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Comparison of Breast Cancer Recurrence and Outcome Patterns Between Patients Treated From 1986 to 1992 and From 2004 to 2008

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
To determine whether the patterns of relapse according to estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status changed in the contemporary era.

Patients and Methods
Female patients referred to the British Columbia Cancer Agency with biopsy-proven stage I to III breast cancer (BC), diagnosed between 1986 and 1992 (cohort 1 [C1]) and between mid-2004 and 2008 (cohort 2 [C2]), and with known ER and HER2 status were eligible. Data were prospectively collected. C2 patients were matched to C1 patients for stage, grade, and ER and HER2 status. The primary end point was hazard rate of relapse (HRR) for BC by study cohort according to biomarker status. Secondary outcomes included HRR according to stage, grade, and age and hazard rate of death (HRD).

Results
After matching, 7,178 patients were included (3,589 patients in each cohort). BC subtype distribution was as following ER positive/HER2 negative, 70.8%; ER positive/HER2 positive, 6.9%; ER negative/HER2 positive, 6.6%; and ER negative/HER2 negative, 15.8%. For the overall population, the HRR approximately halved in all yearly intervals to year 9 in C2 compared with C1. Differences in HRR between cohorts were greater in the initial five intervals for HER2-positive and ER-negative/HER2-negative BC. The HRR decreased in C2 compared with C1 for all disease stages and grades. The HRD in C2 also decreased compared with C1, although to a lesser extent.

Conclusion
Although the pattern of relapse remains similar, there has been a significant improvement in BC relapse-free survival. Outcomes have improved for all BC subtypes, especially HER2-positive and ER-negative/HER2-negative BC, with the early spike in disease recurrence markedly decreased. These contemporary hazard rates are important for treatment decisions, patient discussions, and planning clinical trials of early BC.

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INTRODUCTION

Breast cancer (BC) is the most common cancer diagnosed among women in the United States and the second leading cause of cancer death among women.[1] More than 90% of all BCs are diagnosed at a localized stage and treated with curative intent.[2]

In the 1990s, Saphner et al[3] reported different patterns of BC recurrence according to estrogen receptor (ER) positivity for patients diagnosed from 1978 to 1988. The hazard of recurrence for ER-negative patients was higher in years 0 to 5 and decreased significantly with time. For ER-positive patients, the hazards of recurrence remained relatively constant. Between years 3 and 4, the hazard of recurrence for ER-negative and ER-positive patients crossed and was higher for ER-positive patients beyond 5 years. This study was pivotal in our understanding of the patterns of relapse in invasive BC and has been quoted extensively in clinical and research practice.[4-12]

BC is now classified according to molecular factors that predict response to treatment.[13,14] Although patients continue to experience relapse, contemporary studies in early BC report unexpectedly good outcomes in standard treatment arms, requiring much longer follow-up, increased expense, and potential patient exposure to futile experimental therapies.[15-20]

In this large retrospective analysis, our aim was to demonstrate the current patterns of disease relapse and outcomes of patients with BC treated with

curative intent in the modern treatment era (2004 to 2008) and to compare this with a historic cohort from 1986 to 1992 in British Columbia, an era similar to the initial series by Saphner et al.[3]

PATIENTS AND METHODS

Patient Population

We reviewed female patients with biopsy-proven, newly diagnosed, stage I to III BC, who were diagnosed between January 1986 and December 1992 (cohort 1 [C1]) and between July 2004 and December 2008 (cohort 2 [C2]) and referred to the British Columbia Cancer Agency. Patients with unknown ER or human epidermal growth factor receptor 2 (HER2) status, a previous or synchronous invasive BC, or noninvasive BC were excluded.

Data were extracted from the prospectively collected Breast Cancer Outcomes Unit Database to determine clinical, pathologic, treatment, and outcome variables. Health information management professionals trained in data abstraction reviewed the complete medical record of eligible patients. Information, including age at diagnosis, stage,[21] grade, histology, biomarkers (ER and HER2), and lymphovascular invasion, was extracted. Data on systemic therapy (ie, chemotherapy, anti-HER2 therapy, and hormonal therapy) and dates of diagnosis, disease relapse, and death were also obtained.

Disease relapse was defined as any locoregional (within the confines of the ipsilateral breast, chest wall, or regional lymph nodes) or distant BC recurrence after initial therapy. Additional manual electronic chart data extraction was performed for missing values on receptor status and grade. To adjust for possible imbalances, C1 and C2 patients were matched in a 1:1 ratio for disease stage, grade, ER status, and HER2 status.

