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Published in:
British Journal of Surgery
DOI:
10.1002/bjs.10592
Publication date:
2017
Document Version
Publisher's PDF, also known as Version of record
Citation for published version (APA):
Pedersen, R. N., Bhaskaran, K., Heide-Jørgensen, U., Nørgaard, M., Christiansen, P. M., Kroman, N., ... Cronin-Fenton, D. P. (2017). Breast cancer recurrence after reoperation for surgical bleeding. DOI: 10.1002/bjs.10592
Breast cancer recurrence after reoperation for surgical bleeding

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Background: Bleeding activates platelets that can bind tumour cells, potentially promoting metastatic growth in patients with cancer. This study investigated whether reoperation for postoperative bleeding is associated with breast cancer recurrence.

Methods: Using the Danish Breast Cancer Group database and the Danish National Patient Register (DNPR), a cohort of women with incident stage I–III breast cancer, who underwent breast-conserving surgery or mastectomy during 1996–2008 was identified. Information on reoperation for bleeding within 14 days of the primary surgery was retrieved from the DNPR. Follow-up began 14 days after primary surgery and continued until breast cancer recurrence, death, emigration, 10 years of follow-up, or 1 January 2013. Incidence rates of breast cancer recurrence were calculated and Cox regression models were used to quantify the association between reoperation and recurrence, adjusting for potential confounders. Crude and adjusted hazard ratios according to site of recurrence were calculated.

Results: Among 30711 patients (205926 person-years of follow-up), 767 patients had at least one reoperation within 14 days of primary surgery, and 4769 patients developed breast cancer recurrence. Median follow-up was 7.0 years. The incidence of recurrence was 24.0 (95 per cent c.i. 20.2 to 28.6) per 1000 person-years for reoperated patients and 23.1 (22.5 to 23.8) per 1000 person-years for non-reoperated patients. The overall adjusted hazard ratio was 1.06 (95 per cent c.i. 0.89 to 1.26). The estimates did not vary by site of breast cancer recurrence.

Conclusion: In this large cohort study, there was no evidence of an association between reoperation for bleeding and breast cancer recurrence.

Paper accepted 7 April 2017
Published online 7 August 2017 in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.10592

Introduction

Breast cancer is the most common cancer among women, with about 1.67 million new patients diagnosed in 20121. With 522,000 annual breast cancer-related deaths estimated worldwide, it is the leading cause of cancer-related death in women in developing countries, and second only to lung cancer in more developed regions1.

Surgery, either breast-conserving surgery (BCS) or mastectomy, is the primary treatment for breast cancer. Despite its therapeutic intent, surgery causes physiological stress, which, along with anaesthesia2, can lead to transient immunosuppression during the perioperative period3. Such transient immunosuppression may lead to poorer immune detection of cancer cells3.

Postoperative bleeding requiring reoperation occurs in up to 4 per cent of women undergoing surgery for breast cancer4. Depending on the age of the patient and extent of primary surgery (mastectomy versus BCS)5, the use of certain prescription drugs (such as selective serotonin reuptake inhibitors (SSRIs) or glucocorticoids) increases the risk of postoperative bleeding requiring reoperation5,6. However, there is no evidence of an effect of SSRIs and glucocorticoid use on breast cancer recurrence5–7. Bleeding activates platelets, which can bind tumour cells, promoting immune evasion, angiogenesis, tumour cell survival and metastatic growth8. Cancer is associated with a hypercoagulable state9,10, with heightened platelet activation and a correlation with poor prognosis11. Thus, patients

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methods, procedures, medications, and outcomes. The DBCG database undergoes regular follow-up examinations aimed at detecting recurrent disease. The follow-up examinations are conducted to identify any new cases of breast cancer among patients who have previously been diagnosed with breast cancer. The follow-up examinations are conducted by treating physicians and are based on routinely collected registry data and according to Danish regulations do not require separate ethical approval.

Source population and data collection

The registry of the DBCG and the Danish National Patient Register (DNPR) was used to identify all women with an incident diagnosis of operable stage I–III breast cancer who underwent BCS or mastectomy between 1996 and 2008. To ensure that the data is representative of the entire study population, all non-psychiatric hospital admissions since 1977, and on all outpatient and emergency contacts since 1995, and the Danish Cancer Registry were used to identify all women with breast cancer in Denmark, including breast cancer recurrence. These included: diabetes, liver disease, chronic pulmonary disease, peripheral and cerebral vascular disease, any other cancer, myocardial infarction and congestive heart failure. Information on death and emigration was retrieved from the Civil Registration System (CRS). The CRS, established in 1968, contains information on the vital status of all Danish citizens; it is updated daily.

The National Prescription Registry has automatically recorded detailed information on all prescriptions redeemed at Danish community pharmacies since 1995. Information is transferred electronically into the registry at the time of prescription redemption, so the validity of the registry is extremely high. The registry contains detailed information on dispensed prescriptions, including full Anatomical Therapeutic Chemical codes, and date and quantity dispensed. Data on drugs that potentially confound the association between bleeding and recurrence were retrieved, including simvastatin and aspirin, which may modify breast cancer prognosis, and hormone replacement therapy (HRT).

Variables analysed

Age at diagnosis was categorized into decades. Histological grade was defined as low, moderate or high, based on the primary breast cancer surgery and the rate of recurrence among patients with breast cancer in Denmark.

Methods

This study was approved by the Danish Data Protection Agency (Record 2007-58-0010), the Danish Medicines Agency and the Danish Breast Cancer Group (DBCG). The study is based on routinely collected registry data and according to Danish regulations does not require separate ethical approval.

