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Breast cancer-specific survival by clinical subtype among young and elderly in a nationwide cohort

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Abbreviations used: ER=estrogen receptor, PR=progesterone receptor, HER2=human epidermal growth factor receptor 2, TNBC=triple-negative breast cancer, Lum=luminal, HR=hazard ratio, CI=confidence interval, SEER=Surveillance Epidemiology and End Results, CRN=Cancer Registry of Norway, ICD=International Classification of Diseases, IHC=immunohistochemistry.

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NOVELTY AND IMPACT STATEMENTS

Given the increasing numbers of patients with breast cancer, it is important to provide solid estimates of the breast cancer-specific mortality across all age groups and clinical subtypes. Such estimates should come from population-based samples that are representative of the full spectrum of patients in the clinic. Using national cancer registry data of high quality, we found that young women (<40) had a higher breast cancer-specific mortality compared to screen-aged women (50-69), in particularly among luminal A-like tumors, while elderly women (70-89) had a higher breast cancer-specific mortality within all subtypes of breast cancer. Comorbidity is a potential explanation for the remaining survival deficit in elderly women.

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ABSTRACT

Age and tumor subtype are prognostic factors for breast cancer, but it is unclear which matters the most. We used population-based data from a national cancer registry to address this question. We identified 21,384 women diagnosed with breast cancer at ages 20-89 between 2005-2015 in the Cancer Registry of Norway. Subtype was defined using estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (HER2) status as luminal A-like (ER+PR+HER2-), luminal B-like HER2-negative (ER+PR-HER2-), luminal B-like HER2-positive (ER+PR+/-HER2+), HER2-positive (ER-PR-HER2+) and triple-negative (TNBC) (ER-PR-HER2-). Cox regression estimated hazard ratios (HR) for age, subtype and death due to breast cancer, while adjusting for year, grade, TNM stage and treatment.

Young women (20-39) more often had HER2-positive and TNBC tumors, while elderly women (70-89) more often had luminal A-like tumors. Compared to age 50-59, young women had doubled breast cancer-specific mortality rate (HR=2.26, 95% CI 1.81-2.82), while elderly had two to five times higher mortality rate (70-79: HR=2.25, 1.87-2.71; 80-89: HR=5.19, 4.21-6.41). After adjustments the association was non-significant among young women but remained high among elderly. Among luminal A-like subtype, young age was associated with increased breast cancer-specific mortality before adjustment for treatment, while old age was associated with increased mortality in all subtypes.

Age and subtype are strong independent prognostic factors. The elderly always do worse, also after adjustment for subtype. Tumor-associated factors (subtype, grade and stage) largely explain the higher breast cancer-specific mortality among young. However, young women with luminal A-like subtype do worse than middle-aged.

INTRODUCTION

Breast cancer is a heterogeneous malignancy that can be divided into several intrinsic molecular subtypes with different clinical and prognostic characteristics. Landmark papers[1, 2] in the early 2000s identified five main breast cancer molecular subtypes: luminal A and luminal B, normal-breast-like, HER2-positive and basal-like. Although increasingly recognized as important, molecular expression analyses are still not widely used. Instead clinical subtypes are defined by immunohistochemistry results of estrogen receptor (ER), progesterone receptor (PR) and HER2 status with or without additional molecular markers.[3-7] These clinical subtypes have different targeted therapies and different risk of disease recurrence and survival.[8-11]

Age is a strong predictor for survival after breast cancer, with poorer survival among young and elderly women compared to middle-aged women.[12, 13] Young women present more often with aggressive clinical subtypes (triple-negative (TNBC), HER2-positive) and advanced disease at diagnosis.[14-16] Thus a question has been whether the poor survival among young women is solely due to the more aggressive disease in this age group. Several, mainly smaller, studies have assessed the effect of hormone receptor status on breast cancer-specific mortality among young women,[17-21] but only some included subtype information[22-25] and few were population-based.[17, 19, 22, 23] Overall, these studies found a higher breast cancer-specific mortality among young than middle-aged women, and in some also when adjusting for subtype. Interestingly, the poorer survival among young has been found in particular for ER-positive and luminal A-like tumors.

