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Original Article

Impact of type 2 diabetes on complications after primary breast cancer surgery: Danish population-based cohort study

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Abstract

Background: Knowledge is sparse on the impact of type 2 diabetes (T2D) on surgical outcomes after breast cancer surgery. This study investigated the association between T2D and risk of complications after primary breast cancer surgery, and evaluated the biological interaction between T2D and co-morbidities.

Methods: Using the Danish Breast Cancer Group clinical database, a cohort of all Danish women diagnosed with early-stage breast cancer during 1996–2022 was created. All patients underwent mastectomy or breast-conserving surgery. Information on prevalent T2D was collected from Danish medical and prescription registries. Surgical complications were defined as hospital diagnoses for medical or surgical complications developing within 30 days after primary breast cancer surgery. The 30-day cumulative incidence proportion of complications was calculated, and Cox regression was used to estimate HRs. Interaction contrasts were computed to determine the additive interaction between T2D and co-morbidities on the incidence rate of complications.

Results: Among 98 589 women with breast cancer, 6332 (6.4%) had T2D at breast cancer surgery. Overall, 1038 (16.4%) and 9861 (10.7%) women with and without T2D developed surgical complications, yielding cumulative incidence proportions of 16 (95% c.i. 15 to 17) and 11 (10 to 11)% respectively, and a HR of 1.43 (95% c.i. 1.34 to 1.53). The incidence rate of surgical complications explained by the interaction of T2D with moderate and severe co-morbidity was 21 and 42%, respectively.

Conclusion: Women with breast cancer and T2D had a higher risk of complications after primary breast cancer surgery than those without T2D. A synergistic effect of T2D and co-morbidity on surgical complications can explain this association.

Introduction

Breast cancer is the most common cancer in women, with approximately 2.2 million new cases and more than 600 000 cancer-specific deaths worldwide each year[1]. Despite better diagnosis, treatment, and survival from breast cancer over the past 20 years, evidence suggests that improvements in treatment are not necessarily benefitting elderly patients with breast cancer and those with co-morbidities[2–6]. In recent years, the number of women with breast cancer and concomitant diseases has increased[7]. Up to one-third of women with breast cancer have co-morbidity at the time of diagnosis[8]. Among newly diagnosed cases in European settings, the prevalence of type 2 diabetes (T2D) at diagnosis increases from 2% among women aged 45–59 years to 16% in those aged above 75 years[9].

Previous literature[10–12] indicated that patients with prevalent T2D at breast cancer diagnosis have a higher risk of all-cause mortality than their non-T2D counterparts. Furthermore, patients with diabetes who undergo major surgical procedures have a higher risk of readmission, surgical-site infection, impaired wound healing, and extended postoperative hospital stay[13–16].

In recent years, approximately 90% of all women with newly diagnosed breast cancer in Denmark underwent primary surgical treatment by mastectomy or breast-conserving surgery (BCS)[17]. Complications after breast cancer surgery that warrant further surgical intervention are rare, and occur in about 5% of patients up to 60 days after primary surgery[18]. Given the large number of women with breast cancer undergoing surgery each year, a prolonged hospital stay or readmission owing to surgical complications may, however, adversely influence their health and quality of life[19], incurring additional healthcare costs[20].

Although the association between T2D and increasing co-morbidity burden is well documented, the impact of T2D on surgical complications after breast cancer surgery is not clear.

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Previous literature was restricted to studies of outcomes from single complications such as surgical-site infections, many with a sample size of fewer than 350 patients[21], or focused on a more general investigation of risk factors for surgical complications[22,23]. The present large population-based cohort study was conducted to assess the association between T2D and any surgical complication up to 30 days after primary breast cancer surgery. Analyses were stratified by the receipt of neoadjuvant systemic therapy, and the effect of the interaction between T2D and co-morbidities on the incidence of surgical complications after breast cancer surgery was evaluated.