Setting

This was a nationwide cohort study using Danish population-based registries. Denmark is a country with universal healthcare and the DNPR and DBCG database. The registry contains detailed information on all non-psychiatric hospital admissions since 1977, on all outpatient and emergency contacts since 1995, and the Danish Cancer Registry. The DBCG database allows unambiguous individual-level linkage among all Danish administrative and population-based registries, including medical registries.

Source population and data collection

The registry of the DBCG and the Danish National Patient Register (DNPR) was used to identify all women with an incident diagnosis of operable stage I–III breast cancer who underwent BCS or mastectomy between 1996 and 2008. To ensure correct retrieval of the exposure, defined as reoperation for postoperative bleeding within 14 days following primary breast cancer-directed surgery, patients were considered eligible for inclusion in the study if there was a difference of 1 day or less between the recorded date of primary surgery and the recorded date of primary surgery in the DNPR and DBCG database.

The DBCG has registered almost all women with invasive breast cancer in Denmark since 1977. Data on tumour and patient characteristics are collected prospectively by treating physicians. The completeness of registration is approximately 95 per cent. Patients registered in the DBCG database undergo regular follow-up examinations aimed at detecting recurrent disease. The following information was obtained from the DBCG database: age and menopausal status at diagnosis, type of surgery, WHO histological tumour type and grade, lymph node status, tumour size, oestrogen receptor (ER) status, receipt of adjuvant chemotherapy, endocrine therapy (ET) and/or radiation therapy, and date and site of recurrence.

The DNPR has collected data on all non-psychiatric hospital admissions since 1977, and on all outpatient and emergency contacts since 1995. Data in the DNPR include the CPR number, one primary diagnosis, and one or more secondary diagnoses classified according to the ICD, as well as data on diagnostic and surgical procedures.

The DNPR was used to retrieve information on re-operation for bleeding after surgery (Table S1, supporting information) within 14 days following primary surgery for breast cancer. Information was retrieved from the DNPR on potentially confounding other diseases (co-morbidity) registered up to 10 years before the breast cancer diagnosis. These were summarized using the Charlson Co-morbidity Index (CCI), modified to exclude breast cancer diagnoses. Co-morbidity prevalent on the date of breast cancer surgery was studied in order to detect diseases that could potentially confound or modify the association between bleeding after surgery and a later breast cancer recurrence. These included: diabetes, liver disease, chronic pulmonary disease, peripheral and cerebral vascular disease, any other cancer, myocardial infarction and congestive heart failure (Table S2, supporting information). Information on death and emigration was retrieved from the Civil Registration System (CRS). The CRS, established in 1968, contains information on the vital status of all Danish citizens; it is updated daily.

The National Prescription Registry has automatically recorded detailed information on all prescriptions redeemed at Danish community pharmacies since 1995. Information is transferred electronically into the registry at the time of prescription redemption, so the validity of the registry is extremely high. The registry contains detailed information on dispensed prescriptions, including full Anatomical Therapeutic Chemical codes, and date and quantity dispensed. Data on drugs that potentially confound the association between bleeding and recurrence were retrieved, including simvastatin and aspirin, which may modify breast cancer prognosis, and hormone replacement therapy (HRT) (Table S3, supporting information).

Variables analysed

Age at diagnosis was categorized into decades. Histological grade was defined as low, moderate or high, based on the primary breast cancer surgery and the rate of recurrence among patients with breast cancer in Denmark.
Breast cancer recurrence after reoperation for surgical bleeding

Table 1 Baseline characteristics of 30,711 patients diagnosed with stage I–III breast cancer in Denmark, 1996–2008, according to reoperation for postoperative bleeding

|                          | All patients | Recurrence | Total person-years |
|--------------------------|--------------|------------|--------------------|
|                          | Reoperation  | No reoperation | Reoperation | No reoperation |
| Overall                  | (n = 767)    | (n = 29,944) | (n = 128)       | (n = 4643)     |
| Age at diagnosis (years) |              |            |                  |                |
| ≤ 29                     | 0 (0)        | 98 (0.3)   | 0 (0)           | 32 (0.7)       |
| 30–39                    | 30 (3.9)     | 1357 (4.5)| 8 (0.3)        | 31 (0.7)       |
| 40–49                    | 125 (6.0)    | 1127 (5.7)| 20 (0.9)       | 838 (18.0)     |
| 50–59                    | 229 (5.7)    | 8962 (29.9)| 43 (34.1)      | 1455 (31.3)    |
| 60–69                    | 221 (5.4)    | 9258 (30.9)| 31 (24.6)      | 1357 (29.2)    |
| 70–79                    | 117 (5.1)    | 4254 (14.2)| 23 (18.3)      | 576 (12.4)     |
| ≥ 80                     | 27 (3.5)     | 945 (3.2)  | 1 (0.8)        | 74 (1.6)       |
| Menopausal status at diagnosis |          |            |                  |                |
| Premenopausal            | 191 (24.9)   | 8226 (27.5)| 36 (28.6)      | 1380 (29.7)    |
| Postmenopausal           | 576 (75.1)   | 21,704 (72.5)| 90 (71.4)  | 3262 (70.3)    |
| Missing                  | 0 (0)        | 14 (0.0)   | 0 (0)          | 1 (0.0)        |
| Charlson Co-morbidity Index score |       |            |                  |                |
| 0                        | 589 (76.8)   | 23,913 (79.9)| 110 (87.3) | 3879 (83.5) |
| 1                        | 107 (14.0)   | 3357 (11.2)| 12 (9.5)      | 446 (9.6)      |
| 2                        | 47 (6.1)     | 1683 (5.6) | 2 (1.6)       | 209 (4.5)      |
| ≥ 3                      | 24 (3.1)     | 991 (3.2)  | 2 (1.6)       | 109 (2.3)      |
| Specific co-morbidities  |              |            |                  |                |
| Myocardial infarction    | 15 (2.0)     | 356 (1.2)  | 1 (0.8)       | 42 (0.9)       |
| Congestive heart failure | 18 (2.3)     | 385 (1.3)  | 1 (0.8)       | 35 (0.8)       |
| Vascular disease         | 21 (2.7)     | 518 (1.7)  | 1 (0.8)       | 68 (1.5)       |
| Cerebrovascular disease  | 40 (5.2)     | 1013 (3.4) | 1 (0.8)       | 114 (2.5)      |
| Chronic pulmonary disease| 35 (5.1)     | 1459 (4.9) | 7 (5.6)       | 174 (3.7)      |
| Diabetes type 1 and 2    | 20 (2.6)     | 811 (2.7)  | 1 (0.8)       | 114 (2.6)      |
| Diabetes with organ damage| 8 (1.0)   | 346 (1.2)  | 1 (0.8)       | 41 (0.9)       |
| Liver disease            | 10 (1.3)     | 250 (0.8)  | 1 (0.8)       | 33 (0.7)       |
| Any other cancer         | 24 (3.1)     | 1286 (4.3) | 1 (0.8)       | 154 (3.3)      |

