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Article

The Incidence of Breast Cancer Recurrence 10-32 Years After Primary Diagnosis

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Abstract

Background: Extended, more effective breast cancer treatments have increased the prevalence of long-term survivors. We investigated the risk of late breast cancer recurrence (BCR), 10 years or more after primary diagnosis, and associations between patient and tumor characteristics at primary diagnosis and late BCR up to 32 years after primary breast cancer diagnosis. **Methods:** Using the Danish Breast Cancer Group clinical database, we identified all women with an incident early breast cancer diagnosed during 1987-2004. We restricted to women who survived 10 years without a recurrence or second cancer (10-year disease-free survivors) and followed them from 10 years after breast cancer diagnosis date until late recurrence, death, emigration, second cancer, or December 31, 2018. We calculated incidence rates per 1000 person-years and cumulative incidences for late BCR, stratifying by patient and tumor characteristics. Using Cox regression, we calculated adjusted hazard ratios for late BCR accounting for competing risks. **Results:** Among 36 924 women with breast cancer, 20 315 became 10-year disease-free survivors. Of these, 2595 developed late BCR (incidence rate = 15.53 per 1000 person-years, 95% confidence interval = 14.94 to 16.14; cumulative incidence = 16.6%, 95% confidence interval = 15.8% to 17.5%) from year 10 to 32 after primary diagnosis. Tumor size larger than 20 mm, lymph node–positive disease, and estrogen receptor–positive tumors were associated with increased cumulative incidences and hazards for late BCR. **Conclusions:** Recurrences continued to occur up to 32 years after primary diagnosis. Women with high lymph node burden, large tumor size, and estrogen receptor–positive tumors had increased risk of late recurrence. Such patients may warrant extended surveillance, more aggressive treatment, or new therapy approaches.

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Survival after breast cancer has improved due to mammographic screening, facilitating earlier stage at diagnosis and increasingly effective systemic therapy (1). In women with estrogen receptor (ER)–positive and HER2 receptor–negative tumors, at least one-half of breast cancer recurrences (BCRs) occur more than 5 years after primary diagnosis (2). Adjuvant endocrine therapy has therefore been extended to up to 10 years of treatment (3). Yet, the incidence of BCR beyond 10 years after primary diagnosis is not well understood.

Approximately 75% of primary breast tumors have already spread at the time of diagnosis (4), seeding micrometastases at a regional or distant anatomic site (5). These micrometastases survive in a state of tumor dormancy, whereby cell growth is balanced by apoptosis (4,6,7). Alterations in cytokines, immune cells, and growth factors in the tumor microenvironment lead to the cessation of tumor dormancy, prompting full metastatic growth (7).

Circulating tumor cells have been detected in breast cancer survivors decades after their primary cancer treatment (8–10). Case reports document breast tumors that recurred 39 years after primary diagnosis (11,12). A Danish study showed a cumulative incidence of local recurrence of 15% and distant metastases of 21% 20 years after diagnosis among 1847 patients treated with breast-conserving surgery (BCS) during 1989-1999 (13). A

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meta-analysis by Pan et al. (14) included 88 trials representing over 60 000 women with ER-positive breast cancer treated with tamoxifen for 5 years. Between 5 and 20 years after primary diagnosis, the risk of distant recurrence ranged from 13% to 41% depending on the tumor and nodal status of the primary tumor. Similar findings were reported in a study of 3128 breast cancer patients in the United Kingdom (15) and in a Swedish study including 336 luminal A and 126 luminal B patients (16). Higher lymph node burden, larger tumor size, and higher grade were associated with increased risk of recurrence (from 5 years after primary diagnosis) (14).

Better understanding of the risk of late BCR, that is, recurrence 10 years or more after primary diagnosis, will help delineate patients who may be candidates for prolonged follow-up. We therefore used Danish population-based and medical registries to investigate the incidence of late BCR up to 32 years after primary diagnosis. We examined the association of tumor and patient characteristics at primary diagnosis with the risk of late BCR.

Methods

Ethics Approval

This study was approved by the Danish Breast Cancer Group and the Danish Data Protection Agency (Aarhus University, J. no. 2016–051-00001, record no. 552) and adheres to the General Data Protection Regulations. The study is based on routinely collected registry data and according to Danish regulations therefore does not require separate ethical approval.

