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Competing risks of death in women treated with adjuvant aromatase inhibitors for early breast cancer on NCIC CTG MA.27

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Abstract

Baseline patient and tumor characteristics differentially affected type of death in the MA.17 placebo-controlled letrozole trial where cardiovascular death was not separately identified. The MA.27 trial allowed competing risks analysis of breast cancer (BC), cardiovascular, and other type (OT) of death. MA.27 was a phase III adjuvant breast cancer trial of exemestane versus anastrozole. Effects of baseline patient and tumor characteristics were tested for whether factors were associated with (1) all cause mortality and (2) cause-specific mortality. We also fit step-wise forward cause-specific-adjusted models. 7576 women (median age 64 years; 5417 (72 %) < 70 years and 2159 (28 %) ≥70 years) were enrolled and followed for median 4.1 years. The 432 deaths comprised 187 (43 %) BC, 66 (15 %) cardiovascular, and 179 (41 %) OT. Five baseline factors were differentially associated with type of death. Older patients had greater BC ($p = 0.03$), cardiovascular ($p < 0.001$), and other types ($p < 0.001$) of mortality. Patients with pre-existing cardiovascular history had worse cardiovascular mortality ($p < 0.001$); those with worse ECOG performance status had worse OT mortality ($p < 0.001$). Patients with T1 tumors ($p < 0.001$) and progesterone receptor positive had less BC mortality ($p < 0.001$). Fewer BC deaths occurred with node-negative disease ($p < 0.001$), estrogen receptor-positive tumors ($p = 0.001$), and without adjuvant chemotherapy ($p = 0.005$); worse cardiovascular mortality ($p = 0.01$), with trastuzumab; worse OT mortality, for non-whites ($p = 0.03$) and without adjuvant radiotherapy ($p = 0.003$).

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Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

Overall, 57 % of deaths in MA.27 AI-treated patients were non-breast cancer related. Baseline patient and tumor characteristics differentially affected type of death with women 70 or older experiencing more non-breast cancer death.

Keywords

Competing risks; Breast cancer death; Cardiovascular death; Elderly

Introduction

Earlier detection and improved management of breast cancer leads to the prospect that many women diagnosed with early breast cancer now will not die from the disease [1–7]. Cuzick observed that occurrence of deaths that are not disease related could putatively confound efficacy results of adjuvant aromatase inhibitor (AI) trials if the primary endpoint included all types of mortality. He recommended that the primary endpoint for AI trials exclude non-breast cancer death to avoid an apparent dilution of trial therapy effect [7].

We previously found substantive competing risks operative in NCIC clinical trials group (CTG) MA.17. MA.17 was a postmenopausal extended endocrine therapy trial, which was a placebo-controlled trial of the AI letrozole, after 5 years of tamoxifen therapy [6]. In the MA.17 population, 60 % of deaths were not from breast cancer. Those under 70 experienced a rate of 48 % non-breast cancer deaths; those 70 or older had 72 %, non-breast cancer deaths [6]. We identified differential effects of baseline patient and tumor characteristics on type of death. The differences were inferred as indicating potential clinical relevance of the competing risks [6]. Cardiovascular deaths were not separately identifiable, although they were hypothesized to be a major component of non-cancer death.

To date, MA.27 is the largest trial of AI alone therapy; 7576 patients were randomized to two AI, exemestane and anastrozole [9]. The MA.27 trial's primary endpoint of event-free survival (EFS) included all types of death. In two-sided superiority testing, neither exemestane nor anastrozole was superior; the hazard ratio (HR) of exemestane to anastrozole was 1.02 [95 % confidence interval (CI) 0.87–1.18); $p = 0.85$] [9]. At the final analysis, exemestane- and anastrozole-treated patients also did not experience significantly different distant disease-free survival, breast cancer survival, or overall survival. The separate identification of MA.27 cardiovascular deaths permitted refined competing risk assessments. We examined here whether competing risks of death were operative and potentially relevant by way of patient and tumor characteristics differentially affecting type of death.

