Supplementary Material

The incidence of breast cancer recurrence 10-32 years after primary diagnosis

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Table of contents

Supplementary Methods .......................................................................................................................... 3

Data sources ............................................................................................................................................. 3

Covariates .................................................................................................................................................. 3

Multiple imputation .................................................................................................................................. 4

References ................................................................................................................................................... 5

Supplementary Table 1. Sensitivity analyses .......................................................................................... 7

Supplementary Figure 1. Flowchart of the breast cancer cohort and 10-year disease-free survivor cohort ........................................................................................................................................... 8

Supplementary Figure 2. The 10-25 year cumulative incidence of late breast cancer recurrence among 10,963 women diagnosed with early stage estrogen receptor-positive breast cancer between 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis ................................................................. 9

Supplementary Figure 3. The 10-20 year cumulative incidence of late breast cancer recurrence among 10,963 women diagnosed with early stage estrogen receptor (ER)-positive breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis ................................................................................................................................. 10

Supplementary Figure 4. Hazard ratios of late breast cancer recurrence, according to clinico-pathological factors at baseline, among 10,963 women diagnosed with early stage estrogen receptor (ER)-positive breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis ........................................................................................................................................ 13

Supplementary Figure 5. Hazard ratios for distant late breast cancer recurrence, according to clinico-pathological factors at baseline, among 20,315 women diagnosed with early stage breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis ........................................................................................................................................ 15

Supplementary Figure 6. Hazard ratios for loco-regional late breast cancer recurrence, according to clinico-pathological factors at baseline, among 20,315 women diagnosed with early stage breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis ........................................................................................................................................ 17

Supplementary Figure 7. The 10-32 year cumulative incidence of any breast cancer event after, among 20,315 women diagnosed with early stage breast cancer between 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis ........................................................................................................................................ 19

Supplementary Figure 8. The 10-25 year cumulative incidence of any breast cancer event after ten years among 20,315 women diagnosed with early stage breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis ........................................................................................................................................ 20

Supplementary Figure 9. Hazard ratios of any breast cancer event after ten years, according to clinico-pathological factors at baseline, among 20,315 women diagnosed with early stage breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis ........................................................................................................................................ 24

Supplementary Figure 10. Hazard ratios of late breast cancer recurrence, according to clinico-pathological factors at baseline, regarding to imputed and not imputed data ........................................................................................................................................ 26
Supplementary Methods

Data sources

The DBCG\(^1\) has prospectively registered data on invasive breast cancers diagnosed in Denmark since 1976 including data on tumor and patient characteristics. The completeness of registration is high.\(^2\) The DNPR has collected data on all non-psychiatric hospital admissions since 1977 and all outpatient and emergency admissions since 1995.\(^3\) Data in the DNPR include the CPR number, one primary diagnosis, and one or more secondary diagnoses, as well as data on diagnostic and surgical procedures. Since 1997, the Danish Pathology Registry (DPR) has recorded information on all pathology examinations in Denmark using the Systematized Nomenclature of Medicine (SNOMED) classification system.\(^4\) The Danish Cancer Registry (DCR) has obtained information on incident cancers since 1943, and has high registration completeness.\(^5\) The Danish Civil Registration system established in 1968 includes information on vital status and emigration.\(^6\) The Danish Register of Causes of Death registers information on deaths in Denmark since 1970.\(^7\) A database on contralateral breast cancer (CBC) with CBCs since 1978 in Denmark based on information in several registries has previously been established.\(^8\)

Covariates

We used the DBCG to obtain information on patient, tumor and treatment characteristics, including age, and menopausal status at diagnosis, WHO histological tumor type and malignancy grade, lymph node status, tumor size, type of surgery, ER status (ER positive \(\geq 10\%\)), receipt of adjuvant chemotherapy, endocrine therapy (ET), and radiation therapy. Stage was derived from the tumor size and number of involved lymph nodes according to the American Joint Committee on Cancer (AJCC) staging system.\(^9\) ER status was first routinely registered from 1997. We obtained information from the DNPR on potentially confounding comorbid diseases, and summarized these using the Charlson Comorbidity Index (CCI).\(^{10}\)
modified to exclude breast cancer diagnosis. The CCI score was calculated at the date of initial breast cancer diagnosis and ten years after primary diagnosis for 10-year disease-free survivors. Information about emigration and vital status was obtained from the Civil Registration System.