Few studies have assessed the effect of subtype on breast cancer-specific mortality in both young and elderly women. Elderly women tend to have less aggressive tumors (luminal-A like) than

other age groups,[26] but it has not been clear whether the poorer survival among elderly is as strong within subtypes. One large population-based study using SEER data found increased mortality in both young and elderly, but young age was associated with higher breast cancer-specific mortality only among ER/PR-positive tumors.[20] Another multicentre study, assessing the effect of subtype (ER/PR/HER2), found increased mortality only among young women, in particular those with luminal A-like tumors.[25] In contrast, a recent population-based study found increased mortality among elderly in all clinical subtypes, but did not find an increased mortality among the young.[27]

We aimed to assess breast cancer-specific mortality across all ages, using a large nationwide population-based cohort with essentially complete follow-up. We investigated whether the association between age and breast cancer-specific mortality can be explained by clinical subtypes defined by ER/PR/HER2 status and stage of the disease. We also assessed to what extent age and subtype contribute independently to breast cancer-specific mortality.

METHODS

Utilizing data from the Cancer Registry of Norway (CRN), we identified a cohort of women diagnosed with a primary invasive breast cancer. The CRN has recorded all new cases of cancer in Norway since 1953, with information on date of diagnosis, patient and tumor characteristics and follow-up for vital status, including date and cause of death and emigration by routine linkage to other Norwegian population registries. Reporting to the CRN is mandatory by law and the registry database is 98.8% complete.[28] Since 2005, the CRN collects information on hormone receptor status (ER, PR, HER2). In the present study, the inclusion criteria were women aged 20-

89 years with a primary invasive breast cancer (ICD 10=C50) diagnosed between Jan 2005 and Dec 2015, and with no prior history of cancer recorded in the CRN, including n=29,259 women. Between 2005 and 2008 information on hormone receptor status was not collected in women above age 75, hence n=1,809 women aged 75-89 years diagnosed during 2005-2008 were excluded from the study population. Using ICD-O-3 morphology codes,[29] we also excluded tumors which were not morphologically verified (n=93), not confirmed as primary (n=42), or non-epithelial tumors or Paget's disease (n=180). Women with inconsistent information on residency status at time of cancer diagnosis were excluded (n=15). After applying these exclusion criteria, the cohort comprised n=27,120 women.

Information on hormone receptor status (ER, PR, HER2) has been routinely collected for all ages in the CRN since 2009. Between 2005 and 2008, the information on hormone receptor status was collected routinely at the CRN in the mammographic screening programme (ages 50-69), and retrospectively coded from pathology reports for screening-aged women diagnosed outside of the programme, as well as for women aged <50 or 70-74. Women aged 75-89 at diagnosis have no information on hormone receptor status in the CRN between 2005 and 2008.

Information on ER, PR and HER2 status was assessed by IHC and extracted from pathology reports. From 2005 to January 2012, tumors were classified as ER-negative if there was <10% reactivity. From February 2012 onwards, the threshold for ER-negative tumors was changed to <1% reactivity as a result of change in the treatment protocols for patients attending clinics in Norway. PR-negative tumors were defined as those with reactivity of <10%, and PR-positive tumors as those with reactivity ≥10% throughout the study period. HER2 expression status was

routinely assessed with IHC and in general with in situ hybridization if the IHC results were borderline.

Clinical subtype was defined by IHC surrogates for molecular subtype according to the St Gallen 2013 criteria[4, 30] without using Ki67: luminal A-like (ER+PR+HER2-), luminal B-like HER2-negative (ER+PR-HER2-), luminal B-like HER2-positive (ER+PR+HER2+, ER+PR-HER2+), HER2-positive (ER-PR-HER2+), triple-negative (TNBC) (ER-PR-HER2-). Women with ER-PR+HER2+/ER-PR+HER2- (n=287; 1.1%) or missing on any ER, PR or HER2 (n=2,654; 9.8%) were deemed unclassifiable/uncertain subtype and set to missing. Information on grade was available in the CRN throughout the study period, and categorized as: I (well-differentiated), II (moderately differentiated) and the combined group III (poorly differentiated) and IV (undifferentiated, anaplastic) using the 6th digit in the morphology code ICD-O-3.