Setting and Data Sources

We conducted a nationwide cohort study using population-based registries. Denmark's National Health Service provides tax-supported health care to Danish citizens and permanent residents, ensuring equal and free access to all medical care provided by hospitals and general practitioners (17). Using the civil personal registration number, a unique identification number assigned to all Danish residents at birth or immigration, we linked individual-level data from Danish administrative and population-based registries (18), namely the Danish Breast Cancer Group database (DBCG) (19,20), the Danish National Patient Registry (DNPR) (21), the Danish Pathology Registry (DPR) (22), the Danish Cancer Registry (DCR) (23), the Danish Register of Causes of Death (24), and the Danish Civil Registration System (18). In addition, we used data on contralateral breast cancer (CBC) in a database initiated for a previous study (25) (see the Supplementary Methods, available online).

Study Population

We included all women in Denmark diagnosed with an incident early (ie, nondistant metastatic) operable breast cancer on a treatment protocol in DBCG between January 1, 1987, and December 31, 2004. Among these, we identified those who were alive, living in Denmark, without a recurrence or second cancer (CBC or other new primary tumor) 10 years after diagnosis (10-year disease-free survivors). Information about recurrences within the first 10 years was obtained from DBCG. Information about a second cancer within the first 10 years was obtained from DBCG, DNPR, DCR, and the database on CBCs. At the time of writing, the database on CBCs was updated to December 31, 2013. We therefore used the DPR to identify CBCs that occurred from 2014 through 2018. A CBC in the DPR was defined as a new malignant tumor in the breast with opposite laterality codes to the primary tumor. We also used the DNPR to exclude women with metastases within the first 10 years.

Covariates

We used the DBCG to obtain information on patient, tumor, and treatment characteristics, the DNPR to obtain information on potentially confounding comorbid diseases (summarized using the Charlson Comorbidity Index) (26), and the Civil Registration System to obtain information about emigration and vital status (see the Supplementary Methods, available online). For tumor size and lymph node status, we categorized patients into T1 disease (tumor diameter $\leq$20 mm) and T2 disease (tumor diameter, $>$20-50 mm) and combined them with number of involved lymph nodes (N0, no nodes; N1-3, 1-3 nodes; N4-9, 4-9 nodes). We used the DNPR and the DPR to characterize the recurrences into loco-regional or distant recurrences (within the first 6 months after recurrence).

Outcomes

We defined a late BCR as any local, regional, or distant recurrent breast cancer diagnosed 10 years or more after primary breast cancer diagnosis (excluding CBCs). Recurrences are routinely registered in the DBCG database up to 10 years after diagnosis. We therefore used a previously developed and validated algorithm (27) to capture patients who developed late BCR using Danish registries. The algorithm incorporated information on diagnostic, therapeutic, and procedural codes from the DNPR and cancer diagnoses from the DCR, DPR, and the database on CBC (27). Recurrences registered in the DBCG 10 years or more after primary surgery were included as a late recurrence.

Statistical Analyses

We present descriptive characteristics of patient, tumor, and treatment characteristics of all breast cancer patients diagnosed during 1987-2004 in DBCG and of the 10-year disease-free survivors. We followed patients from 10 years after the primary diagnosis date (the earliest start date was January 1, 1997) until late BCR, second cancer, emigration, death, or the end of the study (December 31, 2018). We calculated crude incidence rates (IRs) of late BCR per 1000 person-years (PYs), associated 95% confidence intervals (CIs), and estimated cumulative incidences using the nonparametric Aalen-Johansen estimator, treating death and second cancers as competing risks. We stratified by follow-up time and patient and tumor characteristics at baseline. Cox regression models were used to calculate crude and adjusted hazard ratios (HRs) of recurrence and associated 95% CI, adjusting for patient and tumor characteristics. Competing risk of second cancers and death was censored on the date of event. We verified the proportional hazards assumption by plotting –ln(survival probability) against ln(analysis time) and detected no violations.

In Denmark, ER status was first routinely registered from 1997. We therefore imputed missing data on ER status used for adjustment in the Cox models. We also imputed data on grade (see the Supplementary Methods, available online).

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Sensitivity Analyses

We conducted several sensitivity analyses: 1) we restricted to patients with ER-positive tumors, 2) we included breast cancer–specific death (from the Danish Cause of Death Registry) as an indicator of recurrence in the algorithm, 3) we restricted the outcome to distant recurrence and to loco-regional recurrence, 4) we pooled CBCs and recurrences together because these events are often combined when investigating disease-free survival (19), 5) we changed the definition of an ER-positive tumor for 10% and over tumor cells demonstrating positive nuclear staining (guideline definition in the study period) to 1% or more (current guideline definition; note that the women whose categorization changed would seldom have received endocrine therapy), and 6) in Denmark, tumor grade was evaluated according to the method of Bloom and Richardson modified by Elton and Ellis during the whole study period, but only ductal tumors were evaluated until 2002 (28–30). We therefore stratified our Cox models, comparing grade III with grade I tumors before and after 2002.