**Multiple imputation**

We imputed missing data on estrogen receptor status (35% missing among 10-year disease-free survivors) and grade (3% missing among 10-year disease-free survivors) used for adjustment in the Cox regression models to minimize selection bias and maximize power. We used imputation by chained equations method. We assumed that missing data was missing at random (MAR), meaning that the probability of a data point being missing does not depend on the missing data point, but depends only on the observed data. All covariates (including exposures and outcomes) that were included in the analytic model were included in the imputation (menopausal status, lymph node status, tumor size, age, comorbidity, calendar year, surgery type, endocrine therapy, chemotherapy, and outcomes—late recurrence/death/CBC/other second cancer). To ensure acceptable Monte Carlo error from imputation we created fifty imputed datasets. The imputed models were validated by comparing the mean of the first and last imputed dataset with the complete dataset.
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**Supplementary Table 1.** Sensitivity analyses

| Sensitivity analyses                                      | Person-time | Events | Incidence rate per 1000 PY (95% CI) | Absolute risk, % (95% CI) |
|----------------------------------------------------------|-------------|--------|------------------------------------|---------------------------|
| Using breast cancer specific death as an indicator for recurrence | 167,093     | 2,803  | 16.8 (16.2-17.4)                   | 18.0 (17.2-18.9)          |
| Any breast cancer event (including CBC)                   | 167,091     | 3,718  | 22.3 (21.5-23.0)                   | 25.8 (24.6-26.9)          |
| ER-positive tumor defined as ≥1% tumor cells demonstrate positive nuclear staining |             |        |                                    |                           |
| Positive                                                 | 73,513      | 1,423  | 19.4 (18.4-20.4)                   | 17.2 (16.0-18.4)          |
| Negative                                                 | 22,137      | 163    | 7.4 (6.3-8.6)                      | 7.8 (6.4-9.3)             |

\[a\] 10-32 year cumulative incidence. CBC = Contralateral breast cancer; CI = confidence interval; ER = estrogen receptor; PY = Person-years

\[b\] 10-25 year cumulative incidence
Supplementary Figure 1. Flowchart of the breast cancer cohort and 10-year disease-free survivor cohort. Abbreviations: CBC, Contralateral breast cancer; DBCG, Danish Breast Cancer Group; DNPR, Danish National Patient Registry.

N =36,924
Women with an incident early stage operable breast cancer diagnosed during 1987-2004 and registered in the DBCG database

N =20,315
Women survived 10 years without a recurrence, CBC, or other new primary tumor

n = 9,072
Women was registered with a recurrence in DBCG or a metastasis in DNPR within the first ten years

n = 3,824 women
Developed a CBC or other new primary tumor within the first ten years