Treatment Guidelines for the Two Cohorts

British Columbia has treatment guidelines that evolve with new data. In C1, no systemic therapy (cyclophosphamide, methotrexate, and fluorouracil or doxorubicin and cyclophosphamide) was recommended for node-negative patients with tumors less than 2 cm without lymphovascular invasion. Two years of tamoxifen was given to postmenopausal but not premenopausal women. In C2, policy changes included the introduction of aromatase inhibitors, taxanes, and trastuzumab, as well as the increased use of regional nodal radiotherapy, tamoxifen for premenopausal women, prolonged hormonal therapy from 2 to 5 or more years, and second and third lines of systemic therapy at relapse.[22] The Screening Mammography Program of British Columbia (SMPBC) was implemented in 1988.

BC Classification

BC subtypes were classified according to ER and HER2 status into four categories as follows: ER positive/HER2 negative, ER positive/HER2 positive, ER negative/HER2 positive, and ER negative/HER2 negative. ER status was determined by the dextran-coated charcoal (DCC) biochemical method in C1 at the time of diagnosis.[23] ER status was considered positive if the ER protein level was $\geq$ 10 fmol/mg and negative if the protein level was less than 10 fmol/mg. In cohort 2, ER was evaluated by immunohistochemistry (IHC) staining and was considered positive if staining $\geq$ 1% of tumor tissue.[24,25]

HER2 status was determined by IHC staining. Tumors were considered HER2 positive if they scored 3+ on IHC, indeterminate if 2+, and negative if 1+ or 0. When IHC was indeterminate, tumors were considered HER2 positive with amplification (ratio $\geq$ 2.0) by fluorescence in situ hybridization analysis.[26] For C1 patients, the tissue microarray technique was used to obtain tumor from paraffin-embedded blocks to determine HER2 status, as described in detail by Cheang et al.[24] HER2 was tested by IHC, followed by fluorescence in situ hybridization analysis if required.

Outcome Measures

The primary end point of this study was to compare the hazard rate of BC relapse (hazard rate of relapse [HRR]) between C1 and C2 according to ER status and tumor subtypes and to establish contemporary patterns of relapse.

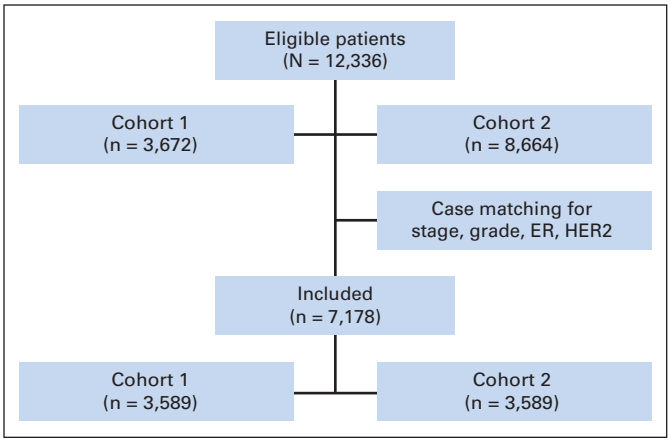

Fig 1. CONSORT diagram. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

Secondary outcomes included the HRR according to disease stage, grade, and age category and the hazard rate of death (HRD).

A relapse event was defined as any disease recurrence. Secondary cancers were censored. A mortality event was defined as death from any cause. For all patients who died of BC without a diagnosis of disease recurrence, a recurrence date was imputed 12 months before the date of death.

Statistical Analysis

The χ^2 and Fisher's exact tests were used to compare characteristics between study cohorts. All statistical tests were two-sided, and $P < .05$ was considered statistically significant. The life-table method was used to calculate the annual hazards of recurrence (HRR) and death (HRD). The annual hazards were plotted at each 1-year interval after diagnosis until year 9, with a total of nine yearly intervals (intervals 0 to 8). The ratio between the hazards of C1 and C2 is demonstrated as C2/C1. SPSS for Windows version 14.0 (SPSS, Chicago, IL) was used for all statistical analyses. The study was approved by the Research Ethics Board of the British Columbia Cancer Agency.

RESULTS

The Breast Cancer Outcomes Unit database identified 12,336 eligible patients. After case matching, 7,178 patients were included in the analysis (3,589 patients in each cohort; Fig 1). Patient characteristics of the entire cohort are listed in Appendix Table A1 (online only), and patient characteristics of the matched cohort are listed in Table 1. All described results will refer to the matched cohort population. Median follow-up times were 15.5 and 6.1 years in C1 and C2, respectively. The delivery of chemotherapy, hormone therapy, and anti-HER2 agent was different between study cohorts. Chemotherapy was given to 26.3% of patients in C1 versus 52.7% of patients in C2 ($P < .001$). ER-positive patients received hormone therapy in 46.7% of patients in C1 versus 86.6% in C2 ($P < .001$). Patients in C1 did not receive any HER2-targeted adjuvant therapy, whereas 72.0% of HER2-positive patients in C2 received adjuvant anti-HER2 treatment.