Results

We included 36 924 women diagnosed with incident early primary breast cancer between January 1, 1987, and December 31, 2004. After exclusions (Supplementary Figure 1, available online), our final cohort consisted of 20 315 10-year disease-free survivors generating 167 091 PY of follow-up. Median follow-up was 7 years (ie, 17 years after primary diagnosis) (interquartile range = 4-11). The characteristics of the women are outlined in Table 1.

Among these 10-year disease-free survivors, 2595 women developed late BCR during follow-up, corresponding to an IR of 15.53 (95% CI = 14.94 to 16.14) per 1000 PY, with highest IR 10-12 years after primary breast cancer diagnosis (IR = 22.10 per 1000 PY, 95% CI = 20.89 to 23.37) (Table 2). The cumulative incidence of late BCR was 8.5% (95% CI = 8.1% to 8.9%), 12.5% (95% CI = 12.0% to 13.0%), 15.2% (95% CI = 14.6% to 15.7%), and 16.6% (95% CI = 15.8% to 17.5%), respectively, 15, 20, 25, and 32 years after primary diagnosis (ie, 5, 10, 15, and 22 years after the start of follo w-up) (Figure 1).

The cumulative incidence 10-25 years after diagnosis increased with increasing lymph node involvement at baseline, ranging from 12.7% (95% CI = 11.9% to 13.5%) in patients with T1N0 to 24.6% (95% CI = 20.7% to 28.6%) for patients with T2N4-9 disease (Figure 2, A and B). The cumulative incidence decreased with increasing tumor grade (Figure 2, C), was highest for patients with grade I tumors and 4 or more lymph nodes, and was lowest for patients with grade III disease and no involved lymph nodes (37.9% [95% CI = 31.3% to 44.6%] and 7.5% [95% CI= 6.1% to 9.0%], respectively, 10-25 years after primary diagnosis; data not tabulated). The cumulative incidence of recurrence 10-25 years after primary diagnosis was 14.4% (95% CI = 13.7% to 15.1%) and 15.5% (95% CI = 15.5% to 17.6%) in patients with tumors sized 20 mm or less and greater than 20 mm, respectively (Figure 2, D). The cumulative incidence of late recurrence was higher in younger patients (data not presented), patients with ER-positive primary tumors (Figure 2, F; Supplementary Figures 2-4, available online), and those treated with BCS compared with mastectomy (Figure 2, G). However, the risk was still 8.1% (95% CI = 6.7% to 9.6%) for women with ER-negative tumors 10-25 years after primary diagnosis (Figure 2, F). There was no difference in cumulative incidence of late recurrence in analyses stratified by calendar year of primary diagnosis.

We observed a higher hazard of late BCR among younger women (<40 years, HR = 1.47, 95% CI = 1.22 to 1.78), women who underwent BCS (HR = 1.38, 95% CI = 1.26 to 1.51), those with high lymph node status (≥4 positive lymph nodes, HR = 2.67, 95% CI = 2.31 to 3.08), those with tumor size greater than 20 mm (HR = 1.23, 95% CI = 1.13 to 1.35), and those who received endocrine therapy (HR = 1.27, 95% CI = 1.13 to 1.43). We observed a lower hazard of late BCR among patients with grade III tumors (HR = 0.57, 95% CI = 0.48 to 0.66), ER-negative tumors (HR = 0.68, 95% CI = 0.59 to 0.79), and those who received chemotherapy (HR = 0.84, 95% CI = 0.74 to 0.96) (Figure 3).

The sensitivity analysis showed that lymph node–positive, grade I or II, and ER-positive tumors were associated with higher hazard ratios of distant late recurrence (Supplementary Figure 5, available online). Low-grade tumors, younger age at diagnosis, and the receipt of BCS were associated with higher hazard ratios of loco-regional late recurrence (Supplementary Figure 6, available online).

We found a higher cumulative incidence of late recurrence among women with ER-positive primary tumors—13.5% (95% CI = 12.1% to 15.0%) for T1N0 to 34.3% (95% CI = 19.9% to 49.3%) for T2N4-9 stage—10-25 years after primary diagnosis. The absolute risks and hazard ratios increased with increasing nodal involvement, tumor size, and younger age at diagnosis (Supplementary Figures 3 and 4, available online). The absolute risk was similar irrespective of grade; however, the adjusted hazard ratios were slightly lower in grade III vs grade I tumors (Supplementary Figures 3 and 4, available online). We did not observe an association between the receipt of endocrine therapy at primary diagnosis and late BCR. Considering CBCs and recurrences as a pooled outcome, the cumulative incidence was 25.8% (95% CI = 24.6% to 26.9%) in a maximum 32 years after primary diagnosis (Supplementary Figure 7, available online). The risk factors were similar as when we restricted the outcome to late recurrence only (Supplementary Figures 8 and 9, available online). Stratifying our Cox models before and after 2002 showed a reduced and increased risk of late recurrence, respectively, for grade III vs grade I tumors, though the latter estimate was imprecise (not presented). Our findings were similar when we used multiple imputation to impute missing data and in the complete case analysis (Supplementary Figure 10, available online). See further results from the sensitivity analyses in Supplementary Table 1 (available online).