n = 3,649
Died

n = 64
Women emigrated
Supplementary Figure 2. The 10-25 year cumulative incidence of late breast cancer recurrence among 10,963 women diagnosed with early stage estrogen receptor-positive breast cancer between 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis.
Supplementary Figure 3. The 10-20 year cumulative incidence of late breast cancer recurrence among 10,963 women diagnosed with early stage estrogen receptor (ER)-positive breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis, stratified according to A) T1 tumors (tumor diameter ≤2.0 cm) and nodal status (N0, no nodes; N1-3, 1 to 3 nodes; N4-9, 4 to 9 nodes), B) T2 tumors (tumor diameter, >2.0 cm to 5.0 cm) and nodal status (N0, no nodes; N1-3, 1 to 3 nodes; N4-9, 4 to 9 nodes), C) Malignancy grade (grade I, II, III or not graded), D) Tumor size (≤20mm or >20mm), E) Lymph node status (N0, N1-3, N≥4), and F) Type of primary surgery (mastectomy + RT, mastectomy, or BCS + RT) aNo confidence intervals are showed due to close lines. bThe unknown category is not shown. Abbreviations: BCS, breast conserving surgery; No., number; RT, radiation therapy.
Supplementary Figure 4. Hazard ratios of late breast cancer recurrence, according to clinico-pathological factors at baseline, among 10,963 women diagnosed with early stage estrogen receptor (ER)-positive breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis. Adjusted for age, calendar period, menopausal status, CCI (ten years after primary diagnosis), stage, grade, endocrine therapy, type of primary surgery and chemotherapy except for the one actually examined. When we examined lymph node status we did not adjust for stage but adjusted for tumor size, when we examined tumor size we did not adjust for stage but lymph node status, when we examined stage we did not adjust for lymph node status and tumor size. The unknown category is not shown. Error bars represent the 95% confidence intervals. Abbreviations: HR, hazard ratio; CI, confidence interval, CCI, Charlson Comorbidity Index; RT, radiation therapy; BCS, breast conserving surgery.
| Baseline characteristics | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|--------------------------|-------------|-------------------|---------------------|
| **Age at diagnosis (years)** |             |                   |                     |
| <40                      | 84 / 435    | 1.41 (1.12 - 1.78)| 1.60 (1.21 - 2.10) |
| 40-49                    | 337 / 2327  | 1.04 (0.91 - 1.19)| 1.10 (0.91 - 1.33) |
| 50-59                    | 519 / 3846  | 1.00              | 1.00                |
| 60-69                    | 398 / 3192  | 0.92 (0.80 - 1.05)| 0.94 (0.81 - 1.08) |
| ≥70                      | 99 / 1163   | 0.82 (0.66 - 1.02)| 0.85 (0.68 - 1.06) |
| **Calendar period**      |             |                   |                     |
| 1987-1991                | 6 / 64      | 0.55 (0.25 - 1.25)| 0.58 (0.26 - 1.32) |
| 1992-1996                | 321 / 2001  | 0.95 (0.83 - 1.10)| 1.00 (0.86 - 1.15) |
| 1997-2001                | 685 / 4958  | 1.00              | 1.00                |
| 2002-2004                | 393 / 3950  | 0.97 (0.85 - 1.10)| 0.92 (0.81 - 1.06) |
| **Menopausal status**    |             |                   |                     |
| Pre-menopausal           | <550 / 13560| 1.12 (1.01 - 1.25)| 1.04 (0.82 - 1.32) |
| Post-menopausal          | <900 / 7500 | 1.00              | 1.00                |
| **CCI**                  |             |                   |                     |
| 0                        | 1079 / 7988 | 1.00              | 1.00                |
| 1-2                      | 289 / 2551  | 0.84 (0.63 - 1.08)| 0.96 (0.74 - 1.20) |
| ≥3                       | 38 / 424    | 0.92 (0.67 - 1.27)| 0.94 (0.68 - 1.31) |
| **Stage**                |             |                   |                     |
| I                        | 508 / 5150  | 1.00              | 1.00                |
| II                       | 647 / 4713  | 1.49 (1.33 - 1.67)| 1.57 (1.36 - 1.82) |
| III                      | 244 / 1047  | 2.81 (2.41 - 3.27)| 3.04 (2.51 - 3.69) |
| **Tumor size**           |             |                   |                     |
| ≤20mm                    | 871 / 7596  | 1.00              | 1.00                |
| >20mm                    | 534 / 3394  | 1.46 (1.31 - 1.62)| 1.36 (1.20 - 1.53) |
| **Grade**                |             |                   |                     |
| Grade I                  | 495 / 3907  | 1.00              | 1.00                |
| Grade II                 | 531 / 4110  | 1.08 (0.96 - 1.22)| 1.00 (0.88 - 1.14) |
| Grade III                | 115 / 915   | 1.01 (0.82 - 1.25)| 0.85 (0.69 - 1.05) |
| Not graded               | 242 / 1732  | 1.08 (0.93 - 1.26)| 1.07 (0.91 - 1.25) |
| **Lymph node status**    |             |                   |                     |
| Negative                 | 677 / 6990  | 1.00              | 1.00                |
| 1-3 positive nodes       | <500 / 3282 | 1.62 (1.44 - 1.82)| 1.73 (1.49 - 2.02) |
| ≥4 positive nodes        | <250 / 885  | 2.72 (2.34 - 3.16)| 2.91 (2.41 - 3.52) |
| **Endocrine therapy**    |             |                   |                     |
| Yes                      | 772 / 5854  | 1.33 (1.20 - 1.48)| 1.04 (0.90 - 1.21) |
| No                       | 633 / 5109  | 1.00              | 1.00                |
| **Type of primary surgery** |         |                   |                     |
| Mastectomy+RT            | 308 / 1961  | 1.59 (1.38 - 1.83)| 1.06 (0.89 - 1.25) |
| Mastectomy               | 505 / 4494  | 1.00              | 1.00                |
| BCS                      | 591 / 4508  | 1.25 (1.11 - 1.41)| 1.30 (1.14 - 1.47) |
| **Adjuvant chemotherapy** |           |                   |                     |
| Yes                      | 302 / 2154  | 1.13 (0.99 - 1.28)| 0.80 (0.66 - 0.97) |
| No                       | 1103 / 8259 | 1.00              | 1.00                |