Values in parentheses are percentages.

on WHO histological tumour type28. Stage was classified as I, II or III according to the UICC classification (6th edition)29. Lymph node status was defined according to number of involved nodes (0, 1–3, 4 or more). Tumour size was categorized as 20 mm or less, or over 20 mm. ER and adjuvant ET were summarized as: ER+/ET+, ER−/ET−, ER+/ET− or ER−/ET+. Surgery type was either mastectomy or BCS. Treatment with adjuvant chemotherapy was categorized dichotomously. Menopausal status at diagnosis was either premenopausal or postmenopausal, classified according to the DBCG.

Simvastatin and aspirin use were modelled as time-varying co-variables. Longitudinal prescription data were used to define time-updated exposure to these drugs. For each prescription, prescription duration was calculated as pack size (number of pills per pack) multiplied by the number of packages redeemed, assuming that a single pill was taken each day. In defining continuous use, a gap of 30 days was allowed from the end of one prescription (prescription start date + prescription duration) until the start of a new prescription. If a new prescription was redeemed within this window, then exposure was assumed to continue; if not, the patient was considered to have stopped the drug at the end of the 30-day grace period. The patient could later restart if there were further prescriptions. Finally, the resulting time-updated current medical exposure variable lagged by 1 year to allow the effect of the drug to accrue, as any effects on cancer are likely to be delayed, and to minimize confounding by indication. HRT was recorded as a baseline co-variable among women with at least 1 year of prescription history.

Breast cancer recurrence was defined according to the DBCG as any local, regional or distant recurrence, or death, emigration, 10 years of follow-up or 1 January 2013 (end of the study period), whichever came first.
Table 2  Baseline tumour characteristics and treatments of 30,711 patients diagnosed with stage I–III breast cancer in Denmark, 1996–2008, according to reoperation for postoperative bleeding.