Discussion

Slightly over 50% of women with early-stage breast cancer remain disease free for at least 10 years, but recurrences continue to occur long after primary diagnosis. Although we observed the highest cumulative incidence of late recurrence among patients with ER-positive tumors at primary diagnosis, late recurrences also occurred among those with ER-negative primary tumors. Clinical characteristics at primary diagnosis that increased the cumulative incidence and hazards of late recurrence included larger, ER-positive, lymph node–positive, and grade I and II tumors.

The cumulative incidence of late recurrence in our study was lower than that reported in the meta-analysis by Pan et al (14). However, we followed patients from year 10, whereas Pan et al. (14) started follow-up at year 5. The meta-analysis may have overestimated the risk because they used Kaplan-Meier

Table 1. Descriptive characteristics of women diagnosed with early-stage breast cancer between 1987 and 2004 and registered in the Danish Breast Cancer Group clinical database: 10-year disease-free survivor cohort and the entire breast cancer cohort[a]

Characteristic	10-year disease-free survivor cohort[b] No. (%)	Breast cancer cohort[c] No. (%)
Total no. of patients	20 315	36 924
Age at primary diagnosis, median	55	56
<40 y	1122 (5.5)	2229 (6.0)
40-49 y	5125 (25.2)	8120 (22.0)
50-59 y	6882 (33.9)	11 630 (31.5)
60-69 y	5519 (27.2)	10 912 (29.6)
≥70 y	1667 (8.2)	4033 (10.9)
Calendar period of primary breast cancer		
1987-1991	3608 (17.8)	7304 (19.8)
1992-1996	5205 (25.6)	10 085 (27.3)
1997-2001	6666 (32.8)	11 309 (30.6)
2002-2004	4836 (23.8)	8226 (22.3)
Menopausal status		
Premenopausal	7620 (37.5)	12 373 (33.5)
Postmenopausal	12 690 (62.5)	24 544 (66.5)
Unknown	5 (0.02)	7 (0.02)
CCI score at primary breast cancer diagnosis		
0	18 515 (91.1)	32 644 (88.4)
1-2	1710 (8.4)	3925 (10.6)
≥3	90 (0.4)	355 (1.0)
Stage		
I	9374 (46.1)	13 978 (37.9)
II	9034 (44.5)	16 237 (44.0)
III	1795 (8.8)	6501 (17.6)
Unknown	112 (0.6)	208 (0.6)
Grade		
I	6317 (31.1)	10 120 (27.4)
II	6843 (33.7)	13 132 (35.6)
III	2990 (14.7)	6548 (17.7)
Not graded	3465 (17.1)	5908 (16.0)
Unknown	700 (3.5)	1216 (3.3)
No. of positive lymph nodes		
Negative	13 017 (64.1)	20 256 (54.9)
1-3	5622 (27.7)	10 491 (28.4)
≥ 4	1665 (8.2)	6150 (16.7)
Unknown	11 (0.05)	27 (0.07)
Tumor size		
≤20 mm	13 333 (65.6)	21 221 (57.5)
>20 mm	6977 (34.3)	15 697 (42.5)
Unknown	5 (0.02)	6 (0.02)
ER status		
ER positive	10 963 (54.0)	18 338 (49.7)
ER negative	2982 (14.7)	5778 (15.7)
Unknown	6370 (31.4)	12 808 (34.7)
ER unknown by calendar year[d]		
<1997	5965 (93.6)	12 143 (94.8)
≥1997	405 (6.4)	665 (5.2)
Type of primary surgery		
Mastectomy	10 634 (52.4)	20 380 (55.2)
Mastectomy + RT	2821 (13.9)	6088 (16.5)
BCS + RT	6860 (33.8)	<11 000
Unknown		<5
Allocated to chemotherapy		
No	14 836 (73.0)	26 895 (72.8)
Yes	5479 (27.0)	10 029 (27.2)
Allocated to endocrine therapy		
No	13 310 (65.5)	23 302 (63.1)
Yes	7005 (34.5)	13 662 (36.9)

[a]Cell sizes less than 5 are reported in aggregate to reduce identifiability of individuals in the data. BCS = breast conserving therapy; CCI = Charlson Comorbidity Index; ER = estrogen receptor; RT = radiation therapy.
[b]Women from the breast cancer cohort who reached year 10 without a recurrence or second cancer.
[c]Women with a nonmetastatic breast cancer patients diagnosed during 1987-2004 and registered in the DBCG clinical database.
[d]We stratified ER Unknown status by calendar year as ER testing was introduced into routine clinical practice in 1997.

