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ORIGINAL ARTICLE

Time-dependent prognostic impact of tumor grade in stage I-III breast cancers

M. Mariani[1,2,3†], M. Ochocki[4†], G. Bianchini[1,2], M. Marczyk[3,4] & L. Pusztai[3*]

[1]Medical Oncology, Università Vita-Salute San Raffaele, Milan; [2]Department of Medical Oncology, IRCCS Ospedale San Raffaele, Milan, Italy; [3]Yale Cancer Center, Yale School of Medicine, New Haven, USA; [4]Department of Data Science and Engineering, Silesian University of Technology, Gliwice, Poland

Available online xxx

Background: Breast cancer (BC) mortality risk extends over decades; yet, the temporal prognostic patterns of histological grade across subtypes and stages remain unclear.

Patients and methods: Women with stage I-III BC diagnosed between 2000 and 2018 were identified from Surveillance, Epidemiology, and End Results registries ($N = 767\,218$). Breast cancer-specific mortality (BCSM), as the primary endpoint, was analyzed using cumulative incidence functions including competing risk and annual hazard rates stratified by grade, estrogen receptor (ER) status, stage, and adjuvant chemotherapy. Restricted mean survival time differences were calculated to quantify absolute survival differences across follow-up intervals. Landmark survival analyses were carried out for 0 to <60, 60 to <120, and 120 to <180 months from diagnosis. Time-varying effects of grade were assessed through interval-specific modeling to evaluate nonproportional hazards.

Results: Overall, 23%, 44%, and 33% of cancers were grades 1, 2, and 3, respectively, accounting for 8%, 35%, and 57% of BC deaths. In each consecutive follow-up period, the contribution of grade 1 cancers to BCSM increased, and the contribution of grade 3 cancers decreased. Overall, 59% and 30% of deaths from grades 1 and 3 cancers, respectively, occurred after 5 years. In ER-positive disease, grade 3 tumors showed peak annual hazards between years 3 and 5, whereas grade 1 tumors had lower but sustained hazards extending beyond 10 years; the hazard curves converged between years 10 and 12. In ER-negative disease, early hazards were higher, and convergence also started earlier at years 5-8. Absolute risk was influenced by nodal status and tumor stage within each grade category and follow-up interval.

Conclusion: Grade 1 cancers show sustained risk beyond 10 years, whereas grade 3 cancers exhibit front-loaded risk. These temporal risk patterns, together with other clinical and genomic data, could inform extended endocrine therapy decisions and surveillance strategies.

Key words: breast cancer, breast cancer-specific survival, late recurrence, tumor grade

INTRODUCTION

Over the past decades, outcomes for patients with breast cancer (BC) have substantially improved.[1] This progress is attributed to widespread adoption of mammographic screening[2] and the development of increasingly more effective systemic adjuvant therapies.[3-5] Since 2017, over 80% of newly diagnosed BCs are stage I cancers in the United States.[6] Paradoxically, from 2000 to 2017, the proportion of BC-specific deaths from stage I and II cancers increased from 16% to 23%, and from 31% to 40%, respectively, whereas the contribution from stage III cancers declined from 36% to 30%.[6] This shift is attributed to fewer stage II-III BCs due to extensive screening, and fewer metastatic recurrences (and therefore death) in high-risk stage II and III cancers due to highly effective multidrug adjuvant therapies.

The risk of distant recurrence extends into decades after initial diagnosis, particularly among estrogen receptor (ER)-positive BCs.[7] Some of the most widely used molecular prognostic tests that guide chemotherapy treatment selection in early-stage ER-positive cancer accurately predict early recurrences but lose prognostic power for late recurrences that occur after 5 years.[8] Currently, the Breast Cancer Index is the only molecular assay that has a clinically validated late recurrence predictive function, but has limited availability globally.[9] Histological grade, tumor size,

*Correspondence to: Dr Lajos Pusztai, Breast Medical Oncology, Yale Cancer Center, Suirte 120, 300 George Street, New Haven, CT 06511, USA. Tel +1 203 737 8309

E-mail: lajos.pusztai@yale.edu (L. Pusztai).

†Both authors contributed equally to this work.

and lymph node status are independent and broadly available anatomic-pathological prognostic predictors.[9] However, their time-dependent impact on the risk of recurrence is not fully understood. Earlier studies suggested that the number of positive lymph nodes is a powerful predictor of early recurrence, but the annual hazard decreases rapidly over time.[10]

A gene expression study showed that cancers with low proliferation have a continuously increasing risk of relapse over time, with absolute risk higher after 5 years than seen for high proliferation cancers.[11] Histological grade is highly correlated with the proliferative status of BC because mitotic count is one of the components of histological grading.[12] We hypothesize that low-grade tumors, despite their favorable short-term prognosis, exhibit a persistent cumulative risk beyond 5 years and contribute substantially to late recurrence and BC mortality across all stages. Thus, we studied the time-dependent and nonproportional prognostic impact of histological grade on breast cancer-specific mortality (BCSM) in the US Surveillance, Epidemiology, and End Results (SEER) incidence database.