Supplementary Figure 5. Hazard ratios for distant late breast cancer recurrence, according to clinico-pathological factors at baseline, among 20,315 women diagnosed with early stage breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis. Adjusted for age, calendar period, menopausal status, CCI (ten years after primary diagnosis), stage, grade, estrogen receptor status, endocrine therapy, type of primary surgery and chemotherapy except for the one actually examined. When we examined lymph node status we did not adjust for stage but adjusted for tumor size, when we examined tumor size we did not adjust for stage but lymph node status, when we examined stage we did not adjust for lymph node status and tumor size. The unknown category is not shown. Error bars represent the 95% confidence intervals. Abbreviations: HR, hazard ratio; CI, confidence interval, CCI, Charlson Comorbidity Index; RT, radiation therapy; BCS, breast conserving surgery.
| Baseline characteristics | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|--------------------------|-------------|-------------------|---------------------|
| **Age at diagnosis (years)** |             |                   |                     |
| <40                      | 64 / 1122   | 0.81 (0.63 - 1.06) | 1.03 (0.76 - 1.40)  |
| 40-49                    | 363 / 5125  | 1.01 (0.88 - 1.16) | 1.12 (0.92 - 1.36)  |
| 50-59                    | 440 / 6882  | 1.00              | 1.00                |
| 60-69                    | 306 / 5519  | 0.98 (0.85 - 1.14) | 0.93 (0.80 - 1.09)  |
| >70                      | 63 / 1667   | 0.85 (0.66 - 1.11) | 0.79 (0.60 - 1.04)  |
| **Calendar period**      |             |                   |                     |
| 1987-1991                | 304 / 3608  | 1.11 (0.95 - 1.30) | 1.23 (1.03 - 1.46)  |
| 1992-1996                | 382 / 5205  | 1.09 (0.94 - 1.26) | 1.23 (1.05 - 1.44)  |
| 1997-2001                | 365 / 6666  | 1.00              | 1.00                |
| 2002-2004                | 185 / 4836  | 0.98 (0.81 - 1.17) | 0.90 (0.75 - 1.08)  |
| **Menopausal status**    |             |                   |                     |
| Pre-menopausal           | 504 / 7620  | 0.97 (0.86 - 1.08) | 0.94 (0.75 - 1.20)  |
| Post-menopausal          | 732 / 12690 | 1.00              |                     |
| **GSI**                  |             |                   |                     |
| 0                        | 1000 / 15457| 1.00              | 1.00                |
| 1-2                      | 213 / 4218  | 0.93 (0.81 - 1.08) | 0.94 (0.81 - 1.09)  |
| >3                       | 23 / 640    | 0.88 (0.58 - 1.33) | 0.86 (0.57 - 1.31)  |
| **Stage**                |             |                   |                     |
| I                        | 409 / 9374  | 1.00              |                     |
| II                       | 578 / 9034  | 1.54 (1.36 - 1.75) | 1.43 (1.23 - 1.66)  |
| III                      | 244 / 1795  | 3.70 (3.16 - 4.34) | 3.32 (2.71 - 4.07)  |
| **Tumor size**           |             |                   |                     |
| <20mm                    | 716 / 13333 | 1.00              |                     |
| >20mm                    | 520 / 6977  | 1.42 (1.27 - 1.59) | 1.23 (1.09 - 1.39)  |
| **Grade**                |             |                   |                     |
| Grad I                   | 441 / 6317  | 1.00              |                     |
| Grad II                  | 451 / 6843  | 0.96 (0.84 - 1.10) | 0.86 (0.75 - 0.99)  |
| Grad III                 | 95 / 2960   | 0.45 (0.36 - 0.57) | 0.49 (0.38 - 0.62)  |
| Not graded               | 221 / 3465  | 0.87 (0.74 - 1.03) | 0.88 (0.75 - 1.04)  |
| **Lymph node status**    |             |                   |                     |
| Negative                 | 571 / 13017 | 1.00              |                     |
| 1-3 positive nodes       | 436 / 5622  | 1.93 (1.70 - 2.19) | 1.86 (1.57 - 2.20)  |
| >4 positive nodes        | 229 / 1665  | 3.77 (3.23 - 4.40) | 3.75 (3.07 - 4.59)  |
| **Estrogen receptor status** |         |                   |                     |
| Negative                 | 701 / 2982  | 0.52 (0.44 - 0.63) | 0.66 (0.53 - 0.84)  |
| Positive                 | 650 / 10663 | 1.00              |                     |
| **Endocrine therapy**    |             |                   |                     |
| Yes                      | 521 / 7005  | 1.93 (1.72 - 2.16) | 1.45 (1.23 - 1.72)  |
| No                       | 715 / 13310 | 1.00              |                     |
| **Type of primary surgery** |           |                   |                     |
| Mastectomy+RT            | 239 / 2821  | 1.62 (1.39 - 1.87) | 1.11 (0.93 - 1.33)  |
| Mastectomy               | 699 / 10634 | 1.00              |                     |
| BCS                      | 296 / 6860  | 0.76 (0.68 - 0.87) | 0.81 (0.70 - 0.94)  |
| Adjuvant chemotherapy    |             |                   |                     |
| Yes                      | 299 / 5479  | 0.85 (0.75 - 0.97) | 0.89 (0.73 - 1.07)  |
| No                       | 537 / 14836 | 1.00              |                     |
Supplementary Figure 6. Hazard ratios for loco-regional late breast cancer recurrence, according to clinico-pathological factors at baseline, among 20,315 women diagnosed with early stage breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis. Adjusted for age, calendar period, menopausal status, CCI (ten years after primary diagnosis), stage, grade estrogen receptor status, endocrine therapy, type of primary surgery and chemotherapy except for the one actually examined. When we examined lymph node status we did not adjust for stage but adjusted for tumor size, when we examined tumor size we did not adjust for stage but lymph node status, when we examined stage we did not adjust for lymph node status and tumor size. *The unknown category is not shown. Error bars represent the 95% confidence intervals. Abbreviations: HR, hazard ratio; CI, confidence interval, CCI, Charlson Comorbidity Index; RT, radiation therapy; BCS, breast conserving surgery
### Baseline characteristics