Table 2. Incidence rates of late breast cancer recurrence stratified by follow-up time 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[a]

Years since breast cancer diagnosis	No. of recurrences	Person-years	Crude incidence rates per 1000 person-years (95% CI)
Overall	2595	167 091	15.53 (14.94 to 16.14)
10-12	1234	55 841	22.10 (20.89 to 23.36)
13-15	646	45 541	14.18 (13.13 to 15.32)
16-18	353	30 035	11.75 (10.59 to 13.04)
19-21	210	18 328	11.46 (10.00 to 13.12)
22-25	105	10 376	10.12 (8.36 to 12.25)
>25	47	6969	6.74 (5.07 to 8.98)

[a]CI = confidence interval.

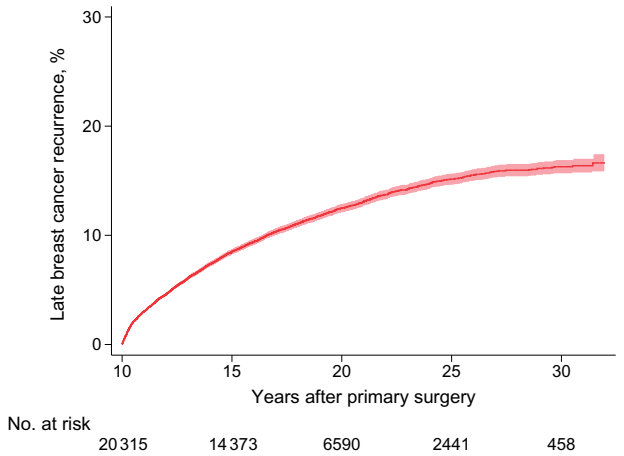

Figure 1. The cumulative incidence of late breast cancer recurrence among women diagnosed with early-stage breast cancer between 1987 and 2004, alive and without a recurrence or second cancer 10 years after primary diagnosis.

methods, which do not account for competing risks (31). We computed a cumulative incidence function, considering death and second cancers as competing risks. Furthermore, when we changed the outcome to incorporate both recurrence and CBCs, our cumulative incidence was similar to the cumulative incidence of breast cancer–specific death reported in a prospective cohort study by Leone et al. (32).

The meta-analysis by Pan et al. (14) did not investigate the association of primary breast cancer surgery with late recurrence. Our observed elevated cumulative incidence and hazards of loco-regional late recurrence among women who underwent BCS compared with patients who received mastectomy may reflect residual disease in the surgical margins (33). However, local disease control has improved since the diagnostic period of our study population (34). Furthermore, patients who undergo a mastectomy have a reduced risk of loco-regional recurrence due to breast removal. Nonetheless, local recurrences 10 years or more after BCS may be new primary tumors rather than "true recurrences" (35). Local recurrence after BCS has a better prognosis than local recurrence after mastectomy and higher long-term survival (28). We had comprehensive information on tumor characteristics, but patients who underwent BCS may have had less aggressive disease than patients who underwent a mastectomy. Our findings of a lower risk of distant late recurrence among patients who received a BCS may therefore be prone to confounding by severity.

Pan et al. (14) found that higher lymph node status, larger tumor diameter, and higher tumor grade increased the risk of recurrence after 5 years. We found similar patterns for tumor size and nodal status when starting follow-up 10 years after primary diagnosis, but somewhat conflicting findings for grade. This might be due to several reasons. First, Pan et al. (14) restricted to trials, including ER-positive women allocated to endocrine therapy. In contrast, our study population was more heterogeneous in terms of the risk of recurrence. Second, stratifying our Cox models to after 2002 showed findings in line with those by Pan et al. (14). Third, treatment guidelines in Denmark recommend treatment based on risk groups that include tumor grade. Early in the study period, grade I tumors were considered low risk and grade II-III as high risk, but the high-risk group has gradually extended (36). Thus, patients diagnosed early in the study period might have received less treatment consistent with guidelines at the time of their diagnosis. Finally, the effect of grade was most pronounced among patients with an unknown or negative ER status. When we restricted to ER-positive patients, the association of grade attenuated.