Pathologic TNM stage was categorized into I, IIA, IIB, IIIA, IIIB or IV.[31] For patients with unknown pathologic TNM stage, the CRN uses both pathological and clinical notifications to stage the extent of the disease in coherence with the SEER Summary staging Manual 2000 (see: https://seer.cancer.gov/tools/ssm/), also described elsewhere.[32] SEER summary stage was defined as: localized (the tumor has not spread to other organs, equals to stage I), regional stage (metastasis to regional lymph nodes, equals to stage II), local infiltration to skin and/or chest wall (equals to stage III), and distant stage (metastasis to distant lymph nodes or organs, equals to stage IV).

Information on mode of detection (screen-detected or not) is not routinely recorded in the CRN and was not available in the current dataset. Type of surgery was categorized as mastectomy, breast conserving surgery or no surgery. Planned adjuvant treatment was only available for 14,897 (55%) of the women and of varying reporting quality over study period.

Statistical methods

The endpoint in all analyses was death due to breast cancer. Women were followed from date of breast cancer diagnosis until death due to breast cancer or censoring due to emigration, death due to another cause than breast cancer, or end of follow up in Dec 2015, whichever came first. Follow-up was also censored at 7 years since diagnosis as the oldest women (75-89) only were followed from 2009 to 2015. Cause-specific mortality rates were analyzed using Cox regression models estimating hazard ratios (HR) with 95% confidence intervals (CI) as measure of association between age at diagnosis (categorized 20-39, 40-49, 50-59, 60-69, 70-79, 80-89 years), subtype and cause-specific mortality rates. The models included covariates for age, year of diagnosis, subtype, grade, TNM stage and surgery in a stepwise manner. In a subset analysis, the models also included planned adjuvant treatment. Effect modification by age and subtype was assessed in interaction models: (1) estimating the effect of age within subtype groups (age 50-59 as reference), (2) estimating effects of age and subtype using a common reference group (luminal A-like, age 50-59), and (3) estimating the effect of subtype within age groups (luminal A-like as reference). Likelihood ratios tests assessed the interaction between age and subtype. Only women with complete information on all covariates in the fully adjusted models were included in the regression analyses. All tests were 2-sided and the significance level was 5%. Analyses were performed in Stata version 15.1/IC.[33]

Sensitivity analyses included: (1) a restriction to diagnosis years 2009-2015, (2) a restriction to stage I-III, (3) an investigation of the proportional hazards assumption by including separate effects 0-3 and 3-7 years after diagnosis, and (4) a relative survival analysis using flexible parametric models[34, 35] to assess the impact of misclassification of cause of death among the elderly on the results.[36]

The study was approved by the Regional Committee for Medical and Health Research Ethics in the South-East Health Region of Norway.

RESULTS

Young women (20-39) had higher rates of TNBC, luminal B-like HER2-positive and HER2-positive tumors, while middle-aged (40-49), screening-aged (50-69) and elderly women (70-89) had more luminal A-like tumors (Table 1). Compared to screening-aged women, young women had more high grade tumors, while elderly women had more medium grade tumors. Both young and elderly women had more advanced stage than screening-aged women. Young women had more mastectomies, while elderly women more often had no surgery and less planned adjuvant treatment.