Disease Relapse

One thousand seven hundred four patients experienced disease relapse in the first 9 years of follow-up. The HRR approximately halved in C2 compared with C1 up to year 7. After year 7, the C2/C1 HRR ratio decreased to less than 0.5, but the number of long-term follow-up patients in C2 diminished (Data Supplement).

Table 1. Patient Characteristics of Matched Cohorts

Characteristic	Cohort 1 (1986 to 1992; n = 3,589) No. of Patients	%	Cohort 2 (mid-2004 to 2008; n = 3,589) No. of Patients	%	*P*
Age, years					
Median	60		58		
Range	23-95		23-97		
< 40	272	7.6	200	5.6	< .001
40-49	763	21.3	776	21.6	
50-59	731	20.4	955	26.6	
60-69	944	26.3	831	23.2	
≥ 70	879	24.5	827	23.0	
ER status					
ER negative	803	22.4	803	22.4	
ER positive	2,786	77.6	2,786	77.6	
Biomarkers					
ER positive/HER2 negative	2,540	70.8	2,540	70.8	
ER positive/HER2 positive	246	6.9	246	6.9	
ER negative/HER2 positive	237	6.6	237	6.6	
ER negative/HER2 negative	566	15.8	566	15.8	
Stage					
I	1,237	34.5	1,237	34.5	
II	1,660	46.3	1,660	46.3	
III	678	18.9	678	18.9	
Unknown	14	0.4	14	0.4	
Grade					
1	180	5.0	180	5.0	
2	1,446	40.3	1,446	40.3	
3	1,887	52.6	1,887	52.6	
Unknown	76	2.1	76	2.1	
Histology					< .001
Invasive ductal	3,322	92.6	3,296	91.8	
Invasive lobular	198	5.5	275	7.7	
Other	69	1.9	18	0.5	
LVI					.018
LVI positive	948	26.4	870	24.2	
LVI negative	2,439	68.0	2,549	71.0	
Unknown	202	5.6	170	4.7	
Adjuvant chemotherapy					< .001
Yes	943	26.3	1,893	52.7	
First generation	676	71.7	202	10.7	
Second generation	159	16.9	517	27.3	
Third generation	108	11.5	1,174	62.0	
No	2,644	73.7	1,691	47.1	
Unknown	2	0.1	5	0.1	
Hormone therapy in ER-positive disease					< .001
Yes	1,302	46.7	2,409	86.6	
No	1,484	53.3	373	13.4	
Unknown	0		4	0.1	
Anti-HER2 agent in HER2-positive disease					< .001
Yes	0	0	348	72.0	
No	483	100	135	28.0	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LVI, lymphovascular invasion.

ER Status

The HRR for ER-negative tumors was higher than the HRR for ER-positive tumors during the initial years of follow-up. In C1, the HRR for ER-negative tumors was higher in the first 4 years; the HRR for ER-positive tumors had a smooth peak in the first 3 years and remained relatively stable after year 5. Between years 4 and 5, the hazards of ER-negative and ER-positive patients crossed. In C2, the HRR for ER-negative patients was also higher in the initial 4 years; the HRR for ER-positive patients had a slight peak in the first 3 years and remained relatively stable after year 5. Again, the HRR of ER-negative and ER-positive patients crossed between years 4 and 5 (Fig 2, Table 2).

Despite the same pattern of disease relapse over time for ER-negative and ER-positive patients between study cohorts, the HRR of