Research by Giannakeas et al. (37,38) suggested that cancers randomly reactivate from dormancy and proliferate according to an "annual reactivation rate." By ranking risk groups according to clinicopathological factors, they found lower reactivation rates in low-risk compared with high-risk cancers (37,38). They also concluded that time to death was prolonged among ER-positive and low-risk ER-negative cancers and that the differences in time to death were due to the period of dormancy. Consistent with this, we note that ER-negative patients were also at risk of late recurrence in our study. Nonetheless, the majority of recurrences in ER-negative patients occur within the first 5 years after breast cancer diagnosis (39).

We did not expect a higher risk of late recurrence associated with endocrine therapy. The Early Breast Cancer Trialists' Collaborative Group (40) found a reduced risk of recurrence up to 10 years after diagnosis, but no gain or loss thereafter among patients who received 5 years of tamoxifen (40). For those treated with tamoxifen for 1-2 years, the reduced recurrence rate was evident up to 5 years after diagnosis. However, patients who received 1 year of tamoxifen had a slightly elevated rate ratios of recurrence after 10 years. When we restricted our study cohort to ER-positive women, the increased hazard ratio associated with the receipt of endocrine therapy attenuated to the null. However, analyses restricted to patients with unknown ER status suggested that those treated with endocrine therapy had elevated hazard ratios of late recurrence. These patients were diagnosed at a time when ER status was not routinely tested, but endocrine therapy was allocated for 1-2 years. As such, the increased risk of recurrence after endocrine therapy may not reflect current treatment guidelines.

The strengths of this study include the population-based design within a setting of universal tax-supported health care, large sample size, prospective data collection, and long-term