PATIENTS AND METHODS

Data source and preprocessing

Data from patients diagnosed with BC between 2000 and 2018 ($N = 1\ 143\ 556$) were obtained from the SEER incidence database named SEER Research Plus Data, 18 Registries, Nov 2020 Sub using the SEER Stat 8.4.2 software (US National Cancer Institute, Bethesda, MD) in 'Case Listing' mode. Patients with missing information on tumor stage, histological grade (coded as 'Grade THRU 2017'), tumor size, number of positive lymph nodes, year of diagnosis, vital status, ER, or progesterone receptor (PR) status were excluded. We also excluded patients with stage IV, stage 0, or unknown-stage disease; T0 or *in situ* tumors; bilateral BC; histological grade 4 categorization, which was considered likely misclassification ($n = 6315$); male sex; and more than one primary cancer; or no reported surgical procedure. This study used publicly available, deidentified data from SEER. Because the data are deidentified and publicly available, this study did not involve human subjects as defined by federal regulations and was deemed exempt from institutional review board approval.

Survival analysis

BCSM (time from diagnosis to death from BC, with non-BC deaths as competing events) was the primary endpoint. Differences in BCSM by histological grade were compared using cumulative incidence functions (CIFs) to account for competing mortality. Because non-BC mortality increases over time, CIFs were considered the primary analytic method rather than Kaplan–Meier estimates. Gray's test was used to assess the statistical significance of the difference in survival. Breast cancer-specific survival (BCSS) was calculated as 1 minus the CIF of BCSM. Differences in restricted mean survival times (dRMSTs) that represent the absolute difference between the area under the survival curves were also computed on a monthly time scale in 5-year intervals. Landmark survival analyses were carried out for time intervals 0 to <60, 60 to <120, and 120 to <180 months from diagnosis, in which the starting time points of each interval were considered to be time 0 for subsequent survival follow-up. Annual cause-specific hazard rates for BCSM were estimated to evaluate the time-varying impact of tumor grade on BCSM. The obtained hazard rate curves were smoothed with kernel density estimation for better visualization. Analyses were carried out separately for ER-positive and ER-negative cancers. To also assess the possible impact of more effective systemic treatments introduced since 2010, we also carried out an analysis restricted to patients diagnosed between 2010 and 2018. Human epidermal growth factor receptor-2 (HER2) status started to be collected in SEER in 2010, and creating a separate HER2-positive category would limit follow-up to 8 years. To assess the possible impact of HER2-targeted therapies on the grade–outcome interaction, we carried out a separate exploratory analysis of ER-positive cancers stratified by HER2 status.

Multivariate analyses

Multivariate analyses were carried out to assess the impact of age at diagnosis, tumor size, number of positive lymph nodes, receipt of adjuvant chemotherapy, receipt of radiotherapy, tumor grade, and stage on BCSS using the Fine–Gray subdistribution hazard model with BCSM as the main event and any other death as the competing event. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were computed for each variable. To assess interactions with tumor grade, baseline models (without interaction terms) were extended by adding tumor grade and its interaction with each covariate, evaluated separately across all features included in the baseline model. Estimated subdistribution HRs were used to quantify and compare relative risks among subgroups. For models including interaction terms, subgroup-specific HRs were derived by multiplying the relevant main effect and interaction coefficients. The proportional hazards assumption was assessed separately for each covariate using the Schoenfeld test, followed by empirical analysis of the time trends of Schoenfeld residuals.

Statistical analyses were carried out using R version 4.4.1 (The R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at 0.05 in all analyses.

RESULTS

The final analysis included 767 218 patients with stage I-III BC diagnosed between 2000 and 2018 (see Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2026.108352). Baseline patient characteristics are summarized in Table 1. Seventy-seven percent of patients were older than 50 years, 53% had stage I disease, 62% had T1 tumors, and 64% were node-negative. HER2 status was

Table 1. Distribution of clinical subgroups stratified by tumor grade

Patient and cancer variables	Tumor grade 1	Tumor grade 2	Tumor grade 3
	N (%)	*N* (%)	*N* (%)
No. of patients	177 840 (23.18)	337 092 (43.94)	252 286 (32.88)
Age (years)			
<50	29 009 (16.11)	72 493 (40.26)	78 569 (43.63)
≥50	148 831 (25.35)	264 599 (45.07)	173 717 (29.59)
HER2 status			
Negative	93 080 (27.49)	156 526 (46.22)	89 024 (26.29)
Positive	2912 (5.32)	20 792 (37.98)	31 042 (56.7)
Unknown	81 848 (21.89)	159 774 (42.74)	132 220 (35.37)
Tumor stage			
I	133 783 (32.86)	186 573 (45.83)	86 725 (21.3)
II	37 135 (13.84)	114 417 (42.63)	116 856 (43.54)
III	6922 (7.55)	36 102 (39.36)	48 705 (53.1)
Tumor size			
T1	146 379 (30.55)	219 856 (45.89)	112 900 (23.56)
T2	26 174 (11.36)	94 999 (41.23)	109 258 (47.41)
T3	4229 (10.92)	15 942 (41.15)	18 573 (47.94)
T4	1058 (5.6)	6295 (33.29)	11 555 (61.11)
Hormone status			
ER− PR−	10 389 (6.6)	38 229 (24.29)	108 775 (69.11)
ER− PR+	561 (6.62)	2122 (25.05)	5787 (68.32)
ER+ PR−	18 597 (20.31)	39 465 (43.1)	33 494 (36.58)
ER+ PR+	148 293 (29.09)	257 276 (50.47)	104 230 (20.45)
Lymph node status			
Negative	136 176 (27.46)	217 080 (43.77)	142 646 (28.76)
Positive	41 664 (15.36)	120 012 (44.23)	109 640 (40.41)
Radiotherapy			
Yes	102 862 (24.51)	184 809 (44.03)	132 067 (31.46)
No	74 978 (21.58)	152 283 (43.82)	120 219 (34.6)
Chemotherapy			
Yes	28 640 (9)	122 922 (38.64)	166 538 (52.35)
No	149 200 (33.22)	214 170 (47.69)	85 748 (19.09)
Death cause			
Alive	146 964 (24.59)	266 889 (44.65)	183 880 (30.76)
BCS	5658 (8.02)	24 971 (35.39)	39 937 (56.6)
Other	25 218 (25.49)	45 232 (45.73)	28 469 (28.78)

