# Type 2 Diabetes, but Not Insulin (Analog) Treatment, Is Associated With More Advanced Stages of Breast Cancer: A National Linkage of Cancer and Pharmacy Registries

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## OBJECTIVE

**To investigate whether women with type 2 diabetes (T2D) develop a more advanced stage of breast cancer and whether treatment with insulin (analogs) is associated with specific breast cancer characteristics.**

## RESEARCH DESIGN AND METHODS

**For this nested case-control study, women with breast cancer diagnosed in 2002–2014 were selected from the linked Netherlands Cancer Registry–PHARMO Database Network (*N* = 33,377). T2D was defined as receiving two or more dispensings of noninsulin blood glucose–lowering drugs prior to breast cancer diagnosis. Women with T2D were matched to women without diabetes. Among women with T2D, insulin users and nonusers were compared. Multivariable ordinal logistic regression was used to investigate the association between T2D/insulin and breast cancer characteristics, including TNM classification (tumor size, lymph node status, metastasis), morphology, grade, estrogen receptor and progesterone receptor (PR), human epidermal growth factor receptor 2, and molecular subtype.**

## RESULTS

**Women with T2D (*n* = 1,567) were more often diagnosed with a more advanced tumor stage (odds ratio 1.28 [95% CI 13–1.44]) and a higher grade (1.22 [1.08–1.39]) though less often with a PR-negative breast tumor (0.77 [0.67–0.89]) than women without diabetes (*n* = 6,267). No associations were found for the other breast cancer characteristics. Women with T2D using insulin (*n* = 388) were not diagnosed with different breast cancer characteristics compared with women with T2D not using insulin (*n* = 1,179).**

## CONCLUSIONS

**Our study suggests that women with T2D are at increased risk to be diagnosed with a more aggressive type of breast cancer than women without diabetes. No evidence was found that the use of insulin (analogs) is associated with developing more advanced breast cancer tumors.**


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The prevalence of diabetes is increasing worldwide (1). Women with type 2 diabetes (T2D) are at increased risk of developing breast cancer (2), which is the most common malignant tumor in females (3). In the Netherlands, the incidence of breast cancer increased by 65% between 1989 and 2017 (4,5). Furthermore, mortality after breast cancer is 50% higher among women with diabetes compared with women without diabetes, including after correction for tumor stage (6).

Several mechanisms have been suggested for the increased risk of breast cancer among women with T2D, such as common risk factors like obesity (7), the specific metabolic derangements of diabetes itself (i.e., hyperglycemia [8], hyperinsulinemia, and insulin resistance), and the use of insulin and specifically insulin analogs (9–11). Hyperinsulinemia in itself, especially present in people with impaired glucose tolerance, may promote tumor cell growth directly via insulin receptors or indirectly via the insulin-like growth factor 1 (IGF-1) receptor (12). IGF-1, and subsequently the IGF-1 receptor, could act as a growth stimulus for tumor cells and increase tumor growth, invasion, and metastasis (13). In comparison with counterparts without diabetes, patients with breast cancer and diabetes tend to present at later stages (14). However, it is yet unclear what the pathophysiologic interactions between diabetes and breast cancer are and whether improvements in diabetes care can reduce the increased mortality in patients with breast cancer (14). Whether the use of insulin (analogs) is associated with this risk is still uncertain. A large population-based cohort study concluded that long-term use of insulin glargine was associated with an increased risk of breast cancer in women with T2D compared with NPH insulin (15). However, a recent systematic review (16) and a five-country cohort study (17) concluded that insulin (analog) treatment does not impact the risk of breast cancer among women with diabetes compared with women without diabetes. Whether T2D or the use of insulin (analogs) increases the risk of developing a more aggressive or less treatment-responsive tumor is hardly well studied, since most studies lacked detailed tumor or use-of-insulin (analogs) data. Furthermore, the majority of these studies suffered from methodological limitations or lacked power. In the current study, a comprehensive large database with detailed data was used, creating the opportunity to study the association between T2D and breast cancer characteristics. Also, the effect of insulin (analog) use on breast cancer characteristics was studied among women with T2D.

## RESEARCH DESIGNS AND METHODS

### Data Sources

For the current study, data were obtained from the Netherlands Cancer Registry (NCR) and the PHARMO Database Network. The NCR is maintained by the Netherlands Comprehensive Cancer Organization (IKNL) (18) and is notified for new patients with cancer by pathology departments, general hospitals, and radiotherapy institutes. Key information in the NCR includes cancer diagnosis, tumor staging, tumor site and morphology, and primary cancer treatment. Staging of cancer is categorized according to the TNM classification (tumor size, lymph node status, metastasis) developed and maintained by the Union for International Cancer Control. Tumors are classified based on site (topography) and morphology (histology) according to the World Health Organization International Classification of Diseases for Oncology (ICD-O-3).

The PHARMO Database Network is a population-based network of electronic health care databases containing data from both primary and secondary health care settings in the Netherlands. The Out-patient Pharmacy Database of the PHARMO Database Network was used to select women with T2D and to obtain detailed data on the exposure to insulin. The Out-patient Pharmacy Database comprises general practitioner– or specialist-prescribed health care products dispensed by the outpatient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty, and costs. Drug dispensings are coded according to the World Health Organization (Anatomical Therapeutic Chemical [ATC]) classification system. Outpatient pharmacy data cover a catchment area representing 3.6 million residents. The Hospitalization Database and the Clinical Laboratory Database of the PHARMO Database Network were used to characterize women in terms of comorbidities.