Methods

Study design

The NCIC CTG MA.27 trial (ClinicalTrials.gov identifier: NCT00066573) was a phase III cooperative group study that was a multicenter, multinational, randomized, open-label trial approved by health regulatory authorities, and centers' institutional review boards [9]. MA.27 originally had a factorial design, with random assignment to exemestane versus anastrozole, with or without celecoxib (hypothesized to have an anticancer effect), in

postmenopausal women with locally determined hormone receptor-positive primary breast cancer. Assignment to celecoxib was discontinued due to reports of cardiac toxicity. Women enrolled during celecoxib randomization were included in the comparison of exemestane and anastrozole, and stratified by their assignment to celecoxib (yes, no; $N = 1622$) and concomitant prophylactic aspirin use (≤81 mg per day; yes, no; $N = 2209$). After positive results in 2005 of anti-human epidermal growth factor receptor 2 (HER2) therapy in early breast cancer, trastuzumab was permitted in women with locally determined HER2-positive disease and with protocol amendment to stratify by trastuzumab (yes, no;$N = 1915$). Stratification factors throughout the trial were lymph node status (negative, positive, or unknown) and receipt of prior adjuvant chemotherapy (yes, no; $N = 7576$). After providing informed consent, patients were assigned exemestane 25 mg or anastrozole 1 mg daily after a morning meal, for 5 years. Participating collaborative groups were NCIC CTG, Eastern Cooperative Oncology Group (ECOG), Southwest Oncology Group (SWOG), Cancer and Leukemia Group B (CALGB), North Central Cancer Treatment Group (NCCTG), and International Breast Cancer Study Group (IBCSG).

MA.27 data were collected, managed, and analyzed by the NCIC CTG. The final analysis database was utilized for these analyses. Manuscript writing was undertaken by the authors.

Patient population

MA.27 enrolled postmenopausal women 3–12 weeks following completion of initial treatment [9]. Prior hormones, steroids, and raloxifene had to be discontinued ≥3 weeks before randomization. Prior treatment with an AI or tamoxifen was not permitted. The intention-to-treat (ITT) population comprised 7576 patients: 3789 assigned to exemestane and 3787 to anastrozole.

MA.27 study endpoints

The MA.27 primary endpoint was event-free survival (EFS), defined as time from randomization to time of loco-regional or distant disease recurrence, new primary breast cancer, or death from any cause; censoring was at longest follow-up. Overall survival, defined as time from randomization to time of death from any cause, was a secondary endpoint of MA.27; censoring was at longest follow-up. We examined here by ITT, the multivariate time-to-breast cancer specific, cardiovascular, and other types of death.

Primary objective of competing risks investigation

The primary objective of this investigation was to examine whether there was evidence of competing risks operative in the MA.27 trial, by determining whether baseline patient characteristics had significantly different effects indicated for different causes of death.

Statistical analysis

Cumulative hazard plots for breast cancer, cardiovascular, and other type mortality were used to examine the presence of substantive competing risks that is overlapping time periods for different types of death. The indication that substantive competing risks were operative then led to examining whether there were differential associations between baseline patient

and tumor characteristics and types of death. The Lagakos method was used for this purpose [6, 8].

We assumed independent cause-specific risks for death with or from breast cancer, cardiovascular death, and death of other type. We tested 2 hypotheses (H1 and H2):

1. **H1** A factor does not affect type or time to death, $\beta_{BreastCancer} = \beta_{Cardiovasular} = \beta_{OtherType} = 0$, which is tested with a likelihood ratio criterion $(-2\log R)[-\chi^2_{(3)}]$, where $\beta_{BreastCancer}$, $\beta_{Cardiovasular}$, and $\beta_{OtherType}$ are the cause-specific effects of the factor. With rejection of H1, H2 was tested, and
2. **H2** A factor has the same effect for all types of death, $\beta_{BreastCancer} = \beta_{Cardiovasular} = \beta_{OtherType}$, which is tested with $-2\log R[-\chi^2_{(2)}]$. With rejection of H2, a factor was differentially associated with type of death so was assessed separately for effects on cause-specific mortality.

We examined the effects of the baseline MA.27 factors: treatment (exemestane, anastrozole); age (in years); race (white, other); ECOG performance status (0, other); breast surgery (partial, mastectomy); pathologic T (1, other); pathologic N (0, other); estrogen receptor status (ER; negative, positive); progesterone receptor status (PgR; negative, positive); fractures in past 10 years (no, yes); prior raloxifene use (no, yes); cardiovascular history (no, yes); adjuvant radiotherapy (no, yes); adjuvant chemotherapy (no, yes); celecoxib use (no, yes); aspirin use (no, yes); and herceptin use (no, yes).