Values at the boundaries represent the percentage contribution of each subgroup across tumor grades.
ER, estrogen receptor; PR, progesterone receptor.

available for 51% of the cohort, and among these patients, 87% had HER2-negative cancers. Overall, 23%, 44%, and 33% of cancers were grades 1, 2, and 3, respectively. Eight percent of BC deaths were due to grade 1 cancers, and 35% and 57% to grades 2 and 3, respectively.

BCSS decreased with increasing grade, regardless of ER status (Figure 1A and B), PR status, nodal status, or receipt of adjuvant chemotherapy (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2026.108352). Inspection of the survival curves showed that most deaths from grade 3 tumors occurred within 5 years of diagnosis, whereas most deaths from grade 1 cancers occurred after the first 5 years; grade 2 cancers showed an intermediate pattern. The results demonstrate a persistent risk of death from grade 1 tumors throughout the entire follow-up period, regardless of ER status (Figure 1C and D).

In a subset analysis, restricted to patients treated between 2010 and 2018, who received more contemporary systemic therapies, we observed the same temporal trend despite the shorter follow-up (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2026.108352). HER2-targeted therapies were widely used by 2010, and these may also alter the time-dependent impact of grade; therefore, we also examined recurrence by grade trends separately for patients with HER2-positive cancer diagnosed between 2010 and 2018, stratified by ER status. The same visual trend was observed as for the entire study population (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2026.108352). These subset analyses indicate a robust and consistent time-dependent prognostic impact for grade.

In 601 355 patients with ER-positive tumors, the annual BCSM hazard was evaluated by stage and receipt of adjuvant chemotherapy (Figure 2). Grade 3 tumors showed peak annual BCSM hazards ranging from 0.9% at year 5 in the stage I chemotherapy-treated subgroup to 9.0% at year 3, followed by a rapid decline in stage III cancers without adjuvant chemotherapy. Grade 1 tumors showed lower maximum hazards but maintained persistent hazards of 0.2%-2.5% through year 18, except in stage III cancers that received no chemotherapy, which had a peak of 4.4% annual hazard at year 6, followed by a decline (Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2026.108352). Hazard rate curves converged approximately 10-12 years after diagnosis. Notably, among patients with stage II-III, ER-positive cancer treated with chemotherapy, hazards of grade 1 cancers numerically exceeded hazards of grade 3 cancers by year 15 [stage II grade 1: 1.09% (95% CI 0.65% to 1.53%) versus grade 3: 0.88% (95% CI 0.59% to 1.17%); stage III grade 1: 2.00% (95% CI 0.61% to 3.38%) versus grade 3: 1.46% (95% CI 0.86% to 2.05%)].

Among 165 863 patients with ER-negative tumors, early annual BCSM hazards were substantially higher than in ER-positive cancers across all stages (Figure 3). Grade 3 tumors showed peak annual BCSM hazards ranging from 1.4% (stage I, chemotherapy subgroup, at year 2) to 17% (stage III, no chemotherapy group, at year 2) and rapidly declined thereafter. Grade 1 tumors showed later lower peaks and maintained persistent hazards across all stages (Supplementary Tables S3 and S4, available at https://doi.org/10.1016/j.esmoop.2026.108352). Similar to ER-positive disease, the hazard rate curves started to converge 5-8 years after diagnosis (Figure 3). After this time, a numerical, but not statistically significant, excess in BCSM hazard was observed for grade 1 compared with grade 3 ER-negative cancers that received adjuvant chemotherapy.

To further explore this observation, we carried out landmark analyses at three follow-up intervals. BCSS differences in RMST between grades 1 and 3 tumors were largest in the first interval and diminished over later follow-up (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2026.108352). Among ER-positive tumors, the RMST difference favoring grade 1 versus 3 disease was 2.05 months during 0 to <60 months of follow-up, which decreased to 0.83 months for 120 to <180 months of follow-up. In ER-negative tumors, the corresponding differences were 4.31 and 0.15 months,