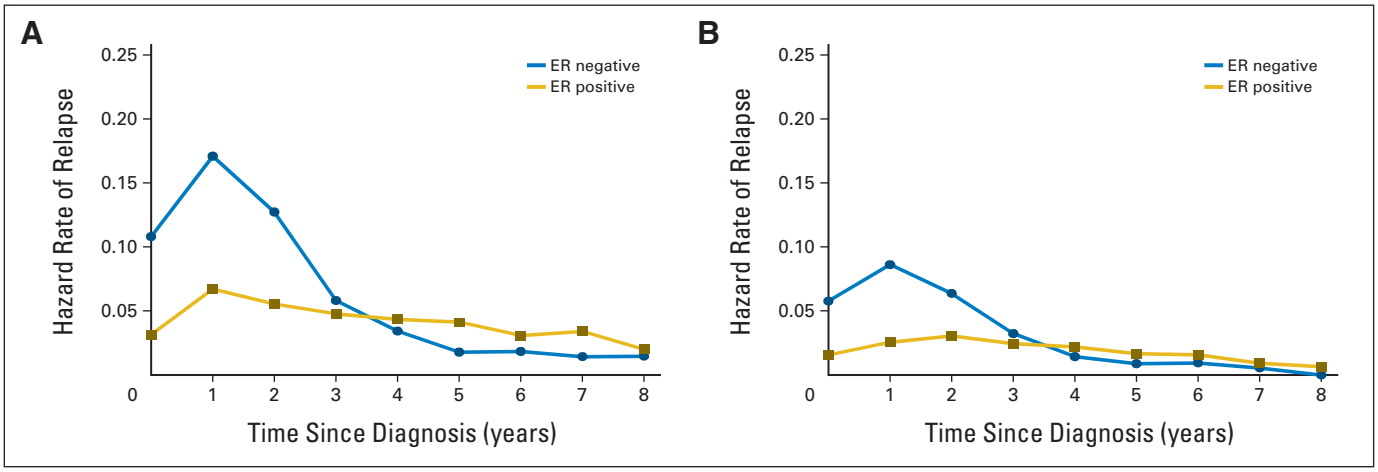

Fig 2. Hazard rate of relapse according to estrogen receptor (ER) status in (A) cohort 1 and (B) cohort 2.

C2 was approximately half of C1 for almost all yearly intervals in ER-negative patients, and the HRR C2/C1 ratio ranged from 0.26 to 0.56 throughout the yearly intervals in ER-positive patients.

Tumor Subtype

The HRR according to tumor subtype was compared between C1 and C2. For ER-positive/HER2-negative tumors, the HRR in C2 ranged from 0.3 to 0.62 of C1 throughout the yearly intervals. For ER-positive/HER2-positive disease, the peak of disease recurrence in the first 5 years seen in C1 was not observed in C2, with an HRR in C2 less than half of that of C1, except for comparison interval 5. For ER-negative/HER2-positive disease, the peak of disease relapse seen in C1 was still present in C2 but reduced in magnitude, with an HRR of C2 lower than 0.5 of C1 in the initial 5 years, with few events afterward. For ER-negative/HER2-negative disease, the HRR of C2 also improved in comparison to C1, but to a lesser extent than for other subtypes. The C2/C1 HRR ratio ranged from 0.55 to 0.87 in the initial seven intervals and then reached zero in both cohorts. The peak of disease recurrence in the initial 5 years persisted in C2 (Fig 3, Table 3).

Disease Stage and Grade

The HRR was lower in C2 compared with C1 across all disease stages (Data Supplement) and tumor grades (Data Supplement).

Age

Age distribution was not uniform between cohorts. Younger patients ($<$ 50 years old) had a higher HRR compared with older patients ($\geq$ 50 years old) in C1 in the first 5 years of follow-up. In C2, this difference was minimal (Data Supplement). Comparing the same age categories, the HRR of C2 is lower than that of C1 for all comparison intervals. Younger patients ($<$ 50 years old) in C1 were less frequently ER positive/HER2 negative and more frequently ER negative/HER2 negative than in C2 (Data Supplement).

Mortality

For the entire study population, the HRD was reduced in C2 compared with C1 during the follow-up time, with the exception of the first yearly interval (Data Supplement). The HRD was higher for ER-negative patients in the first years after diagnosis in both cohorts. For ER-positive patients, the HRD increased over the years and crossed that of the ER-negative patients at year 6 in C1 and at year 5 in C2 (Data Supplement). The greatest relative HRD reductions in C2 were observed in HER2-positive disease. For HER2-negative disease, a reduction in the HRD was not observed across all yearly intervals (Table 4).

Table 2. HRR According to ER Status per Study Cohort

ER Status and Cohort	HRR at 1-Year Interval (%)																	
	0		1		2		3		4		5		6		7		8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
ER positive																		
C1	3.1	0.7	6.7	1.0	5.5	0.9	4.8	0.9	4.3	0.9	4.1	0.9	3.1	0.8	3.4	0.9	2.0	0.7
C2	1.6	0.5	2.6	0.6	3.1	0.7	2.5	0.6	2.2	0.6	1.7	0.6	1.6	0.8	0.9	0.8	0.7	1.3
C2/C1 ratio	0.52		0.39		0.56		0.52		0.51		0.41		0.52		0.26		0.35	
ER negative																		
C1	10.8	2.3	17.1	3.2	12.7	3.0	5.8	2.1	3.4	1.7	1.8	1.2	1.8	1.3	1.4	1.1	1.5	1.2
C2	5.8	1.7	8.6	2.1	6.4	1.9	3.2	1.4	1.4	1.0	0.9	0.9	0.9	1.1	0.6	1.1	0	0
C2/C1 ratio	0.54		0.50		0.50		0.55		0.41		0.50		0.50		0.43		0	

Abbreviations: ER, estrogen receptor; HRR, hazard rate of relapse; SD, standard deviation.