|                         | All patients | Recurrence | Total person-years |
|-------------------------|--------------|------------|-------------------|
|                         | Reoperation  | No reoperation | Reoperation | No reoperation | Reoperation | No reoperation |
|                         | (n = 767)    | (n = 29,944) | (n = 126)        | (n = 4643)    |             |                |
| Overall                 |              |             |                  | 5241          | 200,685     |
| UIICC stage             |              |             |                  |               |             |                |
| I                       | 284 (37.0)   | 10,852 (36.2) | 36 (28.6)        | 1,157 (24.9)  | 2,095       | 78,669         |
| II                      | 367 (47.8)   | 13,465 (45.0) | 52 (41.3)        | 1,844 (39.7)  | 2,539       | 92,554         |
| III                     | 107 (14.0)   | 5,406 (18.1)  | 38 (30.2)        | 1,620 (34.9)  | 550         | 28,262         |
| Missing                 | 9 (1.2)      | 221 (0.7)    | 0 (0)            | 22 (0.5)      | 57          | 1,200          |
| Tumour size (mm)        |              |             |                  |               |             |                |
| ≤ 20                    | 438 (57.1)   | 17,190 (57.4) | 57 (45.2)        | 2,026 (43.6)  | 3,160       | 121,891        |
| > 20                    | 321 (41.9)   | 12,544 (41.9) | 67 (53.2)        | 2,574 (55.4)  | 2,021       | 77,267         |
| Missing                 | 8 (1.0)      | 210 (0.7)    | 2 (1.6)          | 43 (0.9)      | 60          | 1,528          |
| Lymph node status       |              |             |                  |               |             |                |
| Negative                | 405 (52.8)   | 15,522 (51.8) | 51 (40.5)        | 1,807 (38.9)  | 2,963       | 111,142        |
| 1–3 positive nodes      | 255 (33.2)   | 9,147 (30.5)  | 38 (30.2)        | 1,266 (27.3)  | 1,731       | 62,306         |
| ≥ 4 positive nodes      | 104 (13.6)   | 5,151 (17.2)  | 37 (29.4)        | 1,563 (33.7)  | 533         | 26,735         |
| Missing                 | 3 (0.4)      | 124 (0.4)    | 0 (0)            | 7 (0.2)       | 14          | 502            |
| Histological grade      |              |             |                  |               |             |                |
| Low                     | 621 (81.0)   | 24,522 (81.9) | 105 (83.3)       | 3,846 (82.8)  | 4,218       | 163,024        |
| Moderate                | 100 (13.0)   | 3,301 (11.0)  | 11 (8.7)         | 548 (11.8)    | 714         | 22,769         |
| High                    | 44 (5.7)     | 1,992 (6.7)   | 9 (7.1)          | 222 (4.8)     | 297         | 13,972         |
| Missing                 | 2 (0.3)      | 129 (0.4)    | 1 (0.8)          | 27 (0.6)      | 11          | 920            |
| ER/adjuvant ET status   |              |             |                  |               |             |                |
| ER/ET=                  | 134 (17.5)   | 5,818 (19.4)  | 21 (16.7)        | 1,174 (25.3)  | 892         | 35,750         |
| ER+/ET−                 | 184 (24.0)   | 7,143 (23.9)  | 25 (19.8)        | 1,087 (23.4)  | 1,399       | 52,922         |
| ER+/ET+                 | 420 (54.8)   | 15,985 (53.4) | 76 (60.3)        | 2,177 (46.9)  | 2,736       | 104,739        |
| ER−/ET−                 | 5 (0.7)      | 181 (0.6)    | 1 (0.8)          | 27 (0.6)      | 39          | 1,330          |
| Unknown                 | 24 (3.1)     | 817 (2.7)    | 3 (2.4)          | 178 (3.8)     | 174         | 5,944          |
| Type of primary surgery |              |             |                  |               |             |                |
| Mastectomy              | 373 (48.6)   | 10,838 (36.2) | 65 (51.6)        | 1,867 (40.2)  | 2,527       | 74,573         |
| Mastectomy + RT         | 159 (20.7)   | 6,486 (21.7)  | 34 (27.0)        | 1,455 (31.1)  | 1,074       | 41,563         |
| BCS + RT                | 235 (30.6)   | 12,620 (42.1) | 27 (21.4)        | 1,331 (28.7)  | 1,639       | 84,550         |
| Adjuvant chemotherapy   |              |             |                  |               |             |                |
| Yes                     | 220 (28.7)   | 10,075 (33.6) | 33 (26.2)        | 1,628 (35.1)  | 1,509       | 65,009         |
| No                      | 547 (71.3)   | 19,869 (66.4) | 93 (73.8)        | 3,015 (64.9)  | 3,732       | 135,676        |
| HRT before diagnosis    |              |             |                  |               |             |                |
| Yes                     | 316 (41.2)   | 12,452 (41.6) | 37 (29.4)        | 1,634 (35.2)  | 2,220       | 83,790         |
| No                      | 451 (58.8)   | 17,492 (58.4) | 89 (70.6)        | 3,009 (64.8)  | 3,021       | 116,896        |
| Drugs taken during study period | | | | | | |
| Simvastatin             | 148 (19.3)   | 6,286 (21.0)  | 7 (5.6)          | 349 (7.5)     | 538         | 22,527         |
| Aspirin (high and low doses) | 190 (24.8) | 6,233 (20.8)  | 15 (11.9)        | 556 (12.0)    | 532         | 17,613         |

Values in parentheses are percentages. ER, oestrogen receptor; ET, endocrine therapy; RT, radiotherapy; BCS, breast-conserving surgery; HRT, hormone replacement therapy.

Statistical analysis

The proportion of patients with breast cancer who did or did not undergo reoperation for bleeding after surgery was calculated, by patient, tumour and treatment characteristics. Incidence rates (IRs) of recurrence per 1000 person-years were calculated, and the 5- and 10-year cumulative incidence of recurrence was estimated according to whether reoperation for bleeding after primary surgery had been undertaken. IRs were also categorized by time after surgery; recurrences developing within 2 years represented very early recurrence, those diagnosed at 2–5 years comprised early recurrence, and recurrences detected after 5 years represented late recurrence.

The proportion of patients with breast cancer receiving mastectomy and BCS over time was calculated, as was the proportion needing a further operation over time.

Cox regression models with time from start of follow-up as the underlying time scale were used to compute crude and adjusted hazard ratios (HRs) for recurrence.
Table 3  Incidence rates and hazard ratios for breast cancer recurrence, according to reoperation for postoperative bleeding, among 30711 women diagnosed with stage I–III breast cancer in Denmark, 1996–2008 with follow-up to 31 December 2012

| Overall (reoperation within 14 days)† | No. of recurrences | Person-years | Crude incidence rate (per 100 000 person-years) | Unadjusted hazard ratio | Adjusted hazard ratio* |
|--------------------------------------|--------------------|--------------|-----------------------------------------------|------------------------|-----------------------|
| No reoperation                       | 4643               | 200 685      | 23.1 (22.5, 23.8)                             | 1.00 (reference)       | 1.00 (reference)      |
| Reoperation                          | 126                | 5241         | 24.0 (20.2, 28.6)                             | 1.05 (0.88, 1.25)      | 1.06 (0.89, 1.26)     |
| Reoperation within 7 days†           |                    |              |                                               |                        |                       |
| No reoperation                       | 4650               | 201 520      | 23.1 (22.4, 23.7)                             | 1.00 (reference)       | 1.00 (reference)      |
| Reoperation                          | 121                | 4995         | 24.2 (20.3, 28.9)                             | 1.06 (0.88, 1.27)      | 1.08 (0.91, 1.30)     |

Values in parentheses are 95 per cent confidence intervals. Hazard ratios with 95 per cent confidence intervals are shown. *Hazard ratios were adjusted for age (as a categorical variable), menopausal status at diagnosis (premenopausal, postmenopausal), lymph node status (negative, 1–3 positive nodes, at least 4 positive nodes), tumour size (20 mm or smaller, larger than 20 mm), histological grade (low, moderate, high), type of surgery, oestrogen receptor (ER) status and receipt of endocrine therapy (ET) (ER+/ET−, ER+/ET+, ER−/ET−, ER−/ET+), receipt of chemotherapy (yes, no), simvastatin use and aspirin use (both as time-varying co-variables lagging by 1 year), co-morbidity, and receipt of hormone replacement therapy before diagnosis (yes, no).
†The total number of patients with recurrence is not identical here because two patients died or developed a recurrence before the start of follow-up on day 14.