The association of each factor with type of death was examined in a model that included all of the factors (the "full-factor" model). Assessment of competing risks by this approach used log-normal survival analysis; this assumption was examined for each type of death with residual plots versus survival time for those who died.[6] For the log-normal analysis, the natural logarithm of survival time (t), $Y = \ln(t)$, is a linear function, $Y = \alpha + \Sigma\beta_j z + \sigma W$, where σ is a scale parameter; for the log-normal model, W is the standard normal distribution, z_j is the jth baseline factor, and β_j is the effect of the jth baseline factor on mortality.

We also examined the effects of the factors with separate cause-specific (breast cancer, cardiovascular, and other types) multivariable analyses by use of the log-normal model. MA.27 design was incorporated by always adjusting the cause-specific survival analyses through inclusion of treatment and the stratification factors. All other factors were considered in step-wise forward regression analyses, with the inclusion of a factor if it had a two-sided p value ≤ 0.05 by the likelihood ratio criterion, which has an approximate χ^2 distribution with 1 df ($\sim\chi^2$ with 1 df). We obtained values for the $\beta_{BreastCancer}$, $\beta_{Cardiovascular}$, and $\beta_{OtherType}$, standard error (SE), and p values, which are based on the assumption that the beta have an approximately normal distribution. For comparability of factor effects, graphical depiction of the results utilized standardized coefficients, β/SE.

Results

MA.27 enrolled 7576 patients between June 2, 2003 and July 31, 2008. At the final analysis, patients had a median 4.1 years follow-up. Patients had a median age of 64.1 years (Table 1): 5417 (72 %) < 70 years and 2159 (28 %) ≥70 years. Patients were hormone receptor positive, either ER positive (+) and/or PgR positive (+).

This report utilized the final analysis follow-up, which is the longest that will ever be available for the full MA.27 trial population. Women experienced 432 deaths during this period, which comprised 187 (43 %) breast cancer deaths, 66 (15 %) cardiovascular deaths, and 179 (41 %) other types of death (A1). Overall, 57 % of deaths in MA.27 patients were non-breast cancer related. The three types of death occurred throughout the follow-up period (Fig. 1.) so we investigated the operation of these competing risks by way of the effects of baseline patient and tumor characteristics on the three types of mortality. The AI therapy, exemestane versus anastrozole, was not associated with mortality ($p = 0.84$). The type of deaths experienced by baseline patient characteristics is provided in Table 1.

Five baseline factors were differentially associated with cause of death. Patient characteristics with differential associations are presented in Fig. 2. Older age was associated with greater breast cancer mortality ($p = 0.03$), cardiovascular death ($p < 0.001$), and other types of mortality ($p < 0.001$). Pre-existing cardiovascular history led to worse cardiovascular mortality ($p < 0.001$). Worse ECOG performance status led to worse other types of death ($p < 0.001$). Figure 3 shows mortality differences by tumor characteristics. T1 tumors were associated with fewer breast cancer deaths ($p < 0.001$); patients with PgR + tumor had less breast cancer mortality ($p < 0.001$). Assessment of factor effects in step-wise modeling of cause-specific mortality (Fig. 4) indicated lower breast cancer mortality with node-negative disease ($p < 0.001$), ER + tumors ($p = 0.001$), and patients who did not receive adjuvant chemotherapy ($p = 0.005$). There was worse cardiovascular mortality ($p = 0.01$) with receipt of trastuzumab. Non-white women had higher other type mortality ($p = 0.03$), while lower other type mortality was seen for those receiving adjuvant radiotherapy ($p = 0.003$).

The assumption of a log-normal model was examined in residual plots of differences between observed and modeled survival times. Ninety-five percent of residuals would be expected to be >−2.0 or < 2.0. The breast cancer residual plot (A2) indicates more small residuals, or better fit, than expected for women who died during the first year after accrual to MA.27; at median follow-up of 4.1 years, no residuals exceeded 2.0. Residuals indicate reasonable support of the log-normal model for cardiovascular (A3) and other types of death (A4) with few residuals <−2.0, none >2.0.

Discussion

Cuzick summarized the experience of AI trials, noting that efficacy results could be confounded by non-disease-related deaths if the primary endpoint of an AI trial included all types of mortality [7]. The primary endpoint for the positive AI trial of extended adjuvant trial MA.17 (included in the Cuzick comparison) included only breast cancer death.