The privacy committees of the PHARMO Institute for Drug Outcomes Research and the NCR approved this study.

### Study Design

A nested case-control study in a retrospective breast cancer cohort was performed. Women with breast cancer and T2D were matched and compared with women with breast cancer without diabetes. Furthermore, women with T2D using insulin (analogs) were compared with women with T2D not using insulin (analogs) (unmatched). Per breast cancer characteristic, case subjects were defined as women diagnosed with a more aggressive/less treatment-responsive outcome. Control subjects were defined as women experiencing a less aggressive/more treatment-responsive outcome.

### Study Population

The source population included all women diagnosed with an invasive breast cancer diagnosis (ICD-O-3 C50.x, stages I–IV) between 2002 and 2014 who were registered in the NCR Out-patient Pharmacy Database from the PHARMO Database Network. The date of the first diagnosis with invasive breast cancer was defined as the index date. For assessment of exposure in the 4 years prior to the index date, all selected women needed to have at least 4 years of continuous enrollment in the PHARMO Database Network prior to the index date. Furthermore, women who underwent oophorectomy at any time prior to the index date were excluded.

Women receiving two or more dispensings of noninsulin blood glucose–lowering drugs (NIBGLDs) (ATC code A10B) in the 4 years prior to their index date were defined as women with T2D. At least two dispensings of NIBGLDs had to be dispensed within 6 months. Women with type 1 diabetes, defined as receiving insulin (analogs) (ATC code A10A) and no NIBGLDs in the 4 years prior to index date, were excluded. Each woman with T2D was matched to up to four women without diabetes (no dispensing for drugs used to treat diabetes [ATC code A10]) on age at index date ($\pm$2 years). Control subjects had to be alive on the index date of their matched case subject and could not be matched more than once. Among women with T2D, women with a dispensing of insulin in the 4-year period prior to the index date were defined as insulin users.

### Patient Characteristics

For all women included, the following general characteristics were determined at index date: age, year of index, and socioeconomic status (SES). SES was derived from Statistics Netherlands, which based SES on salary per four-digit zip code. Furthermore, comedication (use of statins, antihypertensive drugs, glucocorticoids, estrogen-progestogen contraceptives, hormone replacement therapy [HRT] in the year prior to index date) and comorbidities (renal failure, retinopathy, hypertension, stroke, congestive heart failure, ischemic heart disease, peripheral artery disease, cerebrovascular disease in the entire available history) were determined for characterization of patients. Comorbidities were based on hospitalizations, and renal failure was defined as having two or more estimated glomerular filtration rate measurements $<$60 mL/min/1.73 $m^2$ 90–365 days apart. Furthermore, an updated chronic disease score (CDS) was calculated. This score was based on the use of specific classes of medications in the year prior to index date (see Supplementary Table 1). The CDS has been shown to be a valid measure of complications related to an individual patient's burden of chronic somatic diseases and is clearly associated with a fivefold increase in risk of hospitalization and a 10-fold increase in risk of dying (19).

### Exposure of Insulin (Analogs)

#### *Duration of Use*

The cumulative days of exposure in the 4 years prior to index date were calculated for each patient by converting dispensings into treatment episodes of uninterrupted use. As the dosing regimen is hardly ever registered with insulin, the duration of insulin was based on the legal limit of the maximal duration (90 days). In case of an interruption between two dispensings, use of insulin or NIBGLD was considered interrupted if the duration of this gap was less than half the period of the given dispensing, according to the method of Catalan and LeLorier (20).

#### *Dose*

As insulin dose descriptions are hardly ever registered in the Out-patient Pharmacy Database, dose estimations relied on dispensed amounts of insulin over time. Per woman, the average daily dose was calculated as the sum of all dispensed doses during the insulin episodes in the 4 years prior to index date, divided by the cumulative days of exposure for insulin in the 4 years prior to index date.

#### *Insulin Analogs Versus Human Insulin*

Use of human insulin (ATC codes A10AB01, A10AC01, A10AD01, and A10AE01) and use of insulin analogs (ATC code A10A, excluding A10AB01, A10AC01, A10AD01, and A10AE01) in the 4 years prior to index date was determined. The number of women using human insulin only, insulin analog only, or both human and insulin analogs were presented.

### Breast Cancer Characteristics

The following breast cancer characteristics at index date were studied as outcomes, based on the available information in the NCR data: tumor size (T in "TNM" classification), lymph node status (N in TNM classification), distant metastasis (M in TNM classification), stage (I–IV), morphology (ductal, lobular, mixed, other), histological tumor grade (grade 1 [well differentiated], grade 2 [moderately differentiated], grade 3 [poorly differentiated]), hormone receptor status (estrogen receptor [ER], progesterone receptor [PR]), human epidermal growth factor receptor 2 (HER2), and molecular subtypes. Surrogate definitions of molecular subtype were used and based on the immunohistochemical measurement of the (hormone) receptors. Based on the surrogate definitions described by the St. Gallen International Expert Panel (21), the following subtypes were defined: luminal A, luminal B, nonluminal (HER2 positive), and triple negative (see Table 1). As Ki-67 measurement was not available, grade was used to distinguish between luminal A and luminal B (21).

Molecular subtype is associated with different short-term clinical outcome and prognosis. Luminal tumors have the best prognosis compared with nonluminal (HER2 positive) and triple-negative tumors.