Methods

Setting

This nationwide cohort study included all women diagnosed with early-stage operable breast cancer between 1996 and 2022 identified from Danish population-based registries. In Denmark, the Danish National Health Service provides free healthcare services, with unlimited access to all public hospitals and general practitioners[24]. Using a unique identification number assigned to all Danish citizens at birth or immigration, enables individual-level data linkage across all public registries[25]. According to Danish law, approval from ethics committee was not required as only register-based data was used. The study was approved by the Danish Data Protection Agency (Jr. no. 2014-54-0922).

Source population

The clinical database from the Danish Breast Cancer Group (DBCG) was used to identify all women aged 18 years or older with incident early-stage operable breast cancer diagnosed between 1 January 1996 and 30 June 2022. All women underwent primary surgery by either mastectomy or BCS. Information on type and date of surgery was obtained from the DBCG. The DBCG was established in 1977 and contains prospectively collected information on almost all patients diagnosed with non-distant metastatic breast cancer in Denmark[26,27]. Data completeness is in excess of 95% each year[28].

Type 2 diabetes

Prevalent T2D was identified via diagnostic codes or the redemption of at least one prescription for glucose-lowering drugs. Diagnostic codes (ICD-8 and -10) for T2D were ascertained from the Danish National Patient Registry (DNPR), which contains information on all inpatient hospital contacts since 1977, and emergency room and outpatient hospital contacts since 1995[29]. The Danish National Prescription Registry was used to ascertain information on patients who redeemed at least one prescription of a glucose-lowering drug with the Anatomical Therapeutic Classification (ATC) code A10*[30]. To ensure that all patients with T2D were included in the study population, diagnostic codes for both type 1 and 2 diabetes (ICD-8: 249*, 250*; ICD-10: E10*–E14*, G63.2.x, H36.0*, N08.3, O24* (except O24.1)) were included and thereafter restricted to patients with a first diabetes diagnosis after the age of 30 years. Accordingly, all patients with type 1 diabetes were excluded. Women who gave birth within 9 months after a diabetes diagnosis (ICD-8: 650–662; ICD-10: O80*–O84*) were excluded as such diagnoses were likely to represent gestational diabetes.

Outcome

Surgical complications after primary breast cancer surgery were defined by at least one in-hospital readmission or outpatient event for any medical or surgical diagnosis within 30 days after primary surgery. Complications were categorized into subgroups of bleeding, infection, venous thromboembolism, arterial cardiovascular disease, kidney disease, and surgical-site complications, the latter specified as wound infections or reoperations because of bleeding or local infection (*Table S1* shows a full list of diagnostic codes). All ICD-10 codes defining surgical complications were obtained from the DNPR.

Co-variates

The following information on patient, tumour, and treatment characteristics was included from the DBCG: menopausal status (before or after menopause), type of breast surgery (BCS or mastectomy), type of axillary surgery (sentinel lymph node biopsy, axillary lymph node dissection, or combination of the two), number of positive lymph nodes, and neoadjuvant systemic treatment (chemotherapy with or without antihuman epidermal growth factor receptor 2 treatment). Information on tumour (T) category (based on TNM staging: T1, 2 cm or smaller; T2, over 2 cm but no larger than 5 cm; T3, over 5 cm; T4, any size but with extension to chest wall/skin or inflammatory breast cancer) was ascertained from the Danish Cancer Registry (available from 2004 onwards). Information on co-morbidities up to 10 years before the date of breast cancer surgery was obtained from the DNPR. A modified co-morbidity score according to the Charlson Co-morbidity Index (CCI), excluding diabetes and breast cancer, was created (*Table S2*)[31]. This modified CCI was categorized into no (score 0), mild (1), moderate (2–3), and severe (over 3) co-morbidity. Using data from the Danish National Prescription Registry, the following co-medications with at least one prescription redeemed in the year before index date were considered: anticoagulants and aspirin (ATC: B01* + N02BA51, N02BA01), non-aspirin non-steroidal anti-inflammatory drugs (ATC: M01A, except M01AX), systemic glucocorticoids (ATC: H02AB, HA02BX), and selective serotonin reuptake inhibitors (ATC: N06AB). Use of diabetes medications was categorized as metformin only, metformin in combination with other oral drugs, or insulin only.