Meanwhile, MA.27's primary endpoint included non-breast cancer deaths and there was no evidence of a significant treatment effect. In MA.27, we were able to examine whether there were differential effects of baseline patient characteristics on the type of death with separation of non-breast cancer deaths into cardiovascular or other types of death. We found evidence of competing risks in MA.27 with a substantive proportion (57 %) of non-breast cancer deaths that was similar to our previous finding of 60 % in MA.17 [6]. Meanwhile, in the MA.14 trial testing tamoxifen ± octreotide LAR, 38 % of patients' deaths were not from breast cancer [10].

Mechanistically, simultaneous operation of competing risks would not be important if baseline patient and tumor characteristics similarly affected the different types of deaths. We hypothesized that differential effects of factors on breast cancer, cardiovascular, and other type mortality would indicate evidence of competing risks that were potentially clinically relevant and useful for future clinical trial planning. Our approach tested the effects of baseline patient and tumor characteristics on cause of death. As in MA.17 [6], we found differential effects on type of death, particularly, that older MA.27 patients experienced significantly more non-breast cancer death ($p < 0.001$). Perhaps, not surprisingly, pre-existing cardiovascular disease was associated with cardiovascular death, worse ECOG performance status led to more other type deaths, while patients with lower T stage and PgR-positive tumors had less breast cancer mortality.

Additionally, in disease-specific examinations, patients with less lymph node involvement and ER positive tumors also had less breast cancer mortality. Patients who had non-randomized, clinically administered adjuvant chemotherapy had increased breast cancer mortality, which is indicative of a more advanced stage. Although based on only a small number of patients ($N = 74$), we observed that those administered trastuzumab experienced higher cardiovascular mortality. Non-Caucasians experienced increased other type of mortality, which refines the main trial observation that race impacted overall survival [9]. Finally, clinical administration of radiotherapy was associated with better other type mortality which likely reflects better overall health of those offered radiotherapy.

This competing risks assessment was not protocol specified. The data are those from the MA.27 final analysis database, with limited relatively short median 4.1-year follow-up, which is the longest uniform follow-up possible due to trial closure. However, MA.27 is to date the largest AI alone phase III trial, so the evidence is important. Consistently, patients in our AI therapy trials (MA.17 and MA.27) experienced a substantive proportion of non-breast cancer deaths and increased non-breast cancer death with older age. The breast cancer disease attributes of tumor size and hormone receptor status were differentially associated with type of mortality, affecting breast cancer death for the MA.27 primary adjuvant trial MA.27. Previous cardiovascular disease was differentially associated with type of death, through increased unspecified other cause in MA.17 and cardiovascular death in MA.27. The introduction of trastuzumab during late accrual phase of MA.27 resulted in only 74 patients receiving this therapy, so we note with caution the increased cardiovascular mortality in conjunction with AI administration. Likewise, the observation of minority women having increased other type mortality is reported in the context that only 5 % of MA.27's 7576 patients were not white; in the main trial report, race had a significant predictive

effect on overall survival ($p = 0.02$), with minority women on exemestane having significantly fewer deaths than those on anastrozole [9]. The differences in trial conduct and data limit comparability across trials. The only specific characteristic offered for consideration at this time is that a substantive proportion of older patients may be expected to die from causes not related to their disease or treatment.