### Statistical Analyses

The $\chi^2$ test was used to assess whether categorical characteristics (excluding "unknown") differed *1*) between women with breast cancer with T2D and women with breast cancer without diabetes and *2*) among women with breast cancer with T2D: women using insulin (analogs) and women not using insulin (analogs). For continuous characteristics, ANOVA was used.

As most of the breast cancer characteristics in this study are ordinal, categorized with two or more categories, multivariable ordinal logistic regression was used to investigate the two associations: *1*) T2D and breast cancer characteristics and *2*) insulin (analog) treatment and breast cancer characteristics. Separate models were constructed for each exposure (T2D or insulin [analogs]) to evaluate each breast cancer characteristic. Odds ratios (ORs) and their corresponding 95% CI were adjusted for age, year of index date, SES, CDS, and use of glucocorticoids, estrogen-progestogen contraceptives, and HRT in the year prior to the index date and presented for the different breast cancer characteristics. For the comparison between insulin (analogs) versus no insulin (analogs) and breast cancer among women with T2D, ORs were also adjusted for duration of diabetes. Comparisons regarding duration and dose of insulin (analogs) were performed among women with T2D who used insulin (analogs) and adjusted for duration of diabetes, age, CDS, and patient characteristics that statistically significant differed between the two groups ($P < 0.05$). ORs $>$1 indicate that exposed women are more likely to be diagnosed with a worse outcome (see Table 3 for the order from good to worse outcome of each breast cancer characteristic).

**Table 1—Surrogate definitions of molecular subtypes of breast cancer**

| Molecular subtype | Clinico-pathologic definition |
|---|---|
| Luminal A | ER+ and/or PR+, HER2−, and grade 1 or 2 |
| Luminal B | ER+ and/or PR+, HER2−, and grade 3<br>ER+ and/or PR+, HER2+ |
| Nonluminal (HER2 positive) | ER−, PR−, and HER2+ |
| Triple negative | ER−, PR−, and HER2− |

Surrogate definitions of molecular subtypes of breast cancer are from Goldhirsch et al. (21).

Based on the median duration of insulin use, durations for women's insulin use were characterized as "short" (i.e., shorter use than the median duration 3.4 years) or "long" (i.e., same or longer use than the median duration). The same was done for the dose of insulin (median dose was 41.1 international units [IU]). Based on the median dose, women were characterized as "low" and "high."

All data were prepared and analyzed using SAS programs organized within SAS Enterprise Guide, version 4.3 (SAS Institute, Cary, NC), and conducted within Windows using SAS, version 9.2.

#### *Subgroup Analysis*

As insulin analogs have binding affinities and activities to the IGF-1 receptor different from those human insulin has, we performed a subgroup analysis among women with breast cancer and T2D using human insulin only versus women with breast cancer and T2D using insulin analogs only. As the number of women in these groups is expected to be low, ORs and their corresponding CIs were only adjusted for patient characteristics that statistically significant differed between the two groups ($P < 0.05$), except for year of index date. As insulin analogs were marketed later than human insulin, this characteristic differs between these groups by definition.

## RESULTS

### Study Population

Supplementary Fig. 1 shows the flowchart of patient selection; 1,567 women with T2D were matched to 6,267 women without diabetes. Approximately one-quarter of the women with T2D used insulin in the 4 years prior to the index date ($n$ = 388).

### Patient Characteristics

The patient characteristics for women with breast cancer are shown in Table 2, stratified by no diabetes/T2D and by insulin use among women with T2D. Mean age at index date (e.g., first diagnosis of breast cancer diagnosis) was ~71 years. Women with T2D had a slightly lower SES than women without diabetes, and among women with T2D, women using insulin had a lower SES than women not using insulin. Furthermore, use of statins, antihypertensives, and glucocorticosteroids was the highest among women with T2D using insulin, followed by women with T2D not using insulin. A similar pattern was observed for the selected comorbidities and the CDS. The Dutch diabetes guideline advises to determine the indication for an antihypertensive drug and a statin among people with diabetes, explaining the higher proportion of users among women with diabetes. Use of HRT was the highest among women without diabetes (8%) and differed significantly from the use among women with T2D (6%). The same was true among women using insulin (6%) versus women not using insulin (4%) ($P < 0.05$). In general, these results show that women with T2D using insulin had the highest disease severity, followed by women with T2D not using insulin.

### Exposure

Among women with T2D using insulin (analogs) ($N$ = 388), median insulin duration was 3.4 years (interquartile range 1.7–4.0) with an average daily dose of 41.1 IU (23.2–68.6). More than half of the women using insulin only used insulin analogs ($n$ = 236 [61%]), and 15% ($n$ = 59) only used human insulin in the 4 years prior to index date.

Use of NIBGLD was 88% among women with T2D using insulin and 97% among women with T2D not using insulin. Among all, the most commonly used NIBGLD class was metformin, followed by sulfonylurea derivatives.

### Breast Cancer Characteristics

Table 3 presents the breast cancer characteristics of women with breast cancer, stratified by no diabetes/T2D and by insulin use among women with T2D.

Women with T2D tended to have a larger tumor ($P < 0.01$), more lymph nodes affected ($P < 0.05$), a more advanced tumor stage ($P < 0.01$) and grade ($P < 0.05$), and a different distribution in morphology ($P < 0.05$) and less often had a PR-negative breast tumor ($P < 0.0001$). Among women with T2D, distribution of breast cancer characteristics did not differ between women using insulin (analogs) and women not using insulin (analogs).