Statistical analysis

Descriptive characteristics of all study participants according to T2D prevalence at breast cancer diagnosis were tabulated.

Each patient was followed from the date of surgery (index) until the date of complication, death, emigration, 30 days, or 30 June 2022, whichever came first. If a patient had more than one surgical procedure (primary breast cancer surgery with mastectomy or BCS, or reoperation owing to insufficient margins), the date of the final procedure was considered the index date. The overall incidence rate (IR) per 1000 person-days and 30-day cumulative incidence proportion (CIP) of any surgical complication was computed with associated 95% confidence intervals. The cumulative incidence function of surgical complications, according to T2D exposure (with death treated as a competing risk) was plotted. Interaction contrasts were computed to determine the potential synergistic effect of T2D and co-morbidity on the IR of surgical complications[32]. The interaction contrast is defined as a measure of the additive or deficit in the IR above or below what can be explained by the baseline incidence of surgical complications after breast cancer

surgery, the effect of co-morbidity on the IR, and the effect of T2D on the IR[33].

Cox regression models were used to calculate crude and adjusted HRs including 95% confidence intervals comparing the risk of surgical complications according to T2D status after breast cancer surgery. The adjusted model included potential confounding co-variates: age at diagnosis, index year (calendar), T category, type of surgery, and co-morbidities (CCI). The proportional hazards assumptions were verified by log-log plots, and no violations were detected. To account for missing data, multiple imputation of the T category and menopause co-variates was performed as data were expected to be missing at random[34]. To evaluate potential associations further, analyses were stratified by neoadjuvant systemic therapy, calendar period, age, type of surgery, CCI, and baseline co-medications in both breast cancer cohorts and in all the statistical models, and by duration of T2D and type of diabetes medication in the diabetes cohort. The stratified Cox regression models were adjusted for the same confounding factors as in the primary analysis. All statistical analyses began in November 2022 and were completed using Stata® version 17.0 (StataCorp, College Station, TX, USA).

Results

The study population included 98 589 women with incident early-stage breast cancer. A total of 6332 women (6.4%) with breast cancer had T2D at the time of cancer surgery. The median duration of diabetes before primary breast cancer surgery was 6.3 (i.q.r. 2.9–11.4) years. Women with T2D were older at the time of surgery, thus more frequently postmenopausal, and had a higher frequency of co-morbidities (*Table 1*). Furthermore, the proportion of women who redeemed a prescription for any systemic antibiotic within 30 days after the cancer surgery was higher among those with T2D than those without (19.1 *versus* 12.5%).

Table 1 Baseline characteristics of women diagnosed with early-stage breast cancer according to type 2 diabetes prevalence