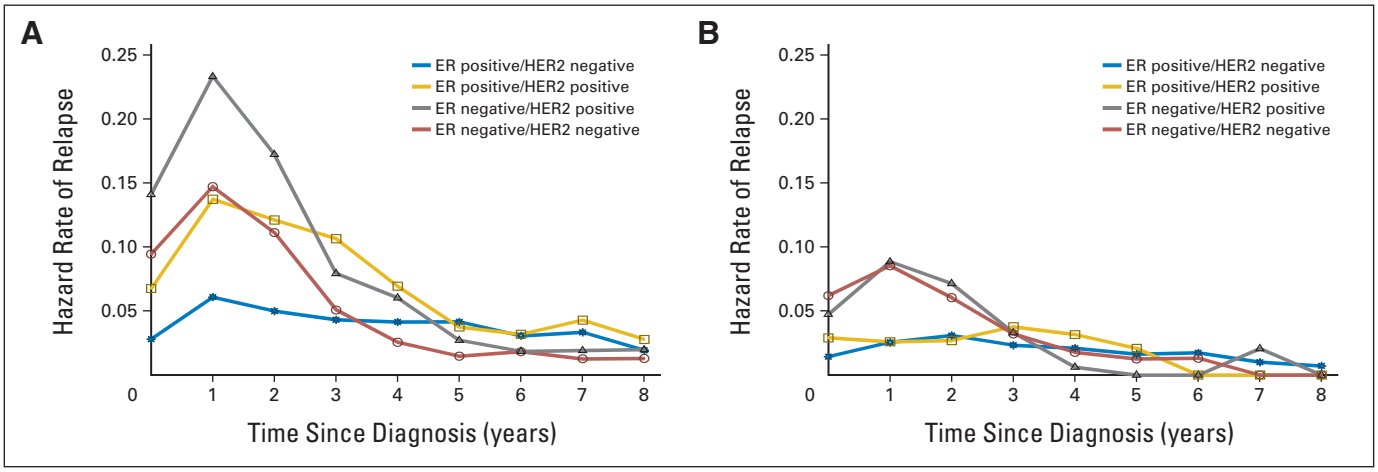

Fig 3. Hazard rate of relapse according to tumor subtype in (A) cohort 1 and (B) cohort 2. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

DISCUSSION

The description by Saphner et al[3] of different patterns of relapse has been a mainstay of clinical practice and research, particularly the discreet outcomes between estrogen-sensitive and estrogen-insensitive tumors.[27,28] Recently, a distinction between the HER2-overexpressing cancers according to ER status has been described.[29] We have shown that the timing and patterns of relapse differ according to BC molecular subtypes and that these patterns persist with current therapies, albeit with better overall outcomes.

After reproducing the curves of Saphner et al[3] in our initial cohort of patients, we have demonstrated that the pattern of relapse over time according to ER status remains similar in a recent cohort. Not only have the HRR curves in C2 improved with better outcomes overall, but also the peak of the curve seen in ER-negative cancers has become attenuated. The HRD in C2 has also maintained a similar pattern compared with C1 but with overall improvements. A higher benefit was again seen in the early peak of mortality in the ER-negative patients. The greatest improvements in outcomes were achieved in the BC subtypes known to be more aggressive, namely the HER2-positive and ER-negative/HER2-negative patients. Although a higher peak of relapse and death remains in the early years after diagnosis, the decrease in relapse rate is likely explained by the use of more comprehensive and appropriate systemic and locoregional treatments with recognition of the subtypes.