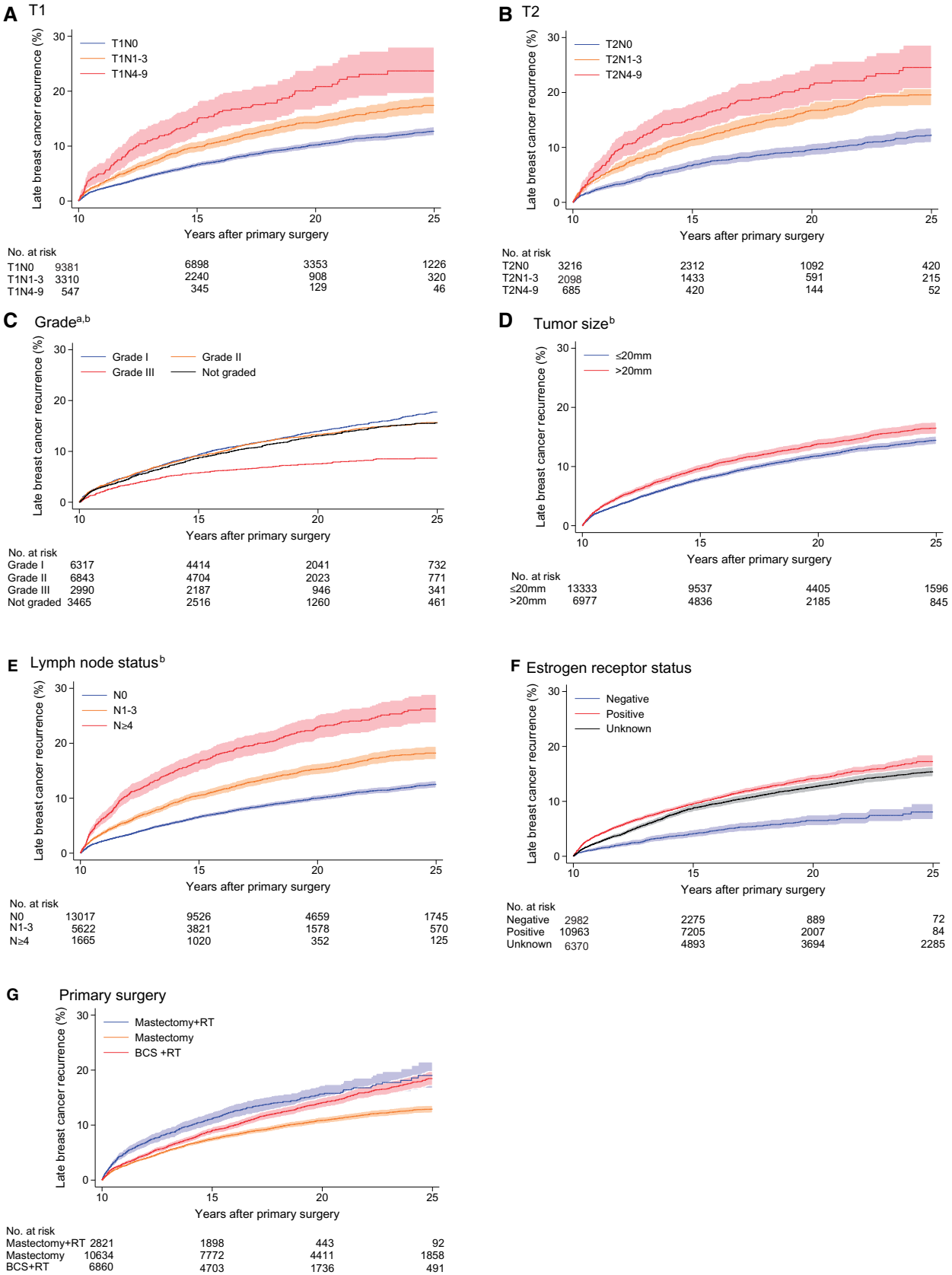

Figure 2. Cumulative incidences of late breast cancer recurrence among 20 315 women diagnosed with early-stage breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis, stratified according to: **A)** T1 tumors (tumor diameter ≤2.0 cm) and nodal status (N0, no nodes; N1-3, 1-3 nodes; N4-9, 4-9 nodes); **B)** T2 tumors (tumor diameter, >2.0-5.0 cm) and nodal status (N0, no nodes; N1-3, 1-3 nodes; N4-9, 4-9 nodes); **C)** malignancy grade (grade I, II, III, or not graded); **D)** tumor size (≤20 or >20 mm); **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) [a]No confidence intervals are shown due to close lines. [b]The unknown category is not shown. BCS = breast-conserving surgery; RT = radiation therapy.

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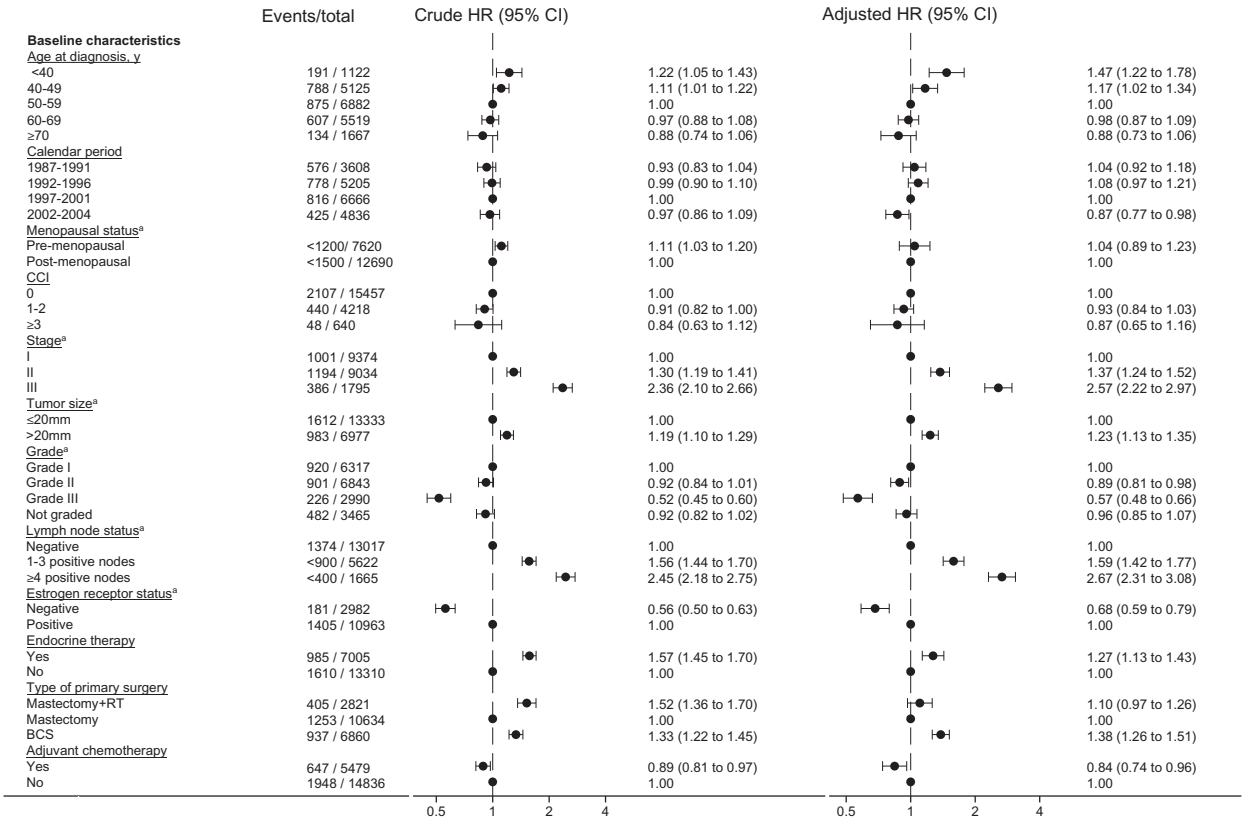