	T2D (n = 6332)	No T2D (n = 92 257)
Age at primary cancer diagnosis (years)		
≤ 44	145 (2.3)	9302 (10.1)
45–54	587 (9.3)	20 288 (22.0)
55–64	1567 (24.8)	25 625 (27.8)
65–74	2212 (34.9)	22 117 (24.0)
≥ 75	1821 (28.8)	14 925 (16.2)
Index year of primary breast cancer surgery		
1996–2003	1011 (16.0)	24 743 (26.8)
2004–2012	2265 (35.8)	33 050 (35.8)
2013–2022	3056 (48.2)	34 464 (37.4)
Type of primary breast cancer surgery		
Mastectomy	2814 (44.4)	41 987 (45.5)
BCS	3518 (55.6)	50 270 (54.5)
T category*		
T1	2743 (54.3)	38 606 (60.2)
T2	1860 (36.8)	20 522 (32.0)
T3	196 (3.9)	2459 (3.8)
T4	76 (1.5)	777 (1.2)
Unknown	178 (3.5)	1809 (2.8)
Missing	1279	28 084
Axillary surgery		
Sentinel lymph node biopsy only	2854 (57.9)	38 574 (57.9)
Axillary lymph node dissection only	990 (20.1)	12 906 (19.4)
Combination of the two	1086 (22.0)	15 144 (22.7)
Missing	1402	25 633
No. of positive lymph nodes		
0	3227 (57.0)	49 043 (58.1)
1–3	1587 (28.0)	24 135 (28.6)
4–9	503 (9.0)	7033 (8.3)
≥ 10	344 (6.0)	4277 (5.1)
Missing	671	7769
Co-morbidity (CCI score)†		
None (0)	3835 (60.6)	73 789 (80.0)
Mild (1)	1224 (19.3)	9773 (10.6)
Moderate (2–3)	981 (15.5)	6692 (7.3)
Severe (> 3)	292 (4.6)	2003 (2.2)
Any neoadjuvant systemic therapy		
Yes	385 (6.1)	5358 (5.8)
No	5947 (93.9)	86 899 (94.2)
Menopausal status		
Premenopausal	489 (7.7)	22 644 (24.6)
Postmenopausal	5827 (92.3)	69 385 (75.4)
Unknown	0 (0)	15 (0)
Missing	16	213
Co-medications at baseline‡		
Non-aspirin NSAIDs	1711 (27.2)	21 063 (22.8)
Anti-coagulants	2668 (42.1)	11 922 (12.9)
Glucocorticoids	425 (6.7)	4660 (5.1)
SSRI	754 (11.9)	6984 (7.8)

Values are n (%) unless otherwise indicated. *Available from 2004 and onwards, based on TNM staging of breast cancer: T1, 2 cm or smaller; T2, over 2 cm but 5 cm or less; T3, over 5 cm; T4, any size but with extension to chest wall/skin or inflammatory breast cancer. †Information on co-morbidities (ICD-8 and -10 codes) in the Charlson Co-morbidity Index (CCI) score was obtained for an interval of 10 years before breast cancer surgery. ‡Baseline exposure of a co-medication (Anatomical Therapeutic Classification codes) is defined by redemption of at least one prescription within 1 year before breast cancer surgery. T2D, type 2 diabetes; BCS, breast-conserving surgery; NSAID, non-steroidal anti-inflammatory drug; SSRI, serotonin selective reuptake inhibitor.

Surgical complications

Overall, 1038 and 9861 women with and without prevalent T2D respectively developed a surgical complication after primary breast cancer surgery, corresponding to a 30-day CIP of 16 (95% c.i. 15 to 17) and 11 (10 to 11)% respectively (*Fig. 1a*). The most frequent surgical complications in women with and without T2D were surgical-site complications (598 (9.4%) and 7222 (7.8%)), arterial cardiovascular complications (318 (5.0%) and 1527 (1.7%)), and infections (199 (3.1%) and 1494 (1.6%)). After adjusting for potential confounders, women with breast cancer and T2D had a higher risk of surgical complications after primary breast cancer surgery than their counterparts without diabetes (adjusted HR 1.43, 95% c.i. 1.34 to 1.53) (*Table 2*).

Among women who underwent neoadjuvant systemic therapy, 385 (6.1%) had T2D and 5358 (5.8%) did not (*Table 2*). Women with T2D had a higher 30-day cumulative risk of surgical complications than those without (30-day CIP 19 (15 to 23) and 10 (9 to 11)% respectively), corresponding to an adjusted HR of 1.72 (1.34 to 2.20) (*Fig. 1b*). The CIP of surgical complications and corresponding HRs were similar to the overall estimates for women who did not receive neoadjuvant systemic therapy. Findings from the other stratified analyses did not vary from the overall findings (*Table S3* and *Fig. S1*).