Recognition of the lower breast cancer mortality risk for postmenopausal, hormone receptor-positive early breast cancer patients raise a cautionary note about the frequent clinical trial decision to include non-breast cancer deaths in a trial's primary endpoint. In clinical practice, we think concomitant patient health, particularly of the elderly, should be integrated in therapeutic management decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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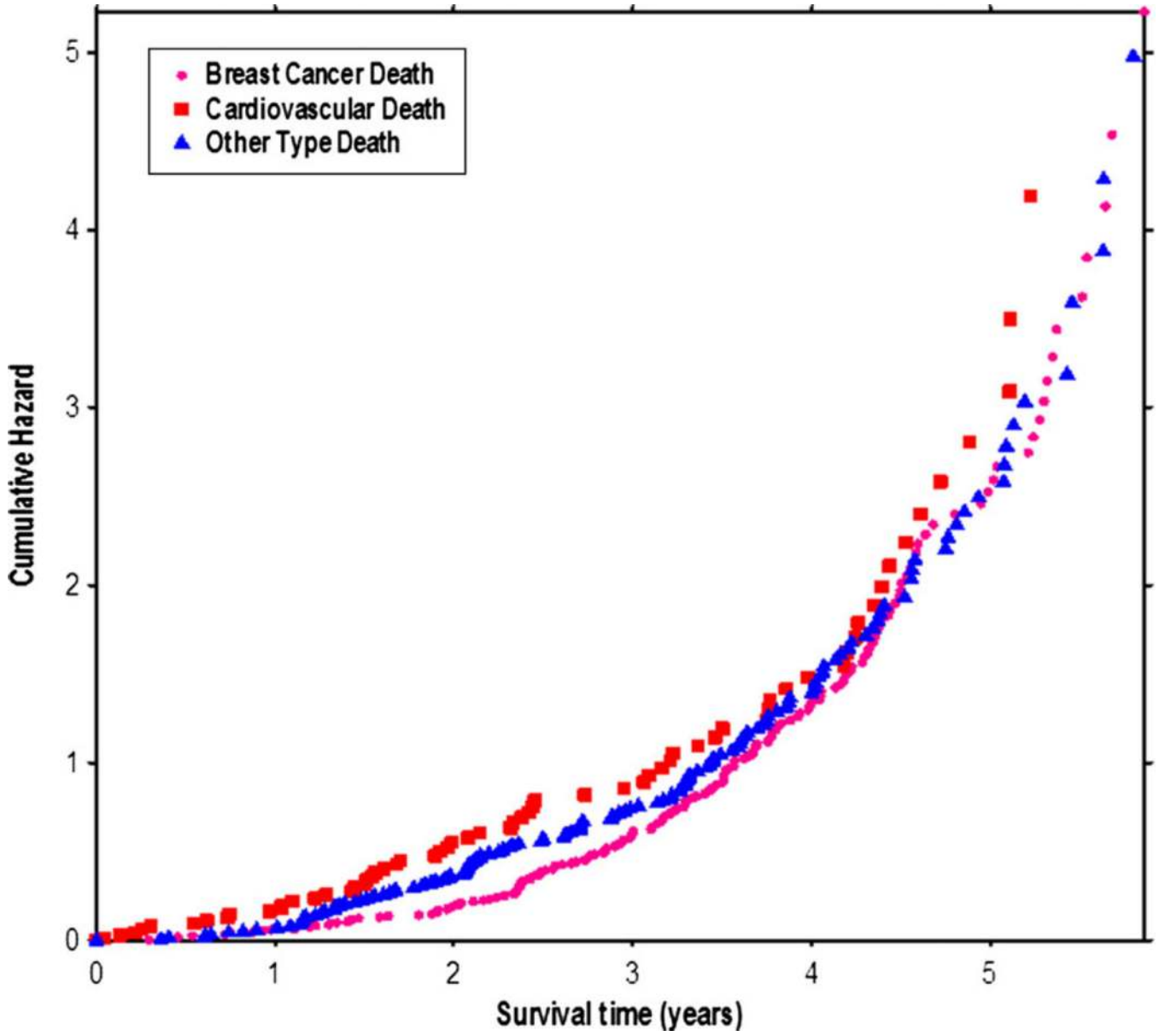

Fig. 1.
Cumulative hazard of death from breast cancer, cardiovascular disease, and other type of death