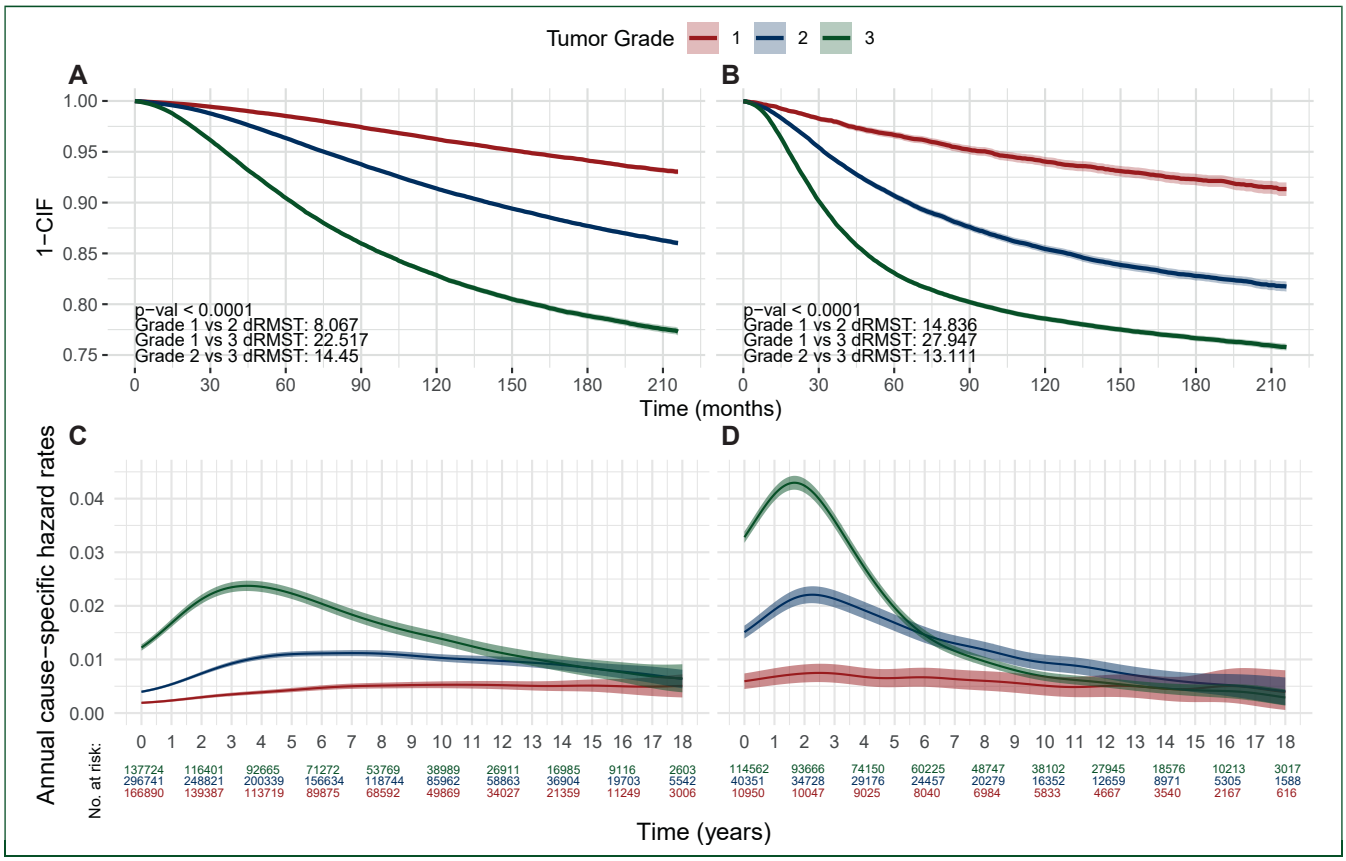

Figure 1. BCSS estimated using the Fine−Gray subdistribution hazard model and corresponding dRMST between tumor grades at 18 years of follow-up (upper panels). The lower panels show the annual hazard of BC-specific death, with the number of individuals at risk over the even-year time points. Analyses are presented separately for ER-positive (A and C) and ER-negative (B and D) patients. *P* values were calculated using Gray's test.
BC, breast cancer; BCSS, breast cancer-specific survival; dRMST, differences in restricted mean survival time; ER, estrogen receptor.

respectively, consistent with convergence of late BC mortality risk between low- and high-grade disease.

The proportional distribution of BCSM by tumor grade was consistent across major clinicopathologic covariates (Table 2). Grade 3 tumors accounted for 47%-84% of deaths across clinical subgroups in the first 60 months, with a steady decline in later intervals. Conversely, the contribution of grade 1 cancers to delayed BC death increased over time. In the ER-positive/PR-positive and ER-positive/PR-negative subgroups, the proportion of deaths attributed to grade 1 tumors increased from 10.32% and 6.05% in the first 60 months to 16.44% and 16.88% in the 120 to <180 months' time frame, respectively (Table 2). In the ER-negative/PR-negative subgroup, the relative proportion of deaths attributed to grade 1 increased from 1.68% in the first 60 months up to 7.81% in the last time interval. Overall, 59% and 30% of deaths from grade 1 and 3 cancers occurred after 5 years, respectively, but absolute risk was strongly associated with nodal status and tumor stage within each histological grade category and follow-up interval (Table 2).

Given violations of the proportional hazards assumption across several covariates, we applied the Fine−Gray multivariate regression model separately for 0 to <60, 60 to <120, and 120 to <180 months follow-up intervals (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2026.108352). Setting grade 1 as the reference, grade 3 tumors had the highest subdistribution HR within the first 60 months: HR 3.30 (95% CI 3.16-3.44), which declined to 2.10 (95% CI 1.99-2.21) from 60 to <120 months and 1.42 (95% CI 1.31-1.53) from 120 to <180 months. Grade 2 tumors had lower HRs across these intervals [1.78 (95% CI 1.70-1.87) in 0 to <60 months; 1.77 (95% CI 1.69-1.85) from 60 to <120 months; 1.55 (95% CI 1.44-1.67) from 120 to <180 months]. Grade versus ER status interaction models revealed no significant interaction for grade 2 tumors throughout all follow-up intervals, whereas the interaction of grade 3 tumors was nonsignificant only in the <60 months interval (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2026.108352). Grade 2 tumors showed no significant interactions and generally exhibited lower HRs than grade 3 tumors in the 0- to 5-year interval, across all models except in age interaction models (Supplementary Tables S7 and S8, available at https://doi.org/10.1016/j.esmoop.2026.108352). Relative HR between tumor grades decreased over time, and the lowest rates were observed in subgroups with more advanced disease, particularly stage II-III tumors and node-positive patients (Supplementary Tables S9-S11 and Figures S6-S8, available at https://doi.org/10.1016/j.esmoop.2026.108352). The