### Association Between T2D/Insulin Treatment and Breast Cancer Characteristics

After adjustment for age, year of index date, SES, CDS, and the use of glucocorticoids, estrogen-progestogen contraceptives, and HRT, women with T2D were more often diagnosed with a larger tumor (OR 1.22 [95% CI 1.08–1.38]), a more advanced lymph node status (1.31 [1.12–1.53]), a more advanced tumor stage (1.28 [1.13–1.44]), and a higher grade (1.22 [1.08–1.39]) but less often with a PR-negative breast cancer (0.77 [0.67–0.89]) than women without T2D. No statistically significant associations were found for the other breast cancer characteristics (Fig. 1 and Supplementary Table 2). Among women with breast cancer and T2D, no statistically signficant associations were found between the use of insulin (analogs) and breast cancer characteristics (Fig. 2 and Supplementary Table 2).

Also, no statistically significant association was found between duration of insulin use and any of the breast cancer characteristics (Supplementary Fig. 2 and Supplementary Table 2). Women with T2D with an average daily insulin dose ≥40.9 IU tended to have smaller tumors (OR 0.63 [95% CI 0.41–0.95]) and less advanced tumors (0.64 [0.43–0.95]) than women with T2D with an average daily insulin dose <40.9 IU. No statistically significant association was found for the other breast cancer characteristics (Supplementary Fig. 3 and Supplementary Table 2).

#### *Subgroup Analyses*

After adjustment for age and use of statins in the year prior to index date, use of insulin analogs ($N$ = 236) was not associated with any of the breast cancer characteristics compared with human insulin ($N$ = 59) (Supplementary Table 2).

## CONCLUSIONS

The results of this retrospective nested case-control study show that T2D was associated with more advanced stages of breast cancer. Women with T2D were at increased risk of being diagnosed with a larger tumor, a more advanced lymph node status, a more advanced tumor stage, and a higher grade but at decreased risk of being diagnosed with a PR-negative tumor than women without diabetes. Among women with T2D, no differences in any pathologic breast cancer characteristic were found between the insulin (analog) users and the noninsulin (analog) users.

The literature regarding the association between diabetes and pathologic breast cancer characteristics is scarce (6,22–27), but the majority is consistent with our findings. These studies also

**Table 2—Patient characteristics of women with breast cancer, stratified by no diabetes/T2D and by insulin use among women with T2D**

| | Women without diabetes: total | Women with T2D | | | *P*, T2D vs. no diabetes | *P*, insulin vs. no insulin |
|---|---|---|---|---|---|---|
| | | Total | Insulin | No insulin | | |
| *N* | 6,267 | 1,567 | 388 | 1,179 | | |
| Age (years) | | | | | 0.80 | 0.19 |
| ≤53 | 330 (5) | 85 (5) | 16 (4) | 69 (6) | | |
| >53 | 5,937 (95) | 1,482 (95) | 372 (96) | 1,110 (94) | | |
| Mean ± SD | 71 ± 11 | 71 ± 11 | 70 ± 10 | 71 ± 11 | | |
| Year of index date | | | | | <0.0001 | 0.27 |
| 2002–2005 | 2,129 (34) | 210 (13) | 44 (11) | 166 (14) | | |
| 2006–2008 | 1,464 (23) | 253 (16) | 57 (15) | 196 (17) | | |
| 2009–2011 | 1,558 (25) | 477 (30) | 118 (30) | 359 (30) | | |
| 2012–2014 | 1,116 (18) | 627 (40) | 169 (44) | 458 (39) | | |
| SES | | | | | <0.05 | 0.05 |
| High | 1,983 (32) | 437 (28) | 88 (23) | 349 (30) | | |
| Middle | 1,995 (32) | 529 (34) | 136 (35) | 393 (33) | | |
| Low | 2,262 (36) | 596 (38) | 162 (42) | 434 (37) | | |
| Unknown | 27 (<0.5) | 5 (<0.5) | 2 (1) | 3 (<0.5) | | |
| Comedication | | | | | | |
| Statins | 1,043 (17) | 970 (62) | 262 (68) | 708 (60) | <0.0001 | <0.01 |
| Antihypertensive drugs | 2,675 (43) | 1,238 (79) | 329 (85) | 909 (77) | <0.0001 | <0.01 |
| Glucocorticoids | 420 (7) | 158 (10) | 51 (13) | 107 (9) | <0.0001 | <0.05 |
| ER-PR contraceptives | 128 (2) | 28 (2) | 7 (2) | 21 (2) | 0.52 | 0.98 |
| HRT | 503 (8) | 88 (6) | 14 (4) | 74 (6) | <0.01 | <0.05 |
| Comorbidities | | | | | | |
| Renal failure | 233 (4) | 140 (9) | 54 (14) | 86 (7) | <0.0001 | <0.0001 |
| Retinopathy | 12 (<0.5) | 13 (1) | 6 (2) | 7 (1) | <0.0001 | 0.07 |
| Hypertension | 284 (5) | 166 (11) | 53 (14) | 113 (10) | <0.0001 | <0.05 |
| Stroke | 109 (2) | 36 (2) | 13 (3) | 23 (2) | 0.14 | 0.11 |
| CHF | 143 (2) | 84 (5) | 38 (10) | 46 (4) | <0.0001 | <0.0001 |
| IHD | 333 (5) | 157 (10) | 61 (16) | 96 (8) | <0.0001 | <0.0001 |
| PAD | 105 (2) | 46 (3) | 16 (4) | 30 (3) | <0.01 | 0.11 |
| Cerebrovascular disease | 207 (3) | 72 (5) | 24 (6) | 48 (4) | <0.05 | 0.08 |
| CDS | | | | | <0.0001 | <0.0001 |
| <7 | 5,049 (81) | 725 (46) | 145 (37) | 580 (49) | | |
| ≥7 | 1,218 (19) | 842 (54) | 243 (63) | 599 (51) | | |
| Duration of diabetes (years) | | | | | n.a. | <0.0001 |
| <1 | | 107 (7) | 0 (0) | 107 (9) | | |
| 1 to <2 | | 140 (9) | 5 (1) | 135 (11) | | |
| 2 to <5 | | 369 (24) | 32 (8) | 337 (29) | | |
| ≥5 | | 804 (51) | 310 (80) | 494 (42) | | |
| Unknown | | 147 (9) | 41 (11) | 106 (9) | | |