| Age at diagnosis (years) | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------------------|--------------|-------------------|----------------------|
| <40                     | 103 / 1122   | 2.02 (1.61 - 2.54)|                      |
| 40-49                   | 323 / 5125   | 1.39 (1.19 - 1.64)|                      |
| 50-59                   | 290 / 6882   | 1.00              |                      |
| 60-69                   | 169 / 5519   | 0.86 (0.71 - 1.04)|                      |
| ≥70                     | 27 / 1667    | 0.59 (0.40 - 0.87)|                      |

| Calendar period         | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------------------|--------------|-------------------|----------------------|
| 1987-1991               | 215 / 3608   | 0.93 (0.77 - 1.13)|                      |
| 1992-1996               | 273 / 5205   | 0.98 (0.83 - 1.17)|                      |
| 1997-2001               | 271 / 6666   | 1.00              |                      |
| 2002-2004               | 143 / 4836   | 1.04 (0.85 - 1.28)|                      |

| Menopausal status*      | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------------------|--------------|-------------------|----------------------|
| Pre-menopausal          | <500 / 7620  | 1.57 (1.36 - 1.79)|                      |
| Post-menopausal         | <450 / 12690 | 1.00              |                      |

| CCI                     | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------------------|--------------|-------------------|----------------------|
| 0                       | 756 / 15457  | 1.00              |                      |
| 1-2                     | 134 / 4216   | 0.79 (0.66 - 0.96)|                      |
| ≥3                      | 12 / 840     | 0.63 (0.36 - 1.12)|                      |

| Stage*                  | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------------------|--------------|-------------------|----------------------|
| I                       | 460 / 9374   | 1.00              |                      |
| II                      | 378 / 9034   | 0.90 (0.76 - 1.03)|                      |
| III                     | 59 / 1795    | 0.79 (0.60 - 0.94)|                      |

| Tumor size*             | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------------------|--------------|-------------------|----------------------|
| ≥20mm                   | 637 / 13333  | 1.00              |                      |
| >20mm                   | 265 / 6977   | 0.81 (0.71 - 0.94)|                      |

| Grade*                  | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------------------|--------------|-------------------|----------------------|
| Grade I                 | 315 / 6317   | 1.00              |                      |
| Grade II                | 296 / 6843   | 0.86 (0.73 - 1.01)|                      |
| Grade III               | 94 / 2990    | 0.62 (0.50 - 0.78)|                      |

| Not graded              | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------------------|--------------|-------------------|----------------------|
| 160 / 3465              | 0.99 (0.82 - 1.18)|                      |

| Lymph node status*      | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------------------|--------------|-------------------|----------------------|
| Negative                | 606 / 13017  | 1.00              |                      |
| 1-3 positive nodes      | <250 / 5622  | 1.00 (0.85 - 1.16)|                      |
| ≥4 positive nodes       | <50 / 1665   | 0.86 (0.66 - 1.14)|                      |

| Estrogen receptor status*| Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|--------------------------|--------------|-------------------|----------------------|
| Negative                 | 88 / 2982    | 0.70 (0.58 - 0.85)|                      |
| Positive                 | 449 / 10963  | 1.00              |                      |