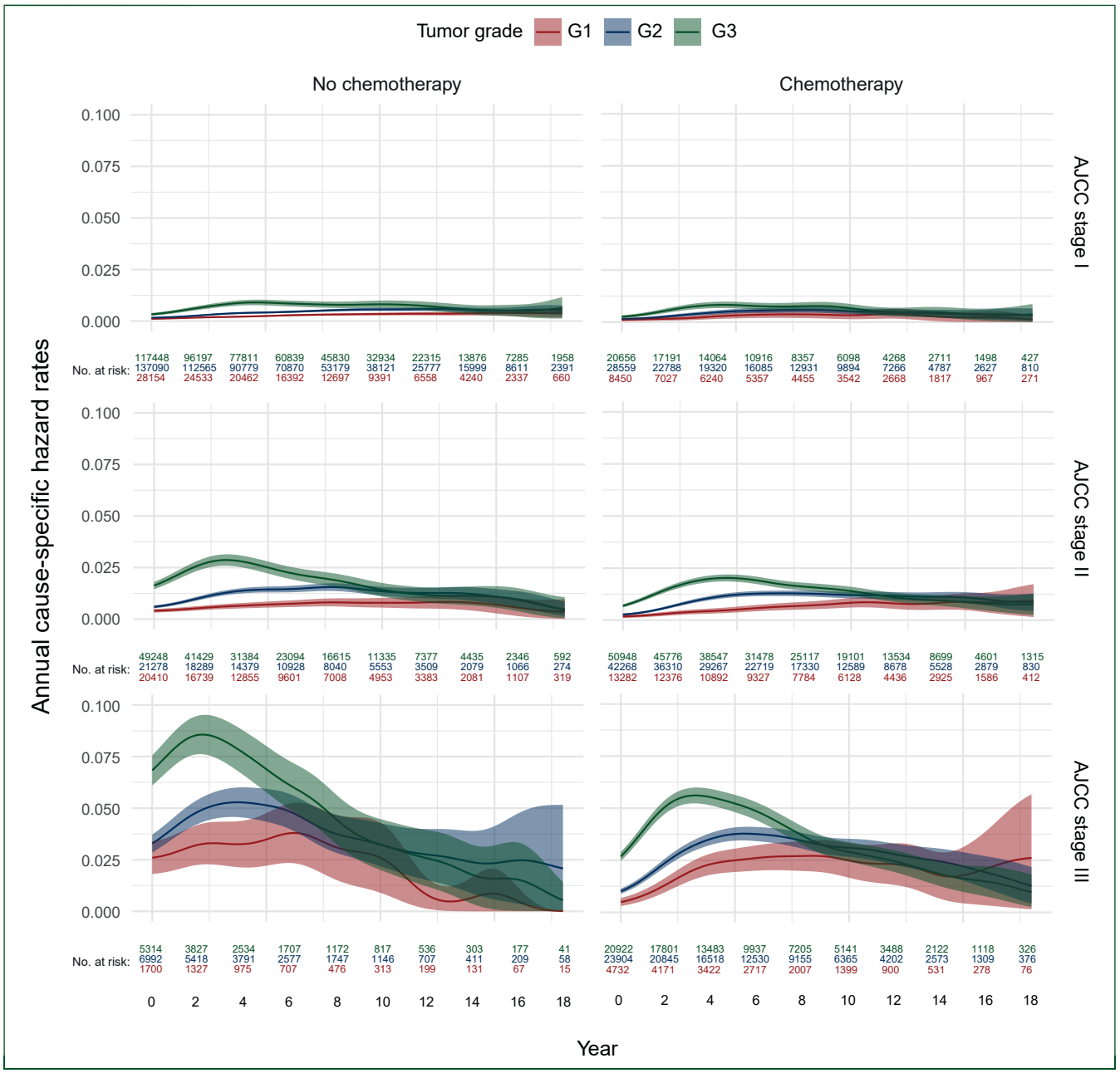

Figure 2. Annual hazard rates for BC-specific death among ER-positive BCs by tumor grade, stratified by stage and receipt of adjuvant chemotherapy. Shaded areas represent 95% CIs. Tables below the panels show the number of individuals at risk at even-year time points.
AJCC, American Joint Committee on Cancer stage I; BC, breast cancer; CIs, confidence intervals; ER, estrogen receptor.

relative HR difference between grades 3 and 2 tumors decreased more rapidly among patients who received chemotherapy and was lowest in the 10- to 15-year interval, suggesting a relatively higher risk of late BCSM for grade 2 tumors extending over 10 years (Supplementary Figure S9, available at https://doi.org/10.1016/j.esmoop.2026.108352).