Data are *n* (%) unless otherwise indicated. CHF, congestive heart failure; IHD, ischemic heart disease; n.a., not applicable; PAD, peripheral artery disease.

concluded that patients with T2D presented with larger tumors (23,24,26,27), higher rates of lymph node metastasis (22–24), more advanced stages (22,27), and higher-grade tumors (25). Furthermore, these studies (6,22–27) also determined the association between diabetes and hormone receptor status (ER, PR, and HER2). Only one study reported a statistically significant association between diabetes and ER (27). Three studies (23,24,27) found that breast cancer among women with diabetes was more often PR negative, which was not found in the current study. Similar to our results, none of the studies reported a statistically significant association between diabetes and HER2. Only Bronsveld et al. (6) and He et al. (22) also reported on molecular subtype. Neither found compelling evidence that women with diabetes develop different breast cancer subtypes than women without diabetes.

Although many of our findings were confirmed in other studies, it should be kept in mind that the studied populations probably differed in terms of race/ethnicity and age. Because disparities in breast cancer characteristics by race and ethnicity are well established (28), results may not be completely generalizable.

Even fewer studies investigated whether the use of insulin (analogs) was associated with breast cancer characteristics (6,25,29). In a retrospective cohort study (29), insulin usage was found to be associated with a higher rate of angiolymphatic invasion, although this was based on nine insulin users only. Bronsveld et al. (6) did not observe evidence for strong associations with clinicopathological subtypes. One study compared the characteristics of insulin (*n* = 219) and noninsulin (*n* = 243) users and did not find statistically significant differences regarding clinicopathological breast cancer characteristics (25).

**Table 3—Breast cancer characteristics of women with breast cancer, stratified by no diabetes/T2D and by insulin use among women with T2D**

| | Women without DM: total | Women with T2D | | | *P*, T2D vs. no DM | *P*, insulin vs. no insulin |
|---|---|---|---|---|---|---|
| | | Total | Insulin | No insulin | | |
| *N* | 6,267 | 1,567 | 388 | 1,179 | | |
| TNM classification | | | | | | |
| Tumor size | | | | | <0.01 | 0.67 |
| 1 | 3,439 (55) | 799 (51) | 192 (49) | 607 (51) | | |
| 2 | 1,859 (30) | 505 (32) | 122 (31) | 383 (32) | | |
| 3 | 204 (3) | 69 (4) | 17 (4) | 52 (4) | | |
| 4 | 319 (5) | 94 (6) | 28 (7) | 66 (6) | | |
| Unknown | 446 (7) | 100 (6) | 29 (7) | 71 (6) | | |
| Lymph node status | | | | | <0.05 | 0.74 |
| 0 | 4,891 (78) | 1,194 (76) | 298 (77) | 896 (76) | | |
| 1 | 974 (16) | 287 (18) | 78 (20) | 209 (18) | | |
| 2 | 37 (1) | 14 (1) | 3 (1) | 11 (1) | | |
| 3 | 48 (1) | 17 (1) | 3 (1) | 14 (1) | | |
| Unknown | 317 (5) | 55 (4) | 6 (2) | 49 (4) | | |
| Metastasis | | | | | 0.06 | 0.18 |
| 0 | 6,024 (96) | 1,490 (95) | 364 (94) | 1,126 (96) | | |
| 1 | 243 (4) | 77 (5) | 24 (6) | 53 (4) | | |
| Stage | | | | | <0.01 | 0.53 |
| I | 3,412 (54) | 771 (49) | 186 (48) | 585 (50) | | |
| II | 2,216 (35) | 613 (39) | 150 (39) | 463 (39) | | |
| III | 345 (6) | 99 (6) | 27 (7) | 72 (6) | | |
| IV | 243 (4) | 77 (5) | 24 (6) | 53 (4) | | |
| Unknown | 51 (1) | 7 (<0.5) | 1 (<0.5) | 6 (1) | | |
| Morphology | | | | | <0.05 | 0.74 |
| Ductal | 4,385 (70) | 1,149 (73) | 289 (74) | 860 (73) | | |
| Lobular | 841 (13) | 187 (12) | 45 (12) | 142 (12) | | |
| Ductal-lobular mixed | 376 (6) | 72 (5) | 14 (4) | 58 (5) | | |
| Other | 665 (11) | 159 (10) | 40 (10) | 119 (10) | | |
| Grade | | | | | <0.05 | 0.63 |
| Grade 1 | 1,401 (22) | 308 (20) | 72 (19) | 236 (20) | | |
| Grade 2 | 2,423 (39) | 581 (37) | 138 (36) | 443 (38) | | |
| Grade 3 | 1,264 (20) | 355 (23) | 93 (24) | 262 (22) | | |
| Unknown | 1,179 (19) | 323 (21) | 85 (22) | 238 (20) | | |
| Hormone receptor status | | | | | | |
| ER | | | | | 0.94 | 0.97 |
| Positive | 4,671 (75) | 1,276 (81) | 316 (81) | 960 (81) | | |
| Negative | 760 (12) | 209 (13) | 52 (13) | 157 (13) | | |
| Unknown | 836 (13) | 82 (5) | 20 (5) | 62 (5) | | |
| PR | | | | | <0.0001 | 0.39 |
| Positive | 3,426 (55) | 1,043 (67) | 263 (68) | 780 (66) | | |
| Negative | 1,797 (29) | 420 (27) | 97 (25) | 323 (27) | | |
| Unknown | 1,044 (17) | 104 (7) | 28 (7) | 76 (6) | | |
| HER2 | | | | | 0.66 | 0.85 |
| Negative | 3,618 (58) | 1,132 (72) | 283 (73) | 849 (72) | | |
| Positive | 455 (7) | 136 (9) | 35 (9) | 101 (9) | | |
| Unknown | 2,194 (35) | 299 (19) | 70 (18) | 229 (19) | | |
| Molecular subtype | | | | | 0.17 | 0.65 |
| Luminal A | 2,384 (38) | 694 (44) | 168 (43) | 526 (45) | | |
| Luminal B | 686 (11) | 241 (15) | 59 (15) | 182 (15) | | |
| Nonluminal (HER2 positive) | 155 (2) | 43 (3) | 14 (4) | 29 (2) | | |
| Triple negative | 402 (6) | 124 (8) | 29 (7) | 95 (8) | | |
| Unknown | 2,640 (42) | 465 (30) | 118 (30) | 347 (29) | | |