Park et al[12] have also demonstrated different HRRs according to BC molecular subtypes in a cohort of patients diagnosed between 1999 and 2005, with the HRR for HER2-positive and triple-negative BC reaching a peak approximately 1 year after diagnosis. A different rate of locoregional relapse was seen, with higher rates for the HER2-positive subgroup. However, the patients in this study were treated before the standard use of adjuvant trastuzumab. Other studies

Table 3. Relapse Hazards According to Study Cohort and Tumor Subgroup

Tumor Subgroup and Cohort	HRR at 1-Year Interval (%)																	
	0		1		2		3		4		5		6		7		8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
ER positive/HER2 negative																		
C1	2.8	0.7	6.1	1.0	5.0	0.9	4.3	0.9	4.1	0.9	4.2	0.9	3.1	0.8	3.3	0.9	1.9	0.7
C2	1.4	0.5	2.6	0.6	3.1	0.7	2.3	0.6	2.1	0.6	1.6	0.6	1.7	0.8	1.0	0.9	0.7	1.4
C2/C1 ratio	0.50		0.43		0.62		0.53		0.51		0.38		0.55		0.30		0.37	
ER positive/HER2 positive																		
C1	6.8	3.3	13.7	0.5	12.1	5.1	10.7	5.1	6.9	4.3	3.8	3.3	3.2	3.1	4.3	3.8	2.8	3.2
C2	2.9	2.2	2.6	2.1	2.7	2.2	3.8	2.6	3.2	2.5	2.1	2.4	0	0	0	0	0	0
C2/C1 ratio	0.43		0.19		0.22		0.36		0.46		0.55		0		0		0	
ER negative/HER2 positive																		
C1	14.1	0.5	23.3	7.0	17.2	6.7	7.9	4.9	6.0	4.5	2.7	3.1	1.9	2.6	1.9	2.7	2.0	2.8
C2	4.8	2.8	8.9	4.0	7.2	3.7	3.3	2.6	0.6	1.2	0	0	0	0	2.1	4.0	0	0
C2/C1 ratio	0.34		0.38		0.42		0.42		0.10		0		0		1.11		0	
ER negative/HER2 negative																		
C1	9.5	2.6	14.7	3.4	11.1	3.2	5.1	2.3	2.6	1.7	1.5	1.3	1.8	1.5	1.3	1.2	1.3	1.3
C2	6.2	2.1	8.5	2.5	6.1	22	3.2	1.7	1.8	1.3	1.3	1.2	1.2	1.5	0	0	0	0
C2/C1 ratio	0.65		0.58		0.55		0.63		0.69		0.87		0.67		0		0	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HRR, hazard rate of relapse; SD, standard deviation.

Table 4. Hazard of Death According to Tumor Subtype

	HRD at 1-Year Interval (%)																	
	0		1		2		3		4		5		6		7		8	
Tumor Subtype and Cohort	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
ER positive/HER2 negative																		
C1	0.5	0.3	2.8	0.7	4.1	0.8	4.2	0.8	4.4	0.9	3.7	0.8	5.8	1.0	5.6	1.1	3.7	0.8
C2	1.3	0.5	1.9	0.5	3.3	0.7	2.7	0.7	3.3	0.8	4.4	1.0	3.6	1.2	3.2	1.5	2.6	2.6
C2/C1 ratio	2.60		0.68		0.80		0.64		0.75		1.19		0.62		0.57		0.70	
ER positive/HER2 positive																		
C1	1.2	1.4	4.6	2.7	12.8	4.7	10.9	4.6	8.0	4.2	8.6	4.5	4.6	3.4	7.7	4.6	8.4	4.9
C2	0.8	1.1	2.9	2.2	1.7	1.7	5.3	3.0	3.9	2.7	1.3	1.8	3.0	3.4	3.9	5.4	0	0
C2/C1 ratio	0.67		0.63		0.13		0.49		0.49		0.15		0.65		0.51		0	
ER negative/HER2 positive																		
C1	3.9	2.5	14.6	5.1	12.4	5.1	13.5	5.6	9.7	5.1	5.2	3.9	1.5	2.1	1.6	2.2	3.2	3.1
C2	0.8	1.2	6.6	3.3	5.1	3.0	9.5	4.3	1.7	1.9	2.1	2.4	0	0	0	0	0	0
C2/C1 ratio	0.21		0.45		0.41		0.70		0.18		0.40		0		0		0	
ER negative/HER2 negative																		
C1	2.7	1.4	9.5	2.6	7.9	2.5	10.5	3.0	5.2	2.2	4.9	2.2	4.3	2.1	2.5	1.6	2.3	1.6
C2	3.2	1.5	6.4	2.2	5.2	2.0	4.4	1.9	5.1	2.1	3.8	2.0	3.7	2.4	0.7	1.4	3.1	6.2
C2/C1 ratio	1.19		0.67		0.66		0.42		0.98		0.78		0.86		0.28		1.35	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HRD, hazard rate of death; SD, standard deviation.

confirm the influence of BC subtypes on the rates of locoregional relapse[30-33] and distant recurrence.[30,34-36]

Our analysis also showed a greater HRR for higher disease stage and grade, which is consistent with the results of Saphner et al[3] and others.[12] However, the biology of the disease inferred by BC subtypes seems to be the major driver. Higher disease stage and tumor grade are associated with a larger percentage of the more aggressive subtypes, namely HER2-positive and ER-negative/HER2-negative disease (Data Supplement). Other studies have confirmed the independent impact of BC subtypes on outcomes after adjusting for other prognostic factors.[30,32,36-38]

We evaluated the impact of age on the HRR as a surrogate marker for menopausal status. In C1, younger age was associated with worse early outcomes compared with an older group of patients. However, this was not true for C2. Saphner et al[3] also showed a worse outcome for premenopausal patients, which is possibly explained by worse disease biology and a lack of appropriate treatment, rather than age alone.