Fig. 1 Forest plot showing associations between reoperation for postoperative bleeding and anatomical site of recurrence. Hazard ratios with 95 per cent confidence intervals are shown. Hazard ratios were adjusted for age (as a categorical variable), menopausal status at diagnosis (premenopausal, postmenopausal), lymph node status (negative, 1–3 positive nodes, at least 4 positive nodes), tumour size (20 mm or smaller, larger than 20 mm), histological grade (low, moderate, high), type of surgery, oestrogen receptor (ER) status and receipt of endocrine therapy (ET) (ER+/ET−, ER+/ET+, ER−/ET−, ER−/ET+), receipt of chemotherapy (yes, no), simvastatin use and aspirin use (both as time-varying co-variables lagging by 1 year), co-morbidity, and receipt of hormone replacement therapy before diagnosis (yes, no). CNS, central nervous system

and associated 95 per cent confidence intervals for reoperation for postoperative bleeding. To model the cause-specific hazard, patients who died without a breast cancer recurrence were censored at the date of death. The adjusted model included the following potential confounders: age group at diagnosis, menopausal status, receipt of chemotherapy, lymph node status, tumour size, tumour grade, type of primary surgery, ER/ET status, co-morbidity, baseline HRT, and simvastatin and aspirin use after diagnosis (coded as time-varying co-variables lagging by 1 year). The analyses were stratified by age, receipt of chemotherapy, UICC stage and type of primary surgery. Crude and adjusted HRs according to site of recurrence were calculated.

The following sensitivity analyses were conducted: changing the 14-day window for reoperation and start of follow-up to 7 days after primary surgery; changing the inclusion criteria from no more than 1 day difference between the recorded date of primary surgery in the DNPR and the DBCG database to no more than 14 days and no more than 31 days; changing the study population to include only patients with stage I and II disease at diagnosis; and excluding patients with previous cancers.
Analyses were performed using Stata® version 13 (StataCorp, College Station, Texas, USA).

**Results**

A total of 33,162 patients with breast cancer who underwent BCS or mastectomy between 1996 and 2008 were identified. The cohort consisted of 30,711 women after exclusion of 2,425 women with more than 1 day difference in the date of surgery, or inconsistency in type of surgery, between the DNPR and the DBCG database, and 26 women who died or had an event registered before the start of follow-up (within 14 days after primary breast cancer surgery). The proportion of patients treated with BCS versus mastectomy increased in recent years accompanied by a decline in the rate of reoperation. Median follow-up was 7.0 years.

**Reoperation after surgery**

Overall, 767 patients (2.5 per cent) had at least one reoperation within 14 days of the primary surgery. Compared with women who were not reoperated, a higher proportion of patients who underwent reoperation were postmenopausal (75.1 versus 72.5 per cent), and had co-morbid disease (CCI score of at least 1: 23.2 versus 20.1 per cent), a history of cerebrovascular disease (5.2 versus 3.4 per cent) and moderate-grade tumours (13.0 versus 11.0 per cent) (Tables 1 and 2). Reoperated patients were more likely to have undergone mastectomy than BCS as primary surgery (69.3 versus 57.9 per cent) and less likely to receive chemotherapy (28.7 versus 33.6 per cent). A higher proportion of patients without reoperation had stage III cancer (18.1 versus 14.0 per cent). Overall, 21.0 per cent of women in the breast cancer cohort had been prescribed aspirin or simvastatin during follow-up, and 41.6 per cent had been prescribed HRT before the breast cancer diagnosis. Reoperated patients were more likely to be concurrent aspirin users.

**Recurrence after reoperation for bleeding**

Overall, 4,769 patients developed breast cancer recurrence during follow-up. The IR of recurrence was 24.0 (95 per cent c.i. 20.2 to 28.6) and 23.1 (22.5 to 23.8) per 1000 person-years for reoperated and non-reoperated patients respectively (Table 3). Regardless of reoperation status, the
incidence rate was higher in the first 2 years after surgery, followed by a decrease (Table S4, supporting information). The 1-year IR of recurrence was 29.1 (13.1 to 44.1) and 21.3 (19.7 to 23.1) per 1000 person-years for reoperated and non-reoperated patients respectively. The IR of recurrence in the second year after primary surgery was 40.7 (28.3 to 58.6) per 1000 person-years for reoperated patients and 34.7 (32.6 to 36.9) per 1000 person-years for non-reoperated patients. After 5 years of follow-up, the IRs for patients who did and did not undergo reoperation were similar: 27.7 (22.6 to 33.9) and 26.9 (26.1 to 27.8) per 1000 person-years respectively. The 5-year cumulative incidence of recurrence was 12.8 and 12.5 per cent for patients with and without reoperation respectively; the 10-year cumulative incidence of recurrence was 19.9 per cent for reoperated patients and 18.9 per cent for non-reoperated patients (Table S5, supporting information).