Among women with T2D, there was no difference in the risk of complications after stratifying by T2D duration (5 years or less *versus* more than 5 years), or by type of diabetes medication. The HRs stratified by co-morbidity tended to increase with increasing co-morbidity burden.

Type 2 diabetes and co-morbidity interaction

Among women with breast cancer without co-morbidity, the 30-day surgical complication IR per 1000 person-days was 4.9 (95% c.i. 4.4 to 5.3) for those with T2D and 3.5 (3.4 to 3.6) for

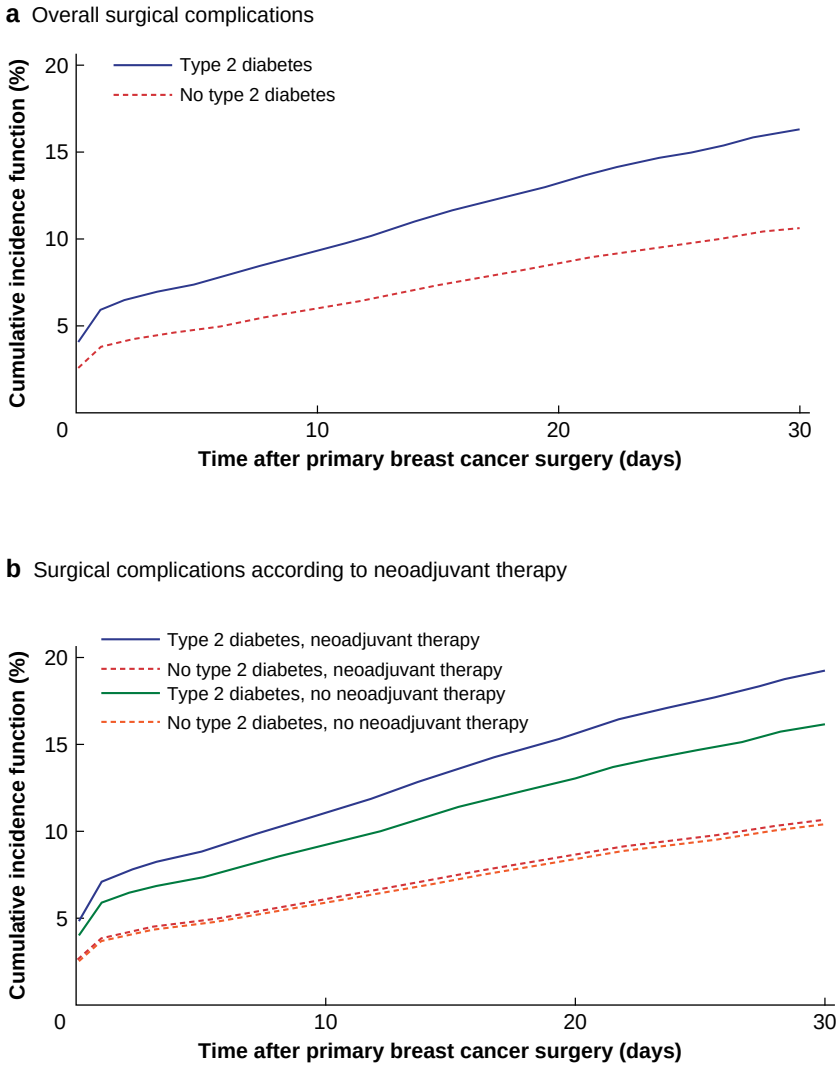

Fig. 1 Cumulative incidence function of overall surgical complications and complications according to neoadjuvant systemic therapy

a Overall surgical complications and **b** complications according to neoadjuvant systemic therapy.