### Endocrine therapy

| Yes                      | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|--------------------------|--------------|-------------------|----------------------|
| 235 / 7000               | 0.95 (0.81 - 1.10)|                      |

| Type of primary surgery  | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|--------------------------|--------------|-------------------|----------------------|
| Mastectomy               | 64 / 2821    | 0.96 (0.73 - 1.26)|                      |
| Mastectomy+RT            | 337 / 10634  | 1.00              |                      |
| BCS                      | 501 / 6860   | 2.76 (2.41 - 3.19)|                      |
| Adjuvant chemotherapy    | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|--------------------------|--------------|-------------------|----------------------|
| Yes                      | 242 / 5479   | 0.99 (0.85 - 1.14)|                      |
| No                       | 602 / 14836  | 1.00              |                      |
**Supplementary Figure 7.** The 10-32 year cumulative incidence of any breast cancer event after, among 20,315 women diagnosed with early stage breast cancer between 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis.
Supplementary Figure 8. The 10-25 year cumulative incidence of any breast cancer event after ten years among 20,315 women diagnosed with early stage breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis, stratified according to A) T1 tumors (tumor diameter ≤2.0 cm) and nodal status (N0, no nodes; N1-3, 1 to 3 nodes; N4-9, 4 to 9 nodes B) T2 tumors (tumor diameter, >2.0 cm to 5.0 cm) and nodal status (N0, no nodes; N1-3, 1 to 3 nodes; N4-9, 4 to 9 nodes C) Malignancy grade (grade I, II, III or not graded), D) Tumor size (≤20mm or >20mm), E) Lymph node status (N0, N1-3, N≥4), F) Estrogen Receptor status (negative, positive or unknown) and G) Type of primary surgery (mastectomy + RT, mastectomy, or BCS + RT). aNote different scale on Y-axis. bNo confidence intervals are showed due to close lines. cThe unknown category is not shown. Abbreviations: BCS, breast conserving surgery; No., number; RT, radiation therapy.
C Grade$^{b,c}$

Any breast cancer event (%)

| Grade     | 10  | 15  | 20  | 25  | 70  |
|-----------|-----|-----|-----|-----|-----|
| Grade I   | 6317| 4414| 2041| 732 |     |
| Grade II  | 6843| 4704| 2023| 771 |     |
| Grade III | 2990| 2187| 946 | 341 |     |
| Not graded| 3485| 2516| 1260| 461 |     |

Years after primary surgery

D Tumor size$^c$

Any breast cancer event (%)

|                | ≤20mm | >20mm |
|----------------|-------|-------|
| No. at Risk    |       |       |
| ≤20mm          | 13333 | 9537  | 4405 | 1596 |
| >20mm          | 8977  | 4836  | 2185 | 845  |

Years after primary surgery
E  Lymph node status$^{a,c}$

| Lymph node status | No. at Risk | Years after primary surgery |
|-------------------|-------------|-----------------------------|
| N0                | 13017       | 10  | 9526 | 4669 | 1745 |
| N1-3              | 5622        | 15  | 3821 | 1578 | 570  |
| N≥4               | 1665        | 20  | 1020 | 352  | 125  |

F  Estrogen receptor status

| Estrogen receptor status | No. at Risk | Years after primary surgery |
|--------------------------|-------------|-----------------------------|
| Negative                 | 2982        | 10  | 2275 | 889  | 72   |
| Positive                 | 10963       | 15  | 7205 | 2007 | 84   |
| Unknown                  | 6370        | 20  | 4893 | 3694 | 2285 |
G  Primary surgery

![Graph showing the percentage of any breast cancer event over years after primary surgery for different surgery types.](image)

| Surgery Type          | 10 Years | 15 Years | 20 Years | 25 Years |
|-----------------------|----------|----------|----------|----------|
| Mastectomy + RT       | 1898     | 443      | 92       |
| Mastectomy            | 7772     | 4411     | 1858     |
| BCS + RT              | 4703     | 1736     | 491      |