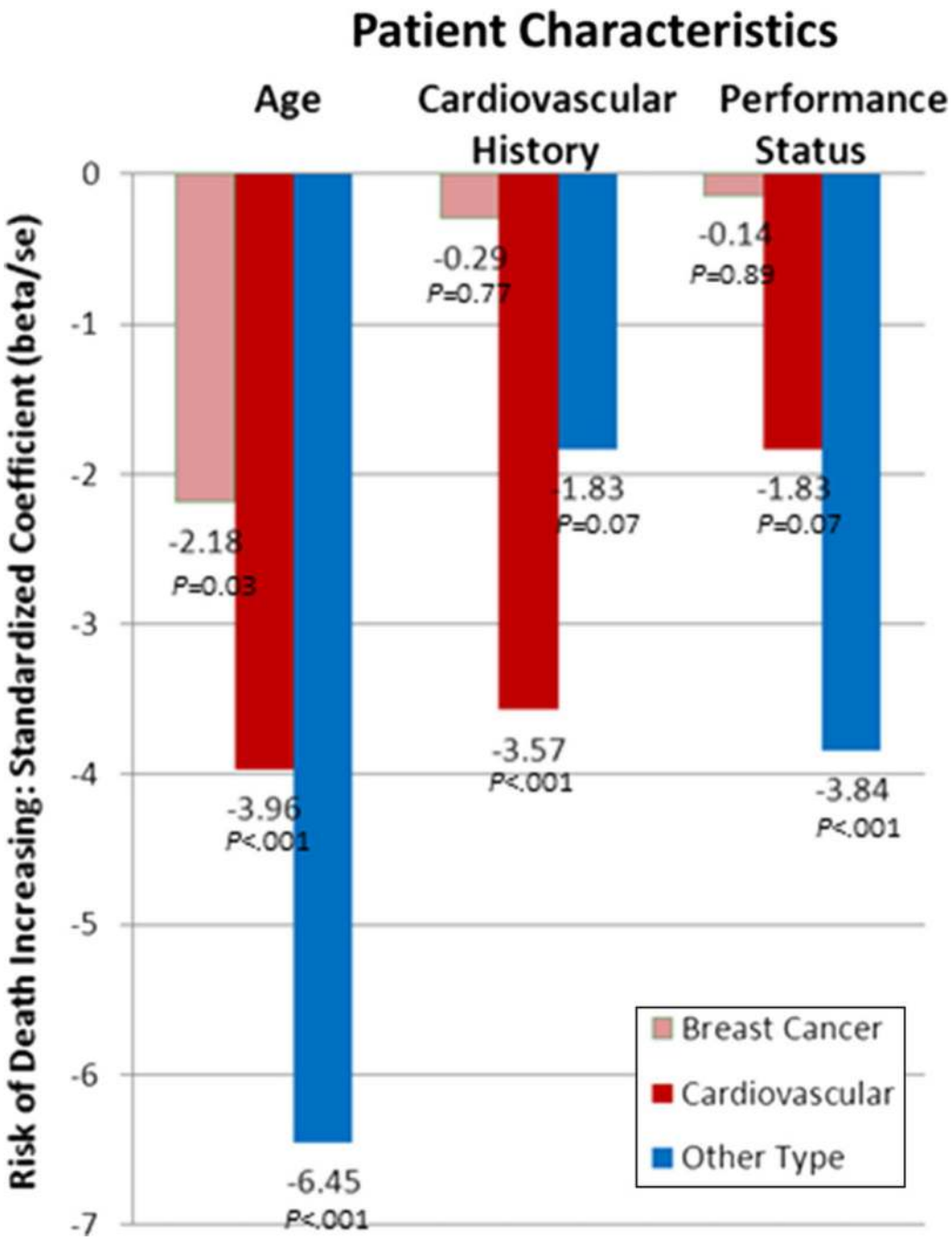

Fig. 2.

Differential effect of patient characteristics on breast cancer, cardiovascular, and other type death. For visual comparability of factor effects, the log-normal model standardized coefficients, β/SE ~ N(0,1), are depicted with *p* values. More negative/positive coefficient indicates association with shorter/longer survival that is significant in two-sided test at 5 % level if the absolute value exceeds 1.96. Age is assessed in years; cardiovascular history is categorized as no versus yes; ECOG performance status is categorized as 0 versus other