Table 2 Surgical complications among women diagnosed with early-stage breast cancer according to type 2 diabetes prevalence and stratified by neoadjuvant systemic therapy

		No. of patients	No. with complication	IR per 1000 person-days	30-day cumulative incidence (%)	Crude HR	Adjusted HR*
Overall exposure cohorts							
BC		92 257	9861	3.8 (3.8, 3.9)	11 (10, 11)	1.00 (reference)	1.00 (reference)
BC and T2D		6332	1038	6.2 (5.8, 6.6)	16 (15, 17)	1.58 (1.49, 1.69)	1.43 (1.34, 1.53)
Stratification cohorts							
No neoadjuvant therapy	BC (reference)	86 899	9306	3.8 (3.8, 3.9)	11 (10, 11)	1.00 (reference)	1.00 (reference)
	BC + T2D	5947	964	6.1 (5.7, 6.5)	16 (15, 17)	1.56 (1.46, 1.67)	1.40 (1.32, 1.51)
Neoadjuvant therapy	BC (reference)	5358	555	3.7 (3.5, 4.1)	10 (9, 11)	1.00 (reference)	1.00 (reference)
	BC + T2D	385	74	7.5 (6.0, 9.4)	19 (15, 23)	1.94 (1.52, 2.47)	1.72 (1.34, 2.20)

Values in parentheses are 95% confidence intervals. *Adjusted for age at diagnosis, index year (calendar), T category, type of surgery, and co-morbidities (Charlson Co-morbidity Index). IR, incidence rate; BC, breast cancer; T2D, type 2 diabetes.

women without T2D. For women with mild co-morbidity, corresponding IRs per 1000 person-days were 7.7 (6.8 to 8.8) and 5.4 (5.1 to 5.7) respectively (Fig. 2). An interaction contrast of 0.9 indicated that interaction accounted for a minor proportion (12%) of the total complication rate in women with T2D and mild co-morbidity. The percentage of the complication IR