No. at Risk
Supplementary Figure 9. Hazard ratios of any breast cancer event after ten years, according to clinico-pathological factors at baseline, among 20,315 women diagnosed with early stage breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis. Adjusted for age, calendar period, menopausal status, CCI (ten years after primary diagnosis), stage, grade, estrogen receptor status, endocrine therapy, type of primary surgery and chemotherapy except for the one actually examined. When we examined lymph node status we did not adjust for stage but adjusted for tumor size, when we examined tumor size we did not adjust for stage but lymph node status, when we examined stage we did not adjust for lymph node status and tumor size. The unknown category is not shown. Error bars represent the 95% confidence intervals Abbreviations: HR, hazard ratio; CI, confidence interval, CCI, Charlson Comorbidity Index; RT, radiation therapy; BCS, breast conserving surgery
| Baseline characteristics | Events/total | Crude HR (95% CI) | Adjusted HR (95% CI) |
|--------------------------|-------------|-------------------|----------------------|
| **Age at diagnosis (years)** | | | |
| <40 | 274 / 1122 | 1.16 (1.02 - 1.32) | 1.27 (1.09 - 1.49) |
| 40-49 | 1129 / 5125 | 1.05 (0.97 - 1.14) | 1.04 (0.94 - 1.16) |
| 50-59 | 1298 / 6982 | 1.00 | 1.00 |
| 60-69 | 846 / 5519 | 0.93 (0.85 - 1.01) | 0.95 (0.87 - 1.04) |
| ≥70 | 171 / 1667 | 0.80 (0.69 - 0.94) | 0.81 (0.69 - 0.96) |
| **Calendar period** | | | |
| 1987-1991 | 885 / 3608 | 0.91 (0.82 - 0.99) | 0.97 (0.87 - 1.07) |
| 1992-1996 | 1128 / 5205 | 0.97 (0.89 - 1.05) | 1.03 (0.94 - 1.13) |
| 1997-2001 | 1150 / 6966 | 1.00 | 1.00 |
| 2002-2004 | 555 / 4836 | 0.96 (0.86 - 1.05) | 0.88 (0.79 - 0.98) |
| **Menopausal status** | | | |
| Pre-menopausal | 1700 / 7620 | 1.12 (1.05 - 1.20) | 1.07 (0.94 - 1.23) |
| Post-menopausal | 2100 / 12690 | 1.00 | 1.00 |
| **Tumor size** | | | |
| ≤20mm | 2347 / 13333 | 1.00 | 1.00 |
| >20mm | 1371 / 6977 | 1.14 (1.07 - 1.22) | 1.19 (1.10 - 1.28) |
| **Grade** | | | |
| Grade I | 1281 / 6517 | 1.00 | 1.00 |
| Grade II | 1279 / 6843 | 0.91 (0.84 - 0.98) | 0.89 (0.82 - 0.97) |
| Grade III | 393 / 2990 | 0.84 (0.58 - 0.72) | 0.71 (0.63 - 0.81) |
| Not graded | 698 / 3465 | 0.94 (0.86 - 1.04) | 0.98 (0.90 - 1.08) |
| **Lymph node status** | | | |
| Negative | 2121 / 13017 | 1.00 | 1.00 |
| 1-3 positive nodes | <1200 / 5522 | 1.38 (1.28 - 1.48) | 1.41 (1.29 - 1.55) |
| ≥4 positive nodes | <500 / 1665 | 2.00 (1.80 - 2.21) | 2.19 (1.90 - 2.51) |
| **Estrogen receptor status** | | | |
| Negative | 313 / 2062 | 0.63 (0.57 - 0.70) | 0.71 (0.63 - 0.81) |
| Positive | 1900 / 10963 | 1.00 | 1.00 |
| **Type of primary surgery** | | | |
| Mastectomy+RT | 538 / 2821 | 1.42 (1.28 - 1.56) | 1.09 (0.97 - 1.22) |
| Mastectomy | 1890 / 10634 | 1.00 | 1.00 |
| BCS | 1290 / 6660 | 1.26 (1.17 - 1.36) | 1.27 (1.18 - 1.37) |
| **Adjuvant chemotherapy** | | | |
| Yes | 933 / 5479 | 0.90 (0.84 - 0.97) | 0.85 (0.76 - 0.94) |
| No | 2785 / 14838 | 1.00 | 1.00 |
Supplementary Figure 10. Hazard ratios of late breast cancer recurrence, according to clinico-pathological factors at baseline, regarding to imputed and not imputed data. Adjusted for age, calendar period, menopausal status, CCI (ten years after primary diagnosis), stage, grade, estrogen receptor status, endocrine therapy, type of primary surgery and chemotherapy except for the one actually examined. When we examined lymph node status we did not adjust for stage but adjusted for tumor size, when we examined tumor size we did not adjust for stage but lymph node status, when we examined stage we did not adjust for lymph node status and tumor size. aThe unknown category is not shown. Error bars represent the 95% confidence intervals Abbreviations: HR, hazard ratio; CI, confidence interval, CCI, Charlson Comorbidity Index; RT, radiation therapy; BCS, breast conserving surgery.
### Baseline characteristics