Among 767 patients who underwent reoperation, there were 126 recurrences in 5241 person-years of follow-up. Among 29444 women who did not undergo reoperation, there were 4643 recurrences in 200685 person-years of follow-up. After adjusting for potential confounders, no association between bleeding after surgery and breast cancer recurrence was observed (adjusted HR 1.06, 95 per cent c.i. 0.89 to 1.26), regardless of time interval of exposure (7 or 14 days after primary operation) (Table 3). This lack of association did not change in sensitivity analyses in which the study population included only patients with stage I and II disease at diagnosis, patients with previous cancers were excluded, or patients with a difference in surgery date between the DNPR and DBCG database of no more than 14 days and no more than 31 days were included (Table S6, supporting information). The estimates did not vary by site of breast cancer recurrence (Fig. 1), and there was no evidence of effect modification in models stratified by age, tumour stage, type of primary surgery or receipt of chemotherapy (Fig. 2).

Discussion

Previous research in Danish patients reported an association between re-excision (owing to insufficient surgical margins within 2 months of BCS) and increased risk of ipsilateral breast tumour recurrence. This finding was, however, largely explained by residual disease. The hypothesis for the present study was that patients who undergo reoperation for postoperative bleeding would be at increased risk of ipsilateral breast tumour recurrence. No evidence was found of an association between reoperation for bleeding after surgery and later breast cancer recurrence, regardless of time interval of exposure (7 or 14 days after the primary operation). Furthermore, the estimates did not vary in analyses stratified by clinical factors, the extent of primary surgery, or by site of breast cancer recurrence. A slight increase in early recurrence among reoperated patients was observed, but the estimates are imprecise.

Research suggests that mastectomy is associated with a higher risk of intraoperative bleeding and postoperative complications than BCS. However, mastectomy alone and BCS combined with radiotherapy have equal efficacy in terms of preventing breast cancer recurrence. Results from the present study show that the association of postoperative bleeding with breast cancer recurrence is not modified by the extent of primary surgery.

The associations observed for reoperation and breast cancer recurrence are not in line with those seen in patients undergoing surgery for gastrointestinal cancers. For example, intraoperative blood loss associated with surgery for upper gastrointestinal tract tumours decreases the activity of natural killer cells, which are the body’s primary defence mechanism against cancer. Research suggests that blood loss during surgery, regardless of whether blood transfusion is given, is a risk factor for peritonel recurrence after curative resection of gastric cancer. The mechanisms for the lack of concordance between these findings and those of the present study on breast cancer are unclear. Blood loss that can be controlled by further operation could be less extensive than blood loss that is sufficient to warrant a blood transfusion.

The main strengths of this study include its large size and population-based nationwide design within a setting of universal tax-supported healthcare. The prospective data collection reduced the potential for selection bias and ensured virtually complete follow-up. Furthermore, comprehensive data on potential confounders, including prescription drug data, were available. The crude estimates were quite similar to the adjusted estimates, and thus there was little evidence of confounding. It is also a strength that reoperation for bleeding after surgery has a surgical procedure code and is therefore well recorded in the database. Although the positive predictive value of this specific procedure code has not been assessed in the DNPR, it is expected to be high, as hospitals in Denmark are reimbursed only after registration of surgical procedures. It is nevertheless possible that other operative procedures could be misclassified as reoperation owing to postoperative bleeding. These include the codes for reoperation for postoperative infection or reoperation owing to other causes, which may include insufficient surgical margins (Table S1, supporting information). However, the latter misclassification is likely to bias the present
findings away from the lack of effect of reoperation as residual disease is well known to be associated with recurrence. The impact of postoperative infection on later breast cancer recurrence remains unclear.

Earlier studies used blood transfusion as a proxy for perioperative bleeding. However, in the case of breast cancer surgery, perioperative bleeding does not always result in blood transfusion. Furthermore, patients who receive blood transfusions are often sicker, with disseminated cancer, and more extensive co-morbidity.

The present study has some limitations. Information was missing on the extent of postoperative bleeding, in terms of actual blood loss. There was no information available on surgical complications that may have precipitated such bleeding. Another concern is the risk of selection bias due to exclusion of patients; however, the excluded patients were younger, had less advanced disease stages at diagnosis, and were less likely to receive mastectomy and ET (Table S7, supporting information). The sensitivity analyses also showed that the inclusion of these patients did not change the present findings (Table S6, supporting information). No information was available on the type of axillary surgery. However, from 2001 to 2006 the sentinel node technique was gradually introduced in Denmark. During the study interval, all women with metastasis of any size in the axilla were offered axillary clearance level I+II as standard care.

Aspirin has been shown to decrease the risk of breast cancer mortality in some studies, but not all. Simvastatin has been consistently associated with a decreased risk of breast cancer recurrence/mortality. Information on prescribed aspirin was available, but it was not possible to account for aspirin bought over the counter. Aspirin formulations are available over the counter in Denmark, but, if prescribed, almost exclusively done so in low doses for cardiovascular prevention. Over-the-counter aspirin is available only in small packs, and supplies for regular use are usually prescribed by physicians and reimbursable via the Danish National Health Insurance System. The proportions of total sales of low-dose aspirin dispensed by prescription, and thus captured in prescription registries, is high (92% per cent in 2012), so residual confounding regarding aspirin is expected to be a minor issue. No information on prescription compliance was available. In Denmark, patients pay part of the cost of redeemed prescriptions, so the estimates are likely to reflect actual use. Adjustment for prescribed aspirin and simvastatin did not change the findings. Finally, despite the large study size, reoperation for postoperative bleeding was relatively rare in this population and thus the precision of some of the estimates is low.

The findings of the present study have important clinical implications, and provide reassurance to patients and physicians that reoperation for postoperative bleeding does not increase the risk of breast cancer recurrence. Patients who undergo reoperation for bleeding are unlikely to need more aggressive adjuvant therapy. Breast cancer surgery involves a soft tissue surface and is often characterized by extensive dissection, which increases the risk of postoperative bleeding; the results may therefore be relevant to other soft tissue surgical procedures.