Data are *n* (%) unless otherwise indicated. DM, diabetes

To our best knowledge, no studies with a nested case-control design looked at the effect of insulin (analog) use on clinicopathological breast cancer characteristics. In our study, no association regarding duration, dose, or type of insulin treatment with regard to breast cancer characteristics was found. However, it might be possible that we had insufficient power to detect a statistically significant association because the overall number of insulin (analog) users was small. Furthermore, the used regression model assumes that some property of the outcome is linearly related to the

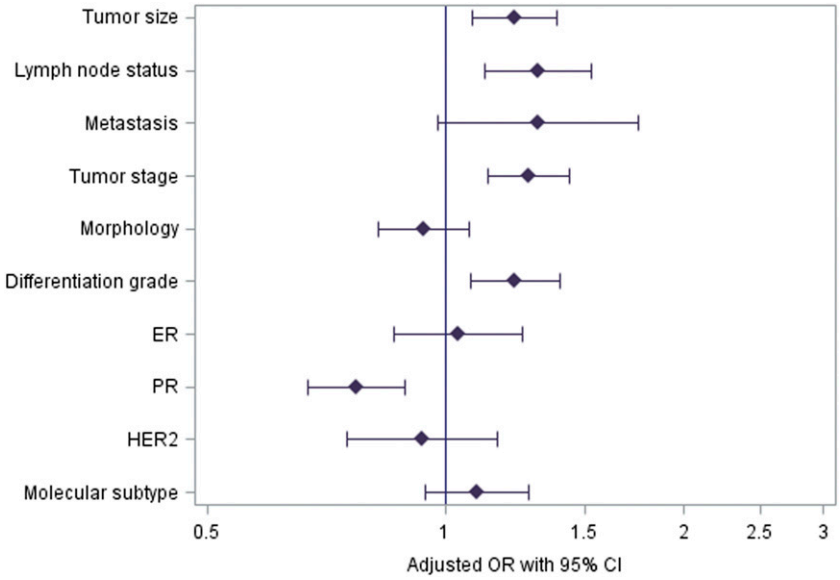


**Figure 1**—Effect of T2D ($N$ = 1,567) vs. no diabetes ($N$ = 6,267) on developing breast cancer characteristics. Model was adjusted for age, year of index date, SES, CDS, and use of glucocorticoids, estrogen-progestogen contraceptives, and HRT in the year prior to index date.

exposure. If larger numbers are available, it will be worthwhile to explore the justification of this assumption or that using cubic spline functions would be more appropriate (30).

Although T2D was associated with more advanced stages of breast cancer, this association is not per definition causal. It is known that there are regional differences in the participation rate for routine screening for breast cancer in the Netherlands. In the large cities in the Randstad, the participation rate is the lowest. However, no differences were observed between women with T2D and women without diabetes regarding the distribution of the large cities in the Randstad versus other cities. Furthermore, it has been hypothesized that women with diabetes might have a lower participation rate because of the concurrent treatment of the chronic diseases associated with diabetes (31). In the Netherlands, women aged 50–75 years are invited to attend a free breast cancer screening mammography regardless of comorbidity. Therefore, it is also likely that there is no difference regarding participation rates among women with and women without diabetes. Furthermore, breast cancers detected in mammography screening are associated with more favorable prognosis than breast cancers found outside of screening because the distribution of molecular subtype of screen-detected breast cancers is different than the distribution of breast cancers found outside of screening (32). In the current study, a subgroup analysis among women eligible for screening (50–75 years of age) showed the same results as the main analyses.