The method of diagnosis has an important prognostic role in BC, and this is a limitation of our study. Reports suggest that patients with tumors detected by screening mammography may have a longer time to distant recurrence and longer survival compared with interval or symptomatically detected BC.[39] This is partially explained by a lead-time bias associated with stage shift. Although matching for stage may decrease the effect, it does not correct for this bias completely because of the within-stage shift that also occurs.[40] Screen-detected cancers also tend to grow more slowly, creating a length-time bias. Matching for tumor biology would theoretically compensate for this bias. The SMPBC began in 1988. An increase in diagnosis was primarily driven by population aging and growth and predates 1988.[41] Moreover, the rate of invasive BC overdiagnosis with the implementation of the SMPBC was modest, reported as 5.4%. Although our matching will not exclude the bias of increased screening in C2, it will reduce its impact.

The introduction of new systemic agents, including chemotherapy,[42-49] HER2-targeted agents,[50-54] and hormonal therapies,[55] in the curative setting has contributed to our results. The HRR plot in C2 of the ER-positive/HER2-positive patients approaches that of the ER-positive/HER2-negative patients, supporting the efficacy of anti-HER2 agents. However, the reduced but persistent peak of early recurrence in ER-negative/HER2-positive disease signals the need for new treatment strategies, including dual HER2 blockade.

The ER-negative/HER2-negative patients also maintain a persistent early peak of disease recurrence, with reduced improvement in C2 compared with C1. These tumors are orphans of efficacious therapy to date. They are recognized as a nonhomogeneous entity that can be further classified into at least six subgroups,[56-58] which challenges research efforts of trials targeted for these smaller, specific biologic groups.[59,60]

The benefit from chemotherapy is known to occur mostly in the initial 3 years after treatment.[61] The improvements seen in our study extend throughout the follow-up period, likely representing both improved treatment strategies and increased screening. In ER-positive patients, the widespread and more prolonged use of hormone therapy and more efficacious agents has affected outcomes. For ER-negative patients, chemotherapy results in dramatic decreases in early recurrence rates. The benefit extends beyond the 3-year period, with no rebound effect, and is probably associated with other treatment advances including greater attention to negative surgical margins and regional radiotherapy in node-positive patients.

Longer follow-up of C2 patients is needed to confirm that ER-positive disease continues to relapse beyond 10 years after diagnosis. Recent evidence showing improved outcomes with extended adjuvant hormonal therapy[18,62,63] may affect the HRR for these patients. Ongoing studies of other targeted agents[64] may also impact late relapse rates of ER-positive tumors, which emphasizes the importance of periodically revisiting the long-term hazard rate patterns.

The use of ER and HER2 status as the only markers to identify the BC subtypes is a potential limitation of our study. Our classification aims to reflect the underlying biology of BC, as an approximation of the molecular subtypes. It is reasonable to assume such correlation based on these two markers, because they remain in daily clinical use. Progesterone receptor is strongly correlated with ER status. Ki-67 methodologies have not been standardized to date.[65] ER status was determined by different but equivalent methodologies in each cohort. The prognostic potential of the DCC and IHC methods is comparable.[66]

To enable a historical cohort comparison, HER2 status was determined retrospectively in C1. Previous manipulation for the DCC technique and long-term tissue storage under possibly suboptimal conditions might have created artifacts, disrupted membrane integrity, and smashed cellular content, which could compromise the individual validity of HER2 testing in C1 patients. However, the large numbers analyzed in our study should compensate for the individual inaccuracy of the test. Technical reasons could also explain the lower incidence of HER2-positive patients in C1. Overall, our BC subgroups are thought to adequately represent the different BC subtypes.

The shorter follow-up time of C2 patients is another possible limitation, and the calculated hazards for the later years may be more uncertain than in C1. However, our large number of study patients at risk seems statistically adequate.

Although we did not analyze treatment differences between BC subtypes, there are standard guidelines for care across all British Columbia Cancer Agency treatment centers and data showing good adherence to policies.[67,68] Thus, the improvement in outcomes in C2 likely reflects the better efficacy of modern evidence-based treatment guidelines.