Acknowledgements

This work was supported by grants from the Danish Cancer Society (R117-A7305-14-S7, R91-A7311-14-S9; to R.N.P.), the Novo Nordisk Foundation (NNF14OC0012281; to D.P.C.-F.), the Lundbeck Foundation (R167-2013-15861; to D.P.C.-F.), the Elfira and Rasmus Riisforts Foundation (to D.P.C.-F.), the Helga and Peter Knorning Foundation (to D.P.C.-F.), the Programme for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation (to H.T.S.), Torben og Alice Frimodts Foundation (to R.N.P.), Fred og Ellen Hindgauds Foundation (to R.N.P.), the Oticon Foundation (to R.N.P.), and the Foundation of 1870 (to R.N.P.). K.B. is funded by a Wellcome Trust/Royal Society Sir Henry Dale fellowship (107731/Z/15/Z). The funding agencies had no role in design of the study; the collection, analysis and interpretation of the data; the writing of the article; or the decision to submit the article for publication.

The Department of Clinical Epidemiology is involved in studies that receive funding from various companies as research grants to (and administered by) Aarhus University. None of these studies have any relation to the present work.

Disclosure: The authors declare no other conflict of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359–E386.
2. Colvin LA, Fallon MT, Buggy DJ. Cancer biology, analgesics, and anaesthetics: is there a link? Br J Anaesth 2012; 109: 140–143.
3. Ash SA, Buggy DJ. Does regional anaesthesia and analgesia or opioid analgesia influence recurrence after primary cancer surgery? An update of available evidence. Best Pract Res Clin Anaesthesiol 2013; 27: 441–456.
4. Hoffmann J. Analysis of surgical and diagnostic quality at a specialist breast unit. Breast 2006; 15: 490–497.
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5 Winther Lietzen L, Cronin-Fenton D, Garne JP, Kroman N, Silliman R, Lash TL. Predictors of re-operation due to post-surgical bleeding in breast cancer patients: a Danish population-based cohort study. *Er J Surg Oncol* 2012; 38: 407–412.

6 Gärnter R, Cronin-Fenton D, Hundborg HH, Pedersen L, Lash TL, Sørensen HT et al. Use of selective serotonin reuptake inhibitors and risk of re-operation due to post-surgical bleeding in breast cancer patients: a Danish population-based cohort study. *BMC Surg* 2010; 10: 3.

7 Lash TL, Pedersen L, Cronin-Fenton D, Ahern TP, Rosenberg CL, Lunetta KL et al. Tamoxifen’s protection against breast cancer recurrence is not reduced by concurrent use of the SSRI citalopram. *Br J Cancer* 2008; 99: 616–621.

8 Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. *Nat Rev Cancer* 2011; 11: 123–134.

9 Sørensen HT, Møller S, Jensen MB, Ejlertsen B, Bjerre KD, Larsen M, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. *N Engl J Med* 1998; 338: 1169–1173.

10 Cronin-Fenton DP, Søndergaard F, Pedersen LA, Fryzek JP, Cetin K, Aquavella J et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997–2006. *Br J Cancer* 2010; 103: 947–953.

11 Sørensen HT, Mellemkjaer L, Olesen JH, Nielsen P, Nielsen GL. Influence of concurrent use of the SSRI citalopram. *Br J Cancer* 2011; 104: 947–953.

12 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Er J Epidemiol* 2014; 29: 541–549.

13 Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000; 287: 2398–2399.

14 Møller S, Jensen MB, Ejlertsen B, Bjerre KD, Larsen M, Hansen HIB et al.; Danish Breast Cancer Cooperative Group. The clinical database and the treatment guidelines of the Danish Breast Cancer Cooperative Group (DBCG); its 30-years experience and future promise. *Acta Oncol* 2008; 47: 506–524.

15 Blichert-Toft M, Nielsen M, Düring M, Møller S, Rank F, Overgaard M et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. *Acta Oncol* 2008; 47: 672–681.

16 Danish Breast Cancer Cooperative Group. *Danish Breast Cancer Cooperative Group Kvalitetsindikatorrapport for Bryskreft*. 2012. www.dbcg.dk [accessed 31 October 2016].

17 Sundhedsstyrelsen. *Opfølgingsprogram for byrskreft*. 2015. www.sundhedsstyrelsen.dk.

18 Lynge E, Søndegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; 39(Suppl 7): 30–33.

19 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.

20 Kiderlen M, de Glas NA, Bastiaannet E, Engels CC, van de Water W, de Craen AJ et al. Diabetes in relation to breast cancer in women: a Danish population-based cohort study. *BMJ* 2015; 351: h6006.

21 Kaplan MA, Pekkola Z, Kucukoner M, Inal A, Urakci Z, Ertugru H et al. Type 2 diabetes mellitus and prognosis in early stage breast cancer women. *Med Oncol* 2012; 29: 1576–1580.

22 Jiralerspong S, Kim ES, Dong W, Feng L, Hordobagyi GN, Giordano SH. Obesity, diabetes, and survival outcomes in a large cohort of early-stage breast cancer patients. *Ann Oncol* 2013; 24: 2506–2514.

23 Lopez-Delgado JC, Esteve F, Favier C, Ventura JL, Mañez R, Farrero E et al. Influence of cirrhosis in cardiac surgery outcomes. *World J Hepatol* 2015; 7: 753–760.

24 Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; 39(Suppl 7): 38–41.

25 Pottegård A, Schmidt SA, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol* 2016; [Epub ahead of print].

26 Holmes MD, Chen WY, Li L, Hertzmark E, Spiegelman D, Hankinson SE. Aspirin intake and survival after breast cancer. *J Clin Oncol* 2010; 28: 1467–1472.