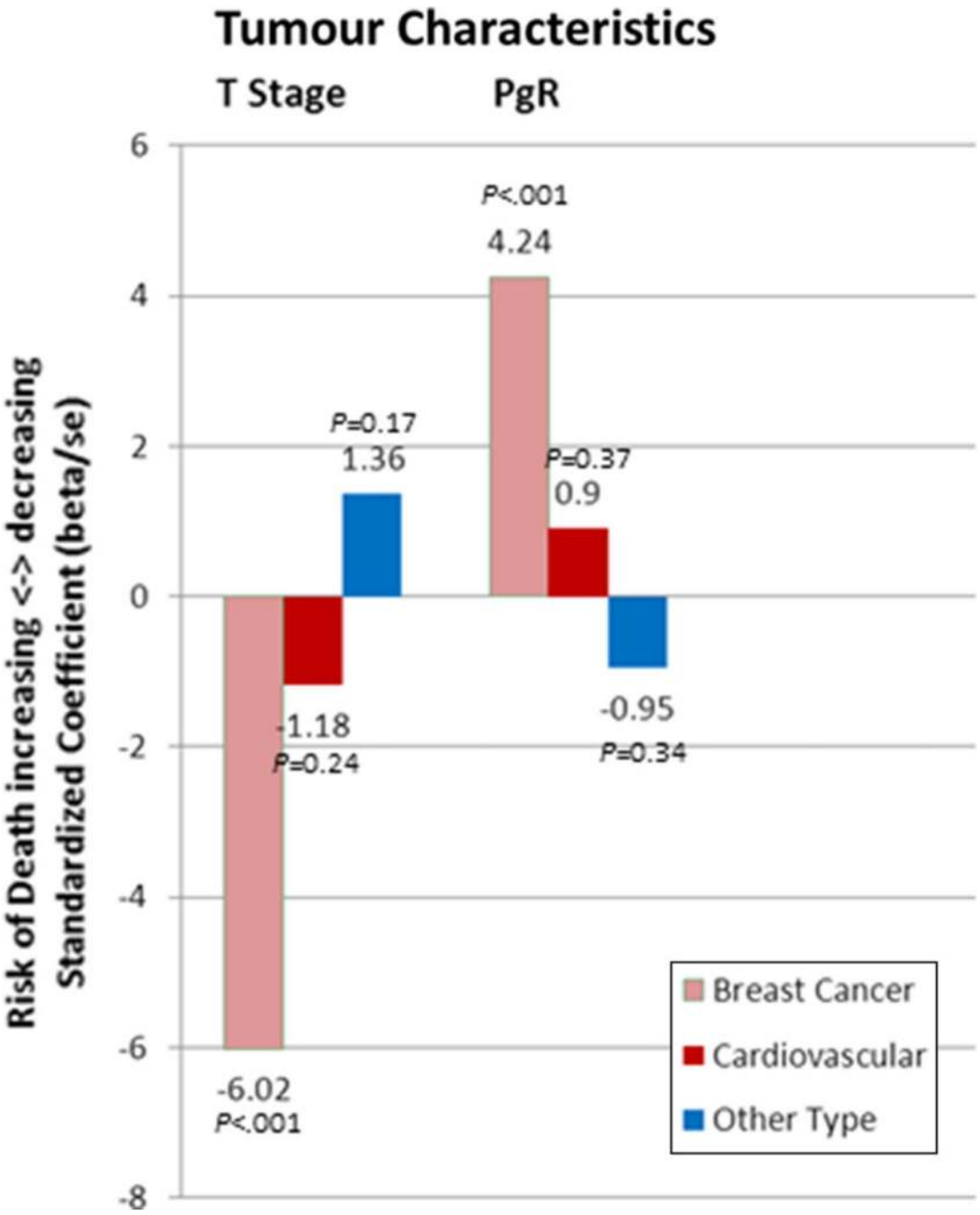

Fig. 3.

Differential effect of tumor characteristics on breast cancer, cardiovascular, and other type death. For visual comparability of factor effects, the log-normal model standardized coefficients, β/SE ~ N(0,1), are depicted with *p* values. More negative/positive coefficient indicates association with shorter/longer survival that is significant in two-sided test at 5 % level if the absolute value exceeds 1.96. Pathologic T stage is categorized as T1 versus other; progesterone receptor (PgR) is categorized as negative versus positive