DISCUSSION

This analysis of more than 700 000 patients with BC showed that the prognostic function of histological grade is time-dependent. Overall, grade 1 cancers have a significantly better prognosis than grade 2 or 3 cancers, with lower cumulative BCSM over 18 years. However, grade 1 cancers demonstrate sustained risk that extends beyond 10 years, which is different from grade 3 cancers that show front-loaded risk. In each consecutive 5-year follow-up period, the contribution of grade 1 cancers to BCSM is increasing, whereas the contribution of grade 3 cancers is decreasing.

In ER-positive/PR-positive and ER-positive/PR-negative cancers, 47% and 60% of BC-specific deaths are due to grade 3 cancers in the first 5 years. Only 10% and 6% of BC-specific deaths were from grade 1 cancers during the same period. Overall, in ER-positive, grade 3 cancers, the annual

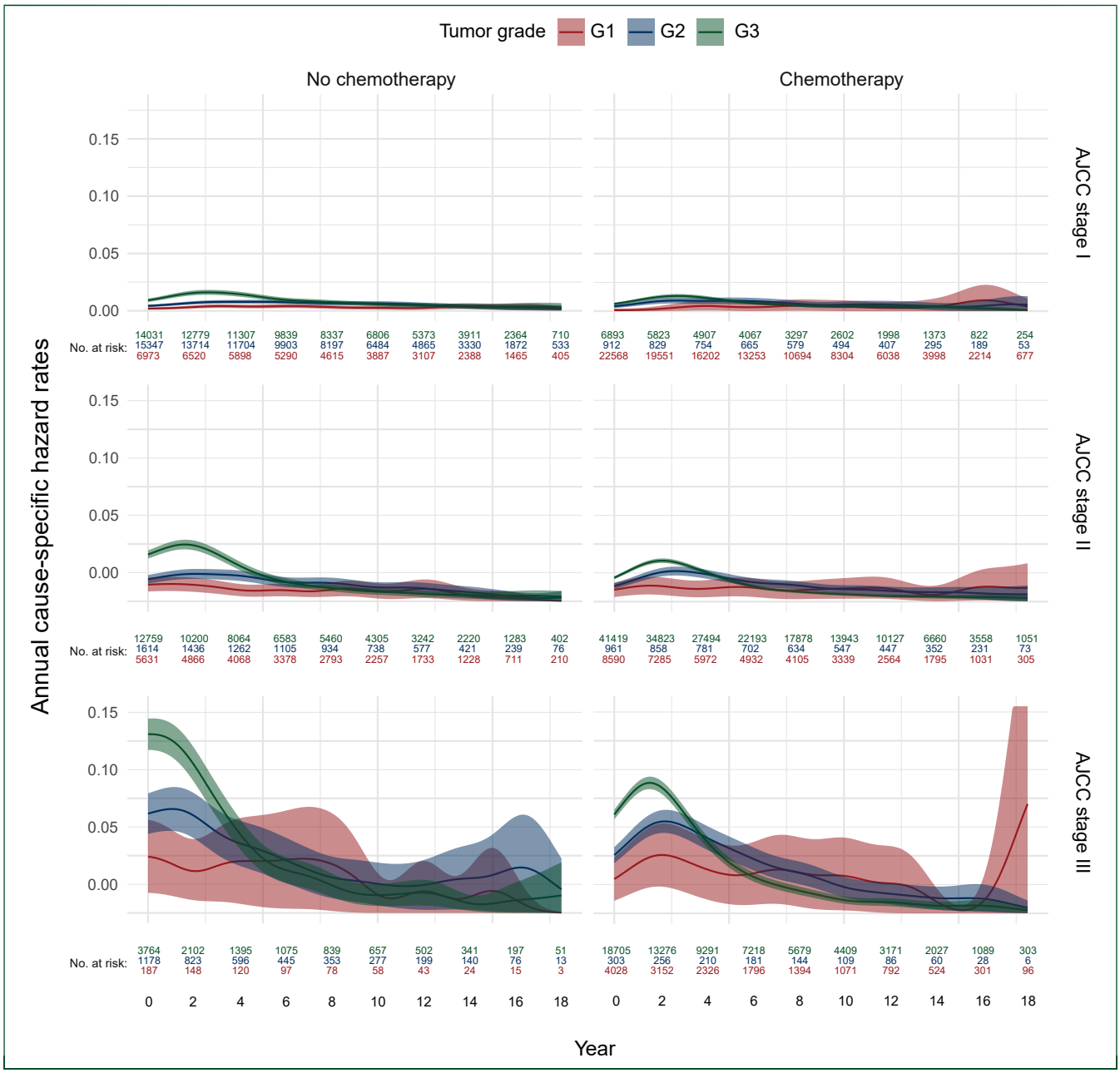

Figure 3. Annual hazard rates for BC-specific death among ER-negative BCs by tumor grade, stratified by stage and receipt of adjuvant chemotherapy. Shaded areas represent 95% CIs. Tables below the panels show the number of individuals at risk at even-year time points.
AJCC, American Joint Committee on Cancer stage I; BC, breast cancer; CIs, confidence intervals; ER, estrogen receptor.

hazard shows a rapid rise with a peak between 3 and 4 years, followed by a steep and steady decline. In contrast, grade 1 cancers slowly reach a plateau around 8 years with continued low risk extending over 15 years. Grade 2 cancers also have a more prolonged period of risk for BC-specific death, but the shape of their annual hazard curve falls between grade 1 and 3 cancers. Gene expression studies showed that grade 2 cancers are a mixture of genomically grade 1 and 2 cancers that are hard to distinguish morphologically. Their annual hazard distribution is consistent with mixed biology. Overall, our findings also align with models of metastatic dormancy, in which low-proliferative cancers give rise to dormant micrometastases capable of late reactivation,[13] whereas high-grade cancers disseminate more rapidly, proliferating micrometastases leading to earlier development of clinically detectable recurrence.[14] We observed these temporal patterns in both ER-negative and ER-positive cancers, indicating a robust biological phenomenon.