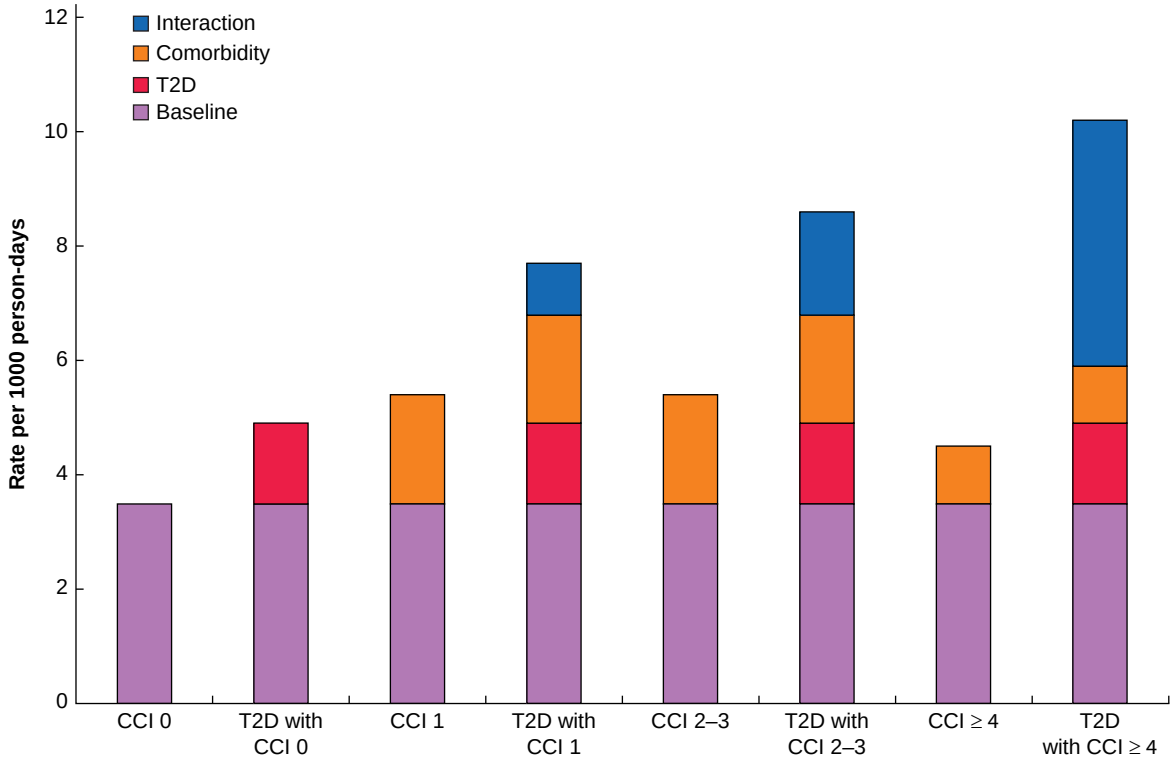

Fig. 2 Proportion of total 30-day surgical complication rate attributable to type 2 diabetes, co-morbidity, and their interaction
CCI, Charlson Co-morbidity Index. T2D, type 2 diabetes.

Table 3 Incidence of overall 30-day surgical complications and interaction contrasts stratified by co-morbidity

Co-morbidity stratum	Cohort	No. of patients	No. with complication	IR per 1000 person-days	30-day cumulative incidence (%)	Interaction contrast	% IR explained by interaction
No co-morbidity	BC (reference)	73 789	7220	3.5 (3.4, 3.6)	9.7 (9.5, 9.9)	Reference	Reference
	BC + T2D	3835	505	4.9 (4.4, 5.3)	13 (12, 14)	–	–
Mild co-morbidity (CCI 1)	BC	9773	1420	5.4 (5.1, 5.7)	14 (14, 15)	–	–
	BC + T2D	1224	245	7.7 (6.8, 8.8)	20 (18, 22)	0.9 (0.7, 1.1)	12
Moderate co-morbidity (CCI 2–3)	BC	6692	973	5.4 (5.1, 5.7)	14 (13, 15)	–	–
	BC + T2D	981	215	8.6 (7.6, 9.9)	22 (19, 24)	1.8 (1.6, 2.0)	21
Severe co-morbidity (CCI > 3)	BC	2003	248	4.5 (4.0, 5.1)	12 (11, 14)	–	–
	BC + T2D	292	73	10.2 (8.1, 12.8)	24 (20, 29)	4.3 (4.0, 4.6)	42

Values in parentheses are 95% confidence intervals. IR, incidence rate; BC, breast cancer; T2D, type 2 diabetes; CCI, Charlson Co-morbidity Index.

explained by interaction in women with moderate and severe co-morbidity, however, was substantially increased to 21% (interaction contrast 1.8) and 42% (interaction contrast 4.3) respectively (*Table 3*).

Discussion

The findings of this study indicate that women with prevalent T2D have a higher risk of surgical complications after primary breast cancer surgery than those without diabetes. This association was stronger among those treated with neoadjuvant systemic therapy. A synergistic effect between T2D and co-morbidity on surgical complications was also observed, with up to 42% of the surgical complication rate being attributable to interaction.

This is the largest study to date evaluating surgical complication rates after breast cancer surgery. The study extends previous research by investigating multiple complications in a direct large-scale comparative setting of women with and without T2D. This is the first study to evaluate the effects of co-morbidity and T2D, and their potential biological interaction, on the risk of surgical complications.

Importantly, the co-morbidity burden itself did not substantially increase the risk of surgical complications. Rather, the excess risk of surgical complications was strongest among women with T2D *and* moderate to severe co-morbidities. This suggests that the association was mainly driven by a biological interaction between T2D and co-morbidity burden.

Previous research[35] showed increased risk of reoperation owing to bleeding after breast cancer surgery among women aged above 80 years who underwent mastectomy and used glucocorticoids. In the present study, women with T2D were generally older than their non-diabetic counterparts at time of breast cancer primary surgery, in line with previous literature[36,37]. After 2011, a larger proportion of women with breast cancer and T2D underwent

surgery compared with earlier time intervals (*Table 1*), most likely explained by the general increase in T2D incidence.