Figure 3. Hazard ratios (HRs) for late breast cancer recurrence, according to clinico-pathological factors at baseline, among 20 315 women diagnosed with early-stage breast cancer in Denmark, 1987-2004, alive and without a recurrence or second cancer 10 years after primary diagnosis. Adjusted for age, calendar period for primary tumor, menopausal status, Charlson Comorbidity Index (CCI; 10 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; and when we examined stage, we did not adjust for lymph node status and tumor size. **Error bars** represent the 95% confidence intervals (CI). [a]The unknown category is not shown. BCS = breast-conserving surgery; RT = radiation therapy.

and complete follow-up as well as the use of a custom-designed and validated algorithm (27). Yet, the positive predictive value of our late BCR algorithm was 86% (95% CI = 78% to 91%), so some of our late BCRs could be false positives. Furthermore, the algorithm for late recurrence suggested a perfect but imprecise sensitivity. Whereas the PPV was calculated based on a sample of 105 patients with an algorithm-defined late recurrence, the sensitivity, specificity, and negative predictive value calculations were derived from a random sample of 114 patients diagnosed with primary breast cancer between 1987 and 2004. Because late recurrence is a rare event, the latter random sample had only a small number of patients with late recurrence, yielding the imprecise sensitivity. Although we cannot rule out a possibility of some misclassification, we find it somewhat reassuring that our cumulative incidence of late recurrence agrees with those reported elsewhere (14,32).

Our late recurrence algorithm incorporated Systematized Nomenclature of Medicine (SNOMED) codes to distinguish recurrent from new primary tumors. However, some late recurrences may be new primary ipsilateral tumors. In Denmark, the DBCG categorize ipsilateral tumors as recurrences. However, pathologists often provide oncologists with their interpretation of whether the tumor is a recurrence or new primary based on localization, hormone receptor profile, and histological subtype. Countries that register cancers according to the Solid Tumor Manual Rules (41) consider ipsilateral tumors as new primaries if they occur over 5 years after a first primary (41). Accordingly, we may have classified more ipsilateral tumors as recurrent tumors compared with other countries. Nonetheless, the absence of routine surveillance for recurrent tumors in most countries makes it difficult to assess how often ipsilateral tumors are coded as recurrences. Such differences in coding practice are important to keep in mind when considering the generalizability of our findings.

The diagnostic period of our study population may not reflect diagnosis and treatment patterns of contemporary breast cancer patients. However, we did not observe differences in the cumulative incidence of late recurrence in analyses stratified by calendar year. We expect that treatment advances during the last decades are likely to have improved prognosis in the first 10 years after breast cancer diagnosis (2).

Our observed high cumulative incidence of late BCR is a concern given the increasing prevalence of long-term survivors. Our findings suggest that a subset of patients—with larger tumors, positive lymph nodes, or ER-positive disease—are at risk of late recurrence. Such patients may warrant extended surveillance, more aggressive treatment, or new therapies. However, prolonged treatment or follow-up may evoke adverse psychological or physiological effects. It is therefore critical to distinguish patients at risk of late recurrence from those who are not likely to develop recurrent disease.

The Clinical Treatment Score at 5 years (CTS5) predicts distant recurrence 5 to 10 years after diagnosis among ER-positive breast cancer patients (42). However, the risk score

overestimates the risk of distant recurrence in high-risk patients (43). Our findings support the need for a model predicting recurrence more than 10 years after diagnosis to select patients in need of prolonged follow-up or treatment.

Our study provides novel insights into the epidemiology of late recurrent breast cancer. Oncologists and health-care professionals working in cancer survivorship settings should be aware of the risk of late recurrence, particularly among women with a history of ER-positive, larger tumors or node-positive disease. Our study advocates for further research to characterize the biology underlying the resurgence of breast cancer long after primary diagnosis to inform strategies for prevention, treatment, and effective follow-up programs. Furthermore, the biology of late recurrences compared with early recurrence needs to be investigated further.

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Data Availability

In accordance with Danish law, this data is not publically accessible and is stored at the Danish Health Authority Research Server. The study protocol, statistical analysis plan are available upon request to the authors.

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