Our results introduce granularity to the often-quoted statistic that 50% of distant recurrences occur after 5 years of follow-up.[7] In grade 3 cancers, most BC deaths indeed occur within 5 years; however, in grade 1 cancers, the majority of BC deaths occur after 5 years of follow-up. Absolute risk is strongly influenced by nodal status and tumor stage within each histological grade category and

Table 2. Numbers and percentages of BCSM by tumor grade across three consecutive follow-up intervals, stratified by clinical variables

Patient and cancer variables	Interval: 0 to <60 months			Interval: 60 to <120 months			Interval: 120 to <180 months		
	T-grade 1	T-grade 2	T-grade 3	T-grade 1	T-grade 2	T-grade 3	T-grade 1	T-grade 2	T-grade 3
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Age (years)									
<50	183 (1.72)	2184 (20.57)	8249 (77.7)	352 (5.91)	2373 (39.82)	3234 (54.27)	184 (9.6)	922 (48.12)	810 (42.28)
≥50	2068 (6.66)	9502 (30.62)	19 458 (62.71)	1812 (12.18)	6869 (46.18)	6195 (41.64)	836 (16.74)	2527 (50.61)	1630 (32.65)
Tumor stage									
I	922 (14.49)	2362 (37.12)	3080 (48.4)	970 (19.02)	2369 (46.44)	1762 (34.54)	505 (22.49)	1127 (50.2)	613 (27.31)
II	784 (4.67)	4580 (27.29)	11 420 (68.04)	727 (8.09)	3945 (43.88)	4318 (48.03)	383 (12.77)	1500 (50.02)	1116 (37.21)
III	545 (2.95)	4744 (25.65)	13 207 (71.4)	467 (6.92)	2928 (43.42)	3349 (49.66)	132 (7.93)	822 (49.37)	711 (42.7)
Tumor size									
T1	1178 (11.1)	3749 (35.33)	5684 (53.57)	1294 (15.76)	3899 (47.49)	3018 (36.76)	682 (19.41)	1814 (51.62)	1018 (28.97)
T2	698 (3.62)	5072 (26.32)	13 502 (70.06)	634 (6.83)	3943 (42.46)	4709 (50.71)	264 (9.88)	1299 (48.63)	1108 (41.48)
T3	231 (3.79)	1601 (26.25)	4267 (69.96)	168 (8.13)	897 (43.42)	1001 (48.45)	58 (12.61)	223 (48.48)	179 (38.91)
T4	144 (2.54)	1264 (22.32)	4254 (75.13)	68 (5.35)	503 (39.54)	701 (55.11)	16 (6.06)	113 (42.8)	135 (51.14)
Hormone status									
ER− PR−	331 (1.68)	3157 (16.06)	16 165 (82.25)	231 (4.67)	1442 (29.15)	3274 (66.18)	106 (7.81)	484 (35.64)	768 (56.55)
ER− PR+	8 (0.84)	139 (14.65)	802 (84.51)	5 (2.07)	78 (32.23)	159 (65.7)	10 (12.66)	28 (35.44)	41 (51.9)
ER+ PR−	368 (6.05)	2069 (34.04)	3641 (59.9)	345 (10.91)	1506 (47.63)	1311 (41.46)	168 (16.88)	504 (50.65)	323 (32.46)
ER+ PR+	1544 (10.32)	6321 (42.24)	7099 (47.44)	1583 (12.68)	6216 (49.79)	4685 (37.53)	736 (16.44)	2433 (54.34)	1308 (29.22)
Lymph node status									
Negative	1004 (8.0)	3690 (29.4)	7855 (62.59)	1089 (13.79)	3474 (44.0)	3332 (42.2)	572 (18.59)	1488 (48.36)	1017 (33.05)
Positive	1247 (4.29)	7996 (27.48)	19 852 (68.23)	1075 (8.31)	5768 (44.57)	6097 (47.12)	448 (11.69)	1961 (51.17)	1423 (37.13)
Radiotherapy									
Yes	901 (4.67)	5145 (26.65)	13 260 (68.68)	1062 (9.61)	4891 (44.27)	5096 (46.12)	587 (15.63)	1816 (48.35)	1353 (36.02)
No	1350 (6.04)	6541 (29.28)	14 447 (64.67)	1102 (11.26)	4351 (44.46)	4333 (44.28)	433 (13.73)	1633 (51.79)	1087 (34.48)
Chemotherapy									
Yes	1637 (10.05)	5826 (35.78)	8818 (54.16)	1414 (16.74)	4133 (48.94)	2898 (34.32)	645 (21.1)	1612 (52.73)	800 (26.17)
No	614 (2.42)	5860 (23.1)	18 889 (74.47)	750 (6.05)	5109 (41.23)	6531 (52.71)	375 (9.74)	1837 (47.69)	1640 (42.58)

Percentages represent the proportion of BC-specific deaths attributable to grade 1, 2, and 3 disease, within each follow-up interval.
BC, breast cancer; BCSM, breast cancer-specific mortality; ER, estrogen receptor; PR, progesterone receptor.

follow-up interval. Stage II and III BCs, even with low-grade histology, carry substantial long-term risks of distant relapse and death from BC.