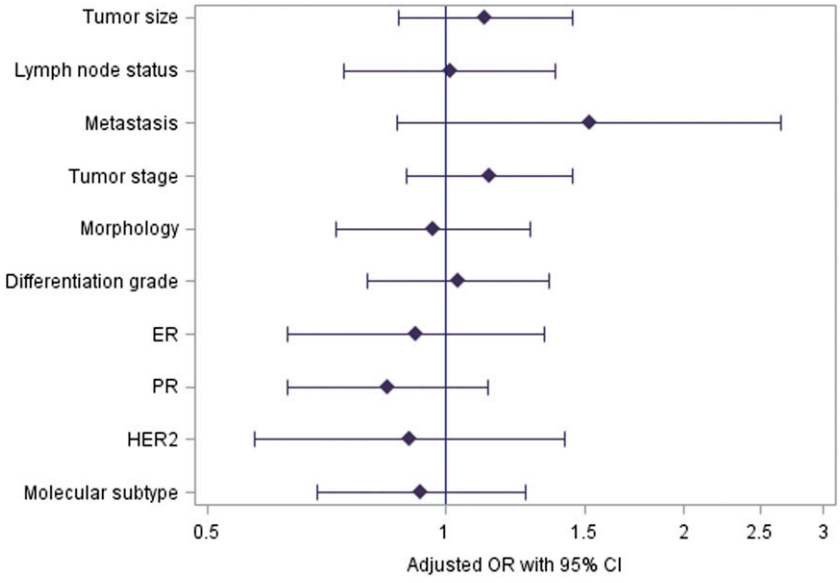


**Figure 2**—Effect of insulin (analog) treatment ($N$ = 388) vs. no insulin (analog) treatment ($N$ = 1,179) on developing breast cancer characteristics among women with T2D. Model was adjusted for duration of T2D, age, year of index date, SES, CDS, and use of glucocorticoids, estrogen-progestogen contraceptives, and HRT in the year prior to index date.

A possible suggested pathway for the association between T2D and breast cancer characteristics is hyperinsulinemia, related to underlying insulin resistance, that might stimulate tumor growth. Insulin may work directly on epithelial cells or indirectly by activating insulin-like growth factor pathways or altering endogenous sex hormones (33–35). Insulin levels are already high in people with impaired glucose tolerance at the time of diagnosis of diabetes (36). Moreover, Goodwin et al. (37) showed that insulin levels were related to tumor stage, nodal stage, and tumor grade. Insulin levels were not related to nuclear grade, lymphatic invasion, ER, or PR. In our study, exogenous insulin did not show an association with different breast cancer characteristics, which might be explained by the fact that insulin analogs may have a metabolic action and a mitogenic action altered from that of human insulin (38).

Some limitations should be kept in mind when interpreting the results of the current study. First, it was not possible to adjust for all important confounders. For instance, no information was available regarding mammography/screening, BMI, or menopausal status. As obesity is a major risk factor for T2D, this could have influenced our results. However, Wolf et al. (27) showed that women with diabetes presented with a larger tumor size at diagnosis and a more advanced stage, even after adjustment for BMI. As the mean age in the current

study was 71 years, our findings primarily apply to postmenopausal women. Whether a period of 4 years prior to breast cancer diagnosis is sufficient to determine cumulative insulin use is also debatable. For the current study, the decision entailed a trade-off between keeping sufficient numbers and a reasonable period to determine insulin use appropriately. Sensitivity analyses regarding the period prior to breast cancer diagnosis was outside the scope of the study. Furthermore, only women pharmaceutically treated for their T2D were included. Some misclassification of T2D might have occurred, as weight loss can result in remission of T2D (39). In interpretation of the results regarding insulin versus no insulin, it should be kept in mind that patients in both groups used NIBGLDs as well. The individual potential associations between NIBGLDs and breast cancer characteristics might have influenced our results. However, we believe that these influences were minimal because both groups had a similar distribution regarding NIBGLD use. The results in our study regarding breast cancer stages and duration, dose, and type of insulin use should be interpreted with caution, as the numbers were low, though with a long follow-up, and results were not even near statistically significant.

Overall, this is the first study using the linkage between the NCR and the Out-patient Pharmacy Database of the PHARMO Database Network for the association between T2D/insulin (analog) use and different pathologic breast cancer characteristics. Through linking of these databases, a unique cohort was created taking advantage of the high-quality data on cancer and detailed information on medication use. This linkage resulted in one of the largest detailed cohorts of women with breast cancer and T2D/insulin (analog) use. Because of the design of the study, misclassification was limited to a minimum.

## Conclusion

Our study suggests that women with T2D present with more advanced breast tumors at diagnosis than women without T2D. Among women with T2D, the use of insulin (analog) is not associated with developing more aggressive breast cancer tumors. Based on the current data we see no reason to restrain the use of insulin (analog) among women with T2D with regard to its effects on breast cancer subtype and expected subsequent prognosis.