27 Ahern TP, Pedersen L, Tarp M, Cronin-Fenton DP, Garne JP, Silliman RA et al. Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study. *J Natl Cancer Inst* 2011; 103: 1461–1468.

28 Tavassoli FA, Devilee P (eds). *Pathology and Genetics of Tumours of the Breast and Female Genital Organs*. WHO/IARC Classification of Tumours (3rd edn), vol. 4. IARC Publications: Lyon, 2003.

29 Sobin LH, Gospodarowicz MK, Wittekind C (eds). *TNM Classification of Malignant Tumours* (6th edn). John Wiley & Sons, Hoboken, 2002.

30 Rugo H. The risk of early recurrence and distant metastases – lessons from the monotherapy adjuvant aromatase inhibitor trials with a focus on BIG I–98. *US Oncological* 2006; 1: 12.

31 Bodilsen A, Bjerre K, Offeresen BV, Vahl P, Ejlertsen B, Overgaard J et al. The influence of repeat surgery and residual disease on recurrence after breast-conserving surgery: a Danish Breast Cancer Cooperative Group Study. *Ann Surg Oncol* 2015; 22(Suppl 3): S476–S485.

32 Chen Z, Xu Y, Shu J, Xu N. Breast-conserving surgery versus modified radical mastectomy in treatment of early stage breast cancer: a retrospective study of 107 cases. *J Cancer Res Ther* 2015; 11(Suppl 1): C29–C31.

33 Chatterjee A, Pyfer B, Czerniecki B, Rosenkranz K, Tchou J, Fisher C. Early postoperative outcomes in lumpectomy versus simple mastectomy. *J Surg Res* 2015; 198: 143–148.
34 Pyfer B, Chatterjee A, Chen L, Nigriny J, Czerniecki B, Tchou J et al. Early postoperative outcomes in breast conservation surgery versus simple mastectomy with implant reconstruction: a NSQIP analysis of 11,645 patients. *Ann Surg Oncol* 2016; 23: 92–98.

35 Litière S, Werutsky G, Fentiman IS, Rutgers E, Christiaens MR, Van Limbergen E et al. Breast conserving therapy versus mastectomy for stage I–II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol* 2012; 13: 412–419.

36 Bruns CJ, Schäfer H, Wolfgarten B, Engert A. Effect of intraoperative blood loss on the function of natural killer cells in tumours of the upper gastrointestinal tract. *Langenbecks Arch Chir Suppl Kongressbd* 1996; 113: 146–149.

37 Kamei T, Kitayama J, Yamashita H, Nagawa H. Intraoperative blood loss is a critical risk factor for peritoneal recurrence after curative resection of advanced gastric cancer. *World J Surg* 2009; 33: 1240–1246.

38 Andreasen JJ, Riis A, Hjortdal VE, Jørgensen J, Sørensen IT, Johnsen SP. Effect of selective serotonin reuptake inhibitors on requirement for allogeneic red blood cell transfusion following coronary artery bypass surgery. *Am J Cardiovac Drugs* 2006; 6: 243–250.

39 Movig KL, Janssen MW, de Waal Malefijt J, Kabel PJ, Leufkens HG, Egberts AC. Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. *Arch Intern Med* 2003; 163: 2354–2358.

40 Friis E, Galatius H, Garne JP. Organized nation-wide implementation of sentinel lymph node biopsy in Denmark. *Acta Oncol* 2008; 47: 556–560.

41 Murray L, Cooper JA, Hughes CM, Powell DG, Cardwell CR. Post-diagnostic prescriptions for low-dose aspirin and breast cancer-specific survival: a nested case–control study in a breast cancer cohort from the UK Clinical Practice. *Breast Cancer Res* 2014; 16: R34.

42 Cronin-Fenton DP, Heide-Jørgensen U, Ahern TP, Lash TL, Christiansen P, Ejlertsen B et al. Low-dose aspirin, nonsteroidal anti-inflammatory drugs, selective COX-2 inhibitors and breast cancer recurrence. *Epidemiology* 2016; 27: 586–593.

43 Ahern TP, Lash TL, Damkier P, Christiansen PM, Cronin-Fenton DP. Statins and breast cancer prognosis: evidence and opportunities. *Lancet Oncol* 2014; 15: e461–e468.

44 Schmidt M, Hallas J, Friis S. Potential of prescription registries to capture individual-level use of aspirin and other nonsteroidal anti-inflammatory drugs in Denmark: trends in utilization 1999–2012. *Clin Epidemiol* 2014; 6: 155–168.

Supporting information

Additional supporting information may be found online in the supporting information tab for this article.

Table S1 ICD-10 codes for surgical procedures among women with stage I, II or III breast cancer in Denmark, 1996–2008 (Word document)

Table S2 ICD codes for co-morbidities (Word document)

Table S3 Confounder drugs (Word document)

Table S4 Incidence of breast cancer recurrence for patients with stage I, II or III breast cancer in Denmark, 1996–2008, according to need for reoperation for postoperative bleeding, stratified by time after surgery (Word document)

Table S5 Five- and 10-year cumulative incidence of breast cancer recurrence for patients with stage I, II or III breast cancer in Denmark, 1996–2008, according to need for reoperation for postoperative bleeding (Word document)

Table S6 Breast cancer recurrences and hazard ratios for patients with stage I and II breast cancer, for patients without any previous cancers, and for patients with more than 1 day between the primary surgery date registered in the Danish National Patient Register and the Danish Breast Cancer Group database (in Denmark, 1996–2008), according to need for reoperation for postoperative bleeding (Word document)

Table S7 Comparison of baseline characteristics of patients retained in the cohort versus those excluded (Word document)