In previous studies[38–41], the proportion of patients with breast cancer receiving neoadjuvant therapy varied from 4.7 to 8.9%. This is likely explained by differences in the study intervals and type of surgery. Neoadjuvant systemic therapy was introduced as a standard regimen in Denmark in 2010. As such, a large proportion of individuals in this study were diagnosed in an era when neoadjuvant systemic therapy was not recommended. In a cohort study of over 132 000 patients with early-stage breast cancer undergoing total mastectomy or BCS from 2010–2017 in Japan, Konishi *et al.*[38] reported that neoadjuvant chemotherapy was not associated with higher risk of short-term surgical complications. Yet, their study did not define the duration of 'short term'. The reported surgical complications were comparable to those in the present study, including surgical-site infections, bleeding, cardiac disease, and focal and systemic infections. Thus, over a similar calendar interval, the findings are consistent among women undergoing mastectomy or BCS, with no differences in complication risk between women treated with or without neoadjuvant systemic therapy, independent of diabetes status. Other studies have shown similar results[39,40,42].

Several issues should be considered when interpreting these findings. In the present large nationwide cohort, with high data completeness and complete follow-up, selection bias was virtually eliminated[29]. Analysis of systematically and prospectively collected data on clinical, tumour, and treatment characteristics enabled the incorporation of potential confounding factors. The completeness of the DNPR is high, and information on T2D was ascertained based both on diagnostic codes from the DNPR and T2D medications from the Danish National Prescription Registry[29,30]. Co-medications were selected based on drugs that may increase the risk of surgical complications and reoperation, especially when assessing the risk of postoperative bleeding. These drugs are more commonly used by individuals with T2D than those without[35,43–45].

Still, this study may be prone to residual confounding owing to lifestyle factors such as smoking, dietary habits, and BMI, which are not recorded routinely in Danish registries. Both BMI and smoking may be more prevalent among individuals with T2D, and both are associated with a higher risk of surgical complications[46–48]. Information on performance status was not available, but patients with breast cancer are not expected to be excluded from surgery because of co-morbidities or poor performance status[49]. Thus, it seems unlikely that selection bias would explain the findings. It is possible that T2D was misclassified, especially among women with preclinical T2D, which would have biased the observed effect estimates to the null. Women who had a pre-existing hospital diagnosis of polycystic ovarian syndrome at time of breast cancer surgery were not excluded. Such women could potentially have been considered to have T2D owing to the use of metformin, the standard treatment for polycystic ovarian syndrome. The total number of such women in this cohort is expected to be very small, and unlikely to have influenced the results.

These findings highlight a need for increased awareness of the potential for surgical complications among patients with T2D undergoing breast cancer surgery. They also suggest that, in the absence of T2D, co-morbidity has a negligible impact on the absolute risk of surgical complications. Further studies are needed to examine the impact of T2D severity, duration, and biological markers, such as haemoglobin A1c levels, on surgical complications in women with breast cancer. These findings may be used to guide the care of women with breast cancer and T2D in the aftermath of the primary surgery.

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This study was not preregistered with an analysis plan in an independent, institutional registry before study initiation.

Author contributions

Kasper Kjærgaard (Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing—original draft, Writing—review & editing), Jannik Wheler (Conceptualization, Methodology, Writing—original draft, Writing—review & editing), Looket Dihge (Conceptualization, Methodology, Writing—review & editing), Peer Christiansen (Validation, Visualization, Writing—review & editing), Signe Borgquist (Funding acquisition, Supervision, Validation, Writing—review & editing), and Deirdre Cronin-Fenton (Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Writing—original draft, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The data that support the findings of this study are available from Danish registries, but restrictions apply to the availability of these data, which were used under licence for the present study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission.

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