| Age at diagnosis (years) | Crude | Complete case | MI |
|--------------------------|-------|---------------|----|
| <40                      |       |               |    |
| 40-49                    | 1.22 (1.05 - 1.43) | 1.54 (1.20 - 1.98) | 1.47 (1.22 - 1.78) |
| 50-59                    | 1.00  | 1.00          | 1.00 |
| 60-69                    | 0.97 (0.88 - 1.08) | 0.93 (0.82 - 1.07) | 0.98 (0.87 - 1.09) |
| >70                      | 0.88 (0.74 - 1.06) | 0.85 (0.68 - 1.05) | 0.88 (0.73 - 1.06) |
| Calendar period          |       |               |    |
| 1987-1991                | 0.93 (0.83 - 1.04) | 0.91 (0.81 - 1.03) | 0.93 (0.84 - 1.03) |
| 1992-1996                | 0.99 (0.90 - 1.10) | 1.01 (0.88 - 1.16) | 1.08 (0.97 - 1.21) |
| 1997-2001                | 1.00  | 1.00          | 1.00 |
| 2002-2004                | 0.97 (0.86 - 1.09) | 0.91 (0.80 - 1.04) | 0.97 (0.77 - 0.98) |
| Menopausal status*       |       |               |    |
| Pre-menopausal           | 1.11 (1.03 - 1.20) | 1.03 (0.86 - 1.24) | 1.04 (0.89 - 1.23) |
| Post-menopausal          | 1.00  | 1.00          | 1.00 |
| CCI                      |       |               |    |
| 0                        | 1.00  | 1.00          | 1.00 |
| 1-2                      | 0.91 (0.82 - 1.00) | 0.92 (0.81 - 1.05) | 0.93 (0.84 - 1.03) |
| 3                        | 0.84 (0.63 - 1.21) | 0.87 (0.63 - 1.21) | 0.87 (0.65 - 1.16) |
| Stage*                   |       |               |    |
| I                        | 1.00  | 1.00          | 1.00 |
| II                       | 1.30 (1.19 - 1.41) | 1.44 (1.26 - 1.65) | 1.37 (1.24 - 1.52) |
| III                      | 2.36 (2.10 - 2.66) | 2.78 (2.32 - 3.34) | 2.57 (2.22 - 2.97) |
| Tumor size*              |       |               |    |
| <20mm                    | 1.00  | 1.00          | 1.00 |
| 20-29mm                  | 1.19 (1.10 - 1.29) | 1.33 (1.19 - 1.49) | 1.23 (1.13 - 1.35) |
| Grade*                   |       |               |    |
| Grade I                  | 1.00  | 1.00          | 1.00 |
| Grade II                 | 0.92 (0.84 - 1.01) | 1.00 (0.89 - 1.13) | 0.89 (0.81 - 0.96) |
| Grade III                | 0.51 (0.44 - 0.59) | 0.76 (0.63 - 0.92) | 0.67 (0.58 - 0.76) |
| Not graded               | 0.92 (0.82 - 1.02) | 1.04 (0.90 - 1.20) | 0.96 (0.85 - 1.07) |
| Lymph node status*       |       |               |    |
| Negative                 | 1.00  | 1.00          | 1.00 |
| 1-3 positive nodes       | 1.56 (1.44 - 1.70) | 1.59 (1.38 - 1.83) | 1.59 (1.42 - 1.77) |
| 4+ positive nodes        | 2.45 (2.18 - 2.75) | 2.70 (2.25 - 3.22) | 2.67 (2.31 - 3.08) |
| Estrogen receptor status*|       |               |    |
| Negative                 | 0.41 (0.35 - 0.48) | 0.51 (0.43 - 0.62) | 0.68 (0.59 - 0.79) |
| Positive                 | 1.00  | 1.00          | 1.00 |
| Hormone therapy          |       |               |    |
| Yes                      | 1.57 (1.45 - 1.70) | 1.12 (0.97 - 1.29) | 1.27 (1.13 - 1.43) |
| No                       | 1.00  | 1.00          | 1.00 |
| Type of primary surgery  |       |               |    |
| Mastectomy+RT            | 1.52 (1.36 - 1.70) | 1.04 (0.89 - 1.22) | 1.10 (0.97 - 1.26) |
| Mastectomy               | 1.00  | 1.00          | 1.00 |
| BCS                      | 1.33 (1.22 - 1.45) | 1.31 (1.16 - 1.47) | 1.38 (1.26 - 1.51) |
| Adjuvant chemotherapy    |       |               |    |
| Yes                      | 0.89 (0.81 - 0.97) | 0.77 (0.65 - 0.91) | 0.84 (0.74 - 0.96) |
| No                       | 1.00  | 1.00          | 1.00 |