In summary, we demonstrated significant improvements in the outcomes of patients with stage I to III BC treated in the modern era compared with a cohort of patients treated in the late 1980s/early 1990s, with a pattern of relapse remaining consistent with the differences in ER status previously described. Although current treatments are more effective, we still see late relapses in patients with ER-positive tumors and an early peak of recurrence in patients with ER-negative cancers. Contemporary patterns of disease recurrence according to BC characteristics and subtypes are of upmost importance to adequately inform patients and physicians about prognosis and also to guide planning of future clinical trials.

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Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

estrogen receptor (ER): ligand-activated nuclear proteins, belonging to the class of nuclear receptors, present in many breast cancer cells that are important in the progression of hormone-dependent cancers. After binding, the receptor-ligand complex activates gene transcription. There are two types of estrogen receptors (ERα and ERβ). ERα is one of the most important proteins controlling breast cancer function. ERβ is present in much lower levels in breast cancer, and its function is uncertain. Estrogen receptor status guides therapeutic decisions in breast cancer.

HER2/*neu* (human epidermal growth factor receptor 2): also called ErbB2. HER2/*neu* belongs to the epidermal growth factor receptor (EGFR) family and is overexpressed in several solid tumors. Like EGFR, it is a tyrosine kinase receptor whose activation leads to proliferative signals within the cells. On activation, the human epidermal growth factor family of receptors are known to form homodimers and heterodimers, each with a distinct signaling activity. Because HER2 is the preferred dimerization partner when heterodimers are formed, it is important for signaling through ligands specific for any members of the family. It is typically overexpressed in several epithelial tumors.

prognostic factor: a measurable patient characteristic that is associated with the subsequent course of disease (whether or not therapy is administered). The identification of a prognostic factor does not necessarily suggest a cause-and-effect relationship. However, within a suitable outcome model, the measurement of a prognostic factor contributes to an estimate of an outcome probability (eg, the probability of disease-free survival within a given time interval).

Appendix

Table A1. Patient Characteristics of Unmatched Cohorts

Characteristic	Cohort 1 (1986 to 1992; n = 3,672)		Cohort 2 (mid-2004 to 2008; n = 8,664)		*P*
	No. of Patients	%	No. of Patients	%	
Age, years					
Median	60		59		
Range	23-95		23-98		
< 40	274	7.5	429	5.0	< .001
40-49	779	21.2	1,800	20.8	
50-59	750	20.4	2,299	26.5	
60-69	962	26.2	2,039	23.5	
≥ 70	907	24.7	2,097	24.2	
ER status					< .001
ER negative	810	22.1	1,624	18.7	
ER positive	2,862	77.9	7,040	81.3	
Biomarkers					< .001
ER positive/HER2 negative	2,615	71.2	6,192	71.5	
ER positive/HER2 positive	247	6.7	848	9.8	
ER negative/HER2 positive	240	6.5	562	6.5	
ER negative/HER2 negative	570	15.5	1,062	12.3	
Stage					< .001
I	1,262	34.4	3,676	42.4	
II	1,707	46.5	3,529	40.7	
III	680	18.5	1,416	16.3	
Unknown	23	0.6	43	0.5	
Grade					< .001
1	180	4.9	1,918	22.1	
2	1,448	39.4	3,441	39.7	
3	1,892	51.5	3,218	37.1	
Unknown	152	4.1	87	1.0	
Histology					
Invasive ductal	3,380	92.0	7,901	91.2	< .001
Invasive lobular	220	6.0	725	8.4	
Other	72	2.0	38	0.4	
LVI					
LVI positive	964	26.3	1,783	20.6	< .001
LVI negative	2,484	67.6	6,508	75.1	
Unknown	224	6.1	373	4.3	
Adjuvant chemotherapy					
Yes	960	26.1	3,956	45.7	< .001
First generation	691	72.0	456	11.5	
Second generation	159	16.6	1,009	25.5	
Third generation	110	11.4	2,491	63.0	
No	2,710	73.8	4,702	54.3	
Unknown	2	0.1	6	0.1	
Hormone therapy in ER-positive disease					
Yes	1,342	46.9	5,950	84.5	< .001
No	1,520	53,1	1,083	15.4	
Unknown	0		7	<0.1	
Anti HER2 agent in HER2-positive disease					
Yes	0	0	998	70.8	< .001
No	487	100	412	29.2	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LVI, lymphovascular invasion.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Comparison of Breast Cancer Recurrence and Outcome Patterns Between Patients Treated From 1986 to 1992 and From 2004 to 2008

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