These findings indicate that the favorable prognostic impact of grade 1 histology should be interpreted with caution because, in these cancers, a substantial proportion of BC deaths occur late. Assuming that most patients with grade 1 disease in our study population received only 5 years of therapy, yet they have a persistent risk of recurrence after 5 years, raises the possibility that they could benefit from extended adjuvant endocrine therapy. We acknowledge that our results cannot inform about whether their outcome would improve with extended therapy, which is better estimated by genomic assays (Breast Cancer Index [Hologic Inc. San Diego, CA], Prosigna [Veracyte Inc., San Francisco, CA], and EndoPredict EPClin [Eurobio Scientific, Les Ulis, France]) if available, or the CTS5 prediction tool.[13]

However, in the absence of access to genomic assays or other molecular tests that could estimate the risk of late recurrence, ER-positive, grade 1 cancers, particularly stage II and III disease, could be considered candidates for extended endocrine therapy based on their prolonged risk for recurrence. The results could also inform long-term surveillance strategies. Currently, follow-up intensity in BC is front-loaded. Both European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines recommend regular follow-up visits every 3 months in the first 2-3 years after treatment (every 6 months for low-risk early BC), every 6 (ESMO), 6-12 (ASCO) months for the next 2 years until year 5, and annually thereafter.[14,15] This strategy is most appropriate for triple-negative and high-grade ER-positive cancers but may not be optimal for stage II-III low-grade cancers, which may require longer-term surveillance.

Our study has several limitations. Information on locoregional or distant recurrence is not available in SEER; therefore, we could not correlate tumor grade with recurrence-free interval or distant metastasis-free survival. However, essentially all BC-specific deaths are due to distant metastatic recurrence. Nevertheless, the annual hazard of BCSM is not the same as the annual hazard for distant recurrence because metastatic relapse precedes BC-specific death by several years. The literature[16] also indicates that ER-positive, grade 1 metastatic cancers have longer postrecurrence survival than grade 3 cancers and living longer with metastatic disease contributes to delayed death from grade 1 cancers. We also have no detailed information on the type of therapy patients received in the adjuvant or metastatic settings. An additional limitation relates to heterogeneity in coding of grade in the SEER database over time and the substantial interobserver variability in histological grading itself. Nevertheless, the consistent time-dependent prognostic effect of grade indicates that the observed effect is robust to inevitable noise in the data.

We recognize that the absolute risks in each disease subset, particularly among stage II-III cancers, will decrease in the coming years due to the adoption of more effective adjuvant therapies and prolongation of life after metastatic recurrence due to new drugs. However, the shape of the annual hazard curves and temporal pattern of recurrence is unlikely to change, and the risk of late recurrence from grade 1 cancers will persist, particularly among the many stage I cancers (which accounted for 53% of our study population) who are not eligible for the newer, more aggressive systemic adjuvant therapies. Lastly, we decided not to analyze HER2-positive cancers separately. Including only cancers with known HER2 status would have reduced the sample size by ∼50% and would have limited follow-up time to ∼8 years. Considering that HER2-positive cancers account for only ∼13% of all BCs and are distributed almost equally into ER-positive and ER-negative subsets, including these patients in their respective ER cohorts in this analysis is unlikely to have altered the results substantially. Future studies using other population-wide registries and datasets will also be required to assess the applicability of our findings to other healthcare systems.

Conclusion

We show that grade 1 and 3 cancers have distinct time-dependent hazards for BC-specific death. Risk is front-loaded for grade 3 cancers, but it is steady and prolonged beyond a decade for grade 1 cancer, regardless of ER status. These patterns together with other clinical variables and genomic information can inform long-term risk assessment and survivorship planning, including considerations for extended adjuvant endocrine therapy and surveillance scheduling.

ETHICAL APPROVAL

Given that only deidentified data were used for this study, institutional review board approval and informed consent were not required.

FUNDING

This work was supported by the Breast Cancer Research Foundation, New York City, NY Investigator Award [grant number BCRF-21-133] to LP. MM and GB are supported in part by a donation from Carmelina Ratto and Carlo Capra.

DISCLOSURE

MM has received support for attending meetings from Gilead and Eli Lilly. GB has received consulting fees from Roche, AstraZeneca, Merck Sharp & Dohme (MSD), Daiichi Sankyo, Gilead, and Sanofi; has served on Advisory Board for Roche, Pfizer, AstraZeneca, Eli Lilly, Novartis, Amgen, MSD, Chugai, Daiichi Sankyo, EISAI, Gilead, Seagen, and Exact Science; has received honoraria from Roche, AstraZeneca, Daiichi Sankyo, Eli Lilly, MSD, Chugai, EISAI, Gilead, Seagen, and Neopharm Israel; and has received support for attending meetings from Roche, Pfizer, MSD, Chugai, and Novartis. LP has received consulting fees and honoraria for advisory board participation from Pfizer, AstraZeneca, Merck, Bristol Myers Squibb, Stemline-Menarini, BeOne, Personalis, Natera, Agendia, Exact Sciences, and Radionetics, and institutional research funding from Pfizer, AstraZeneca, Merck, Menarini-Stemline, Radionetics, and Exact Sciences, and stock options in Ataraxis. Other authors have declared no conflicts of interest.

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