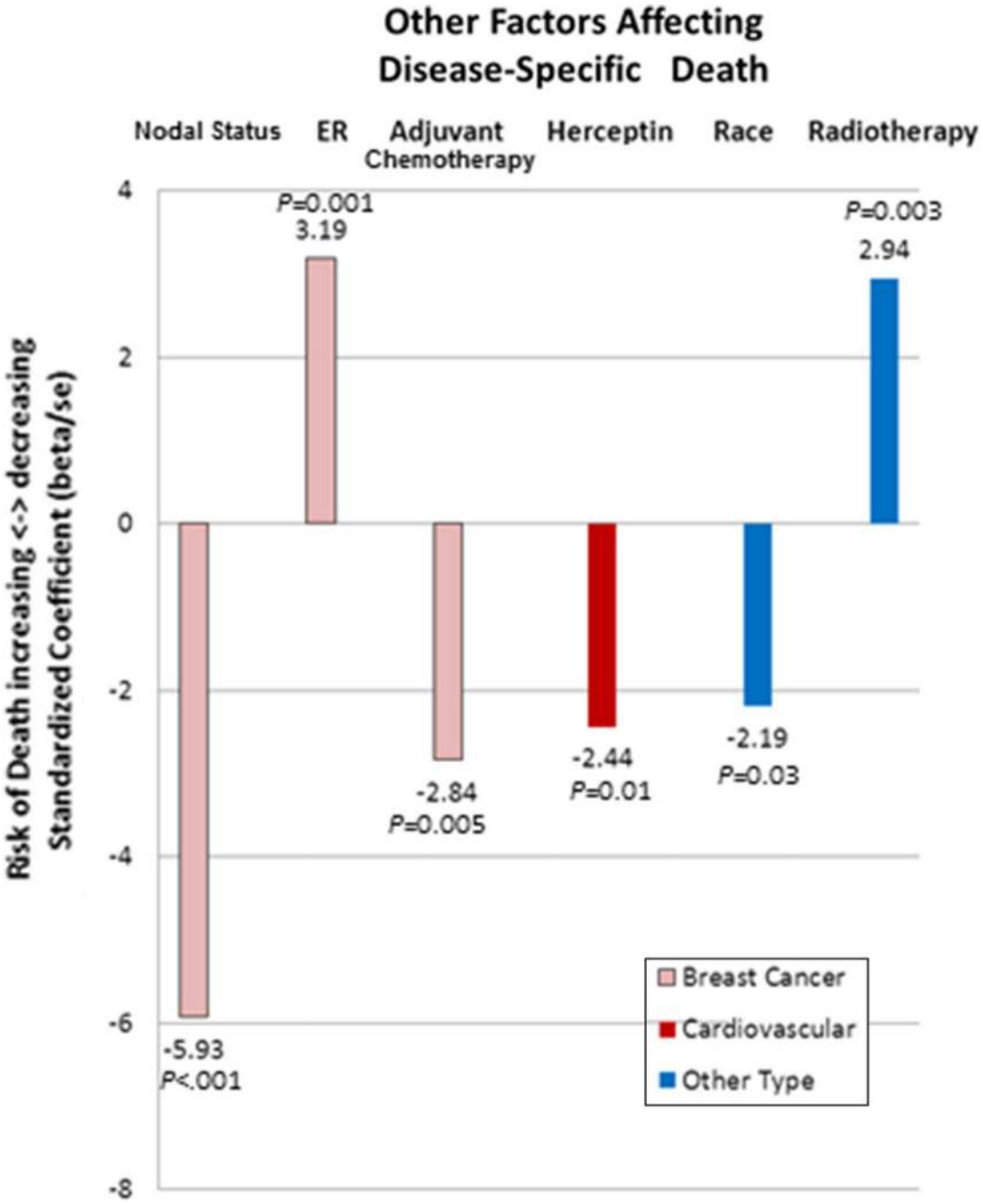

Fig. 4.

Disease-specific effect of patient and tumor characteristics on breast cancer, cardiovascular, and other type death. For visual comparability of factor effects, the log-normal model standardized coefficients, β/SE ~ N(0,1), are depicted with *p* values. More negative/positive coefficient indicates association with shorter/longer survival that is significant in two-sided test at 5 % level if the absolute value exceeds 1.96. Pathologic nodal status is categorized as 0 versus other; estrogen receptor (ER) is categorized as negative versus positive; adjuvant

chemotherapy, herceptin, and adjuvant radiotherapy are categorized as no versus yes; race is categorized as white versus other

Table 1

Baseline patient characteristics

	Total	Deaths			Exemestane	Anastrozole
		Breast	Cardio	Other	*N* (%)	*N* (%)
	N	*N*	*N*	*N*		
All pateints	7576	187	66	179	3789 (100)	3787 (100)
Age (median in years)					63.9	64.3
≥70 years	2159	66	42	115	1090 (29)	1069 (28)
Race–White	7151	176	62	161	3593 (95)	3558 (94)
ECOG performance status 0	6241	142	45	118	3115 (82)	3126 (83)
Partial mastectomy	5163	94	42	100	2609 (69)	2554 (67)
Tumor size T1	5428	61	42	131	2710 (72)	2718 (72)
Nodal status N0	5371	59	45	124	2693 (71)	2678 (71)
ER receptor positive	7525	184	66	178	3766 (99)	3759 (99)
PgR receptor positive	6090	124	51	150	3085 (81)	3005 (79)
Fractures in past 10 years	739	25	9	20	380 (10)	359 (9)
Prior raloxifene use	116	1	0	4	64 (2)	52 (1)
Cardiovascular history	4070	99	56	92	2002 (53)	2068 (55)
Adjuvant radiotherapy	5380	138	37	80	2717 (72)	2663 (70)
Adjuvant chemotherapy	2327	117	11	34	1163 (31)	1164 (31)
Celecoxib use	811	24	7	25	406 (50)	405 (50)
Aspirin use	476	19	7	27	238 (22)	238 (22)
Trastuzumab (since 2006)	74	0	2	2	36 (4)	38 (4)