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**Author Contributions.** J.A.O. researched data and wrote the manuscript. J.A.O., H.K.B., and M.K.S. designed the study. M.P.P.v.H.-S., P.A.J.V., A.A.W.A.v.d.H., H.K.B., R.M.C.H., M.K.S., and G.N. contributed to the discussion and reviewed and edited the manuscript. J.A.O. affirmed that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. J.A.O. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## References

1. World Health Organization. Global Report on Diabetes [Internet], 2016. Available from http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1. Accessed 15 December 2016
2. Liao S, Li J, Wei W, et al. Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. Asian Pac J Cancer Prev 2011;12:1061–1065
3. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108
4. Centraal Bureau voor de Statistiek. Bevolking; kerncijfers [Internet], 2018. Available from http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=37296NED&D1=0-2&D2=39-67&VW=T. Accessed 31 August 2018
5. Integraal Kankercentrum Nederland. Incidentie borst [Internet]. Available from https://www.cijfersoverkanker.nl/selecties/incidentie_borst/img5b8902a6817e0. Accessed 31 August 2018
6. Bronsveld HK, Jensen V, Vahl P, et al. Diabetes and breast cancer subtypes. PLoS One 2017;12:e0170084
7. La Vecchia C, Giordano SH, Hortobagyi GN, Chabner B. Overweight, obesity, diabetes, and risk of breast cancer: interlocking pieces of the puzzle. Oncologist 2011;16:726–729
8. Chang SC, Yang WV. Hyperglycemia, tumorigenesis, and chronic inflammation. Crit Rev Oncol Hematol 2016;108:146–153
9. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52:1766–1777
10. Hemkens LG, Grouven U, Bender R, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia 2009;52:1732–1744
11. Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdòttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies—a population-based follow-up study in Sweden. Diabetologia 2009;52:1745–1754
12. Gallagher EJ, LeRoith D. The proliferating role of insulin and insulin-like growth factors in cancer. Trends Endocrinol Metab 2010;21:610–618
13. Grimberg A. Mechanisms by which IGF-I may promote cancer. Cancer Biol Ther 2003;2:630–635
14. Peairs KS, Barone BB, Snyder CF, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. J Clin Oncol 2011;29:40–46
15. Wu JW, Azoulay L, Majdan A, Boivin JF, Pollak M, Suissa S. Long-term use of long-acting insulin analogs and breast cancer incidence in women with type 2 diabetes. J Clin Oncol 2017;35:3647–3653
16. Bronsveld HK, ter Braak B, Karlstad Ø, et al. Treatment with insulin (analogues) and breast cancer risk in diabetics; a systematic review and meta-analysis of in vitro, animal and human evidence. Breast Cancer Res 2015;17:100
17. But A, De Bruin ML, Bazelier MT, et al. Cancer risk among insulin users: comparing analogues with human insulin in the CARING five-country cohort study. Diabetologia 2017;60:1691–1703
18. Integraal kankercentrum Nederland. Netherlands Cancer Registry (NCR); record, report, improve and regulate [Internet], 2018. Available from https://www.iknl.nl/over-iknl/about-iknl/what. Accessed 24 September 2018
19. Putnam KG, Buist DS, Fishman P, et al. Chronic disease score as a predictor of hospitalization. Epidemiology 2002;13:340–346
20. Catalan VS, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. Value Health 2000;3:417–426
21. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ; Panel members. Strategies for subtypes–dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol 2011;22:1736–1747
22. He DE, Bai JW, Liu J, Du CW, Huang WH, Zhang GJ. Clinicopathological characteristics and prognosis of breast cancer patients with type 2 diabetes mellitus. Mol Clin Oncol 2015;3:607–612
23. Hou G, Zhang S, Zhang X, Wang P, Hao X, Zhang J. Clinical pathological characteristics and prognostic analysis of 1,013 breast cancer patients with diabetes. Breast Cancer Res Treat 2013;137:807–816
24. Liao S, Li J, Wang L, et al. Type 2 diabetes mellitus and characteristics of breast cancer in China. Asian Pac J Cancer Prev 2010;11:933–937
25. Mu L, Zhu N, Zhang J, Xing F, Li D, Wang X. Type 2 diabetes, insulin treatment and prognosis of breast cancer. Diabetes Metab Res Rev 2017;33:e2823
26. Schrauder MG, Fasching PA, Häberle L, et al. Diabetes and prognosis in a breast cancer cohort. J Cancer Res Clin Oncol 2011;137:975–983
27. Wolf I, Sadetzki S, Gluck I, et al. Association between diabetes mellitus and adverse characteristics of breast cancer at presentation. Eur J Cancer 2006;42:1077–1082

28. Ooi SL, Martinez ME, Li CI. Disparities in breast cancer characteristics and outcomes by race/ethnicity. Breast Cancer Res Treat 2011; 127:729–738
29. Goldvaser H, Rizel S, Hendler D, et al. The association between treatment for metabolic disorders and breast cancer characteristics. Int J Endocrinol 2016;2016:4658469
30. Harrell FE Jr., Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. J Natl Cancer Inst 1988;80:1198–1202
31. Maruthur NM, Bolen S, Brancati FL, Clark JM. Obesity and mammography: a systematic review and meta-analysis. J Gen Intern Med 2009;24:665–677
32. Sihto H, Lundin J, Lehtimäki T, et al. Molecular subtypes of breast cancers detected in mammography screening and outside of screening. Clin Cancer Res 2008;14:4103–4110
33. Jiralerspong S, Palla SL, Giordano SH, et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol 2009;27:3297–3302
34. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–591
35. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B. Diabetes mellitus and breast cancer. Lancet Oncol 2005;6:103–111
36. Nijpels G, Popp-Snijders C, Kostense PJ, Bouter LM, Heine RJ. Fasting proinsulin and 2-h post-load glucose levels predict the conversion to NIDDM in subjects with impaired glucose tolerance: the Hoorn Study. Diabetologia 1996; 39:113–118
37. Goodwin PJ, Ennis M, Pritchard KI, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol 2002;20:42–51
38. Varewijck AJ, Janssen JA. Insulin and its analogues and their affinities for the IGF1 receptor. Endocr Relat Cancer 2012;19:F63–F75
39. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018;391:541–551