Ref | Ref |
| Yes | 1,395 | 1.21 (1.15-1.28) | 1.15 (1.09-1.22) | 3,892 | 1.37 (1.32-1.42) | 1.32 (1.28-1.37) |
| Years of diabetes after BC | | | | | | |
| less than 3 | 717 | 1.39 (1.29-1.50) | 1.29 (1.19-1.39) | 1,536 | 1.36 (1.29-1.43) | 1.30 (1.29-1.37) |
| 3 to 6 years | 485 | 1.00 (0.91-1.10) | 0.95 (0.86-1.04) | 1,474 | 1.28 (1.21-1.35) | 1.22 (1.15-1.29) |
| longer than 6 years | 193 | 1.10 (0.94-1.28) | 1.04 (0.89-1.21) | 882 | 1.55 (1.44-1.66) | 1.48 (1.38-1.59) |

* Calculated using Cox regression with adjustment for age, number of mammography screening rounds attended before the BC diagnosis, tumor extent, histology, primary treatment, hypercholesterolemia, hypertension, obesity, Charlson comorbidity index and use of hormonal therapy after the diagnosis

Table 4. Risk of breast cancer (BC) death by diabetes mellitus (DM) within subgroups stratified by background variables. Cohort of 73,170 breast cancer patients diagnosed in Finland between 1995-2013.

| BC baseline characteristics | Risk of BC death | |
|---|---|---|
| | DM before BC | DM after BC |
| | HR (95% CI) | HR (95% CI) |
| **Tumor stage at dg** | | |
| Localized | 1.49 (1.26-1.76) | 1.24 (1.10-1.40) |
| Locally advanced | 1.30 (1.15-1.46) | 1.09 (1.00-1.19) |
| Metastatic | 1.31 (1.16-1.48) | 1.15 (1.03-1.28) |
| **Tumor histology** | | |
| Ductal | 1.40 (1.29-1.53) | 1.15 (1.07-1.23) |
| Lobular | 1.29 (1.08-1.54) | 1.11 (0.97-1.27) |
| Other | 1.17 (0.96-1.42) | 1.15 (0.98-1.36) |
| **Age at dg*** | | |
| 39 or younger | .. | 2.56 (1.24-5.27) |
| 40-55 | 1.14 (0.84-1.56) | 1.33 (1.11-1.60) |
| 56 or older | 1.34 (1.25-1.45) | 1.15 (1.08-1.22) |
| **Year of diagnosis** | | |
| 1995-2004 | 1.25 (1.13-1.38) | 1.11 (1.03-1.19) |
| 2005-2013 | 1.34 (1.21-1.49) | 1.22 (1.11-1.34) |
| **Primary treatment** | | |
| Curative-intent surgery | 1.42 (1.28-1.58) | 1.18 (1.09-1.27) |
| Other | 1.29 (1.17-1.42) | 1.14 (1.05-1.23) |
| **DM before BC diagnosis** | | |
| No | .. | 1.17 (1.08-1.27) |
| **Mammography screening** | | |
| <4 | 1.53 (1.29-1.80) | 1.14 (1.01-1.29) |
| ≥4 | 1.32 (1.22-1.43) | 1.15 (1.08-1.22) |
| **Mammography screen positive*** | | |
| Yes | 2.00 (1.56-2.56) | 1.26 (1.06-1.50) |
| No | 1.32 (1.22-1.42) | 1.14 (1.07-1.21) |

* P for interaction < 0.05. Calculated by adding interaction term between the stratified variable and diabetes status into multivariable-adjusted Cox regression model.