There was a strong J-shaped association between age and breast cancer-specific mortality (Table 2, Figure 1a). Young women (20-39) had a doubled mortality (HR=2.26, 95% CI 1.81-2.82), compared to women aged 50-59 years at diagnosis, while elderly had two to five times higher mortality rate (70-79: HR=2.25, 1.87-2.71; 80-89: HR=5.19, 4.21-6.41, model a). Adjustment for

subtype reduced the HR among young women, whereas the HRs were unchanged in the other age groups (model b). Additional adjustment for grade (model c) and stage (model d) reduced the associations further among young women (20-39: HR=1.31, 1.05-1.64), but only adjustment for stage reduced the association among the elderly women (70-79: HR=2.05, 1.70-2.47, 80-89: HR=3.92, 3.17-4.85). Further adjustment for surgery (model e) reduced the associations among both young (20-39: HR=1.22, 0.97-1.52) and elderly (70-79: HR=1.92, 1.58-2.31, 80-89: HR=2.78, 2.23-3.46). Adjustment for planned adjuvant treatment was assessed in a subset of the women including 11,934 (56%) of the study cohort. Following adjustment for surgery in this subset, additional adjustment for adjuvant treatment did not change the associations (Table 3).

The highest mortality was observed among women with TNBC (HR=4.22, 3.64-4.89) and HER2-positive (HR=2.99, 2.41-3.69) subtypes (Table 2, model b). The HRs were reduced yet remained significant after adjustment for grade, stage and surgery (models c-e), except in women with luminal B-like HER2-positive subtype, who had similar mortality as women with luminal A-like subtype after adjustments for stage and surgery.

When assessing the age effect within subtypes, young age (20-39) was associated with higher breast cancer-specific mortality in women with luminal A-like and luminal B-like HER2-negative tumors (Figure 1b, 1c; Supplemental table S1). After adjustment for grade and stage the associations were reduced in magnitude and only remained significant for luminal A-like subtype (HR=1.52, 1.03-2.26); and after adjustment for surgery the association was no longer significant (HR=1.35, 0.91-2.00). For the more aggressive subtypes (luminal B-like HER2-positive, HER2-positive, TNBC subtypes), the point estimates for young age were increased but non-significant,

in particular among TNBC (HR=1.47, 0.98-2.21), and adjustments reduced the HRs (Figure 1d, 1e, 1f; Supplemental table S1). Elderly women had substantially higher breast cancer-specific mortality than young, middle-aged and screening-aged women for all subtypes, in particular for the more aggressive subtypes, and the associations were reduced but remained significantly increased also after adjustment for grade, stage and surgery.

When assessing subtype effects within age groups, TNBC subtype was associated with increased breast cancer-specific mortality in all age groups compared to luminal A-like subtype (Figure 2a; Supplemental tables S2, S3). Luminal B-like HER2-negative subtype was associated with increased mortality among young, middle-aged and screening-aged women, but the associations reduced after adjustments (Figures 2a-c). Among elderly women, luminal B-like and HER2-positive subtypes were associated with significantly increased mortality after adjustments compared to luminal A-like subtype.

When assessing the effect of age and subtype in combination, a J-shaped age effect was observed in all subtypes (Figure 2a), but after adjustment for grade and stage the associations across age were reduced (Figure 2b). Among elderly there was still a strong mortality gradient across subtypes also after adjustment for surgery (Figure 2c), whereas among patients <70 only TNBC was consistently associated with increased mortality after adjustment for surgery. The overall tests for interaction between age and subtype were non-significant in all models (Figures 2 a-c, p-values 0.1286, 0.1005 and 0.0606, respectively). Effects among the elderly were strong, where for example women aged 80-89 with luminal A-like subtype had similar breast cancer-specific mortality as screening-aged women (50-59) with TNBC subtype.

In sensitivity analyses, restricting the main results of Table 2 to diagnosis years 2009-2015 (Supplemental table S4) or to stage I-III (Supplemental Table S5) yielded essentially unchanged results. The proportional hazards assumption was valid for the age effect, but not for the subtype effect, where TNBC tumors had high early mortality (0-3 years after diagnosis) compared to the other subtypes. However, accounting for non-proportional hazards for subtype in the analysis did not change the age effects. The results from the relative survival analysis were essentially similar to the cause-specific mortality analysis across age groups (Supplemental Table S6), but among women aged 80-89 there was some indication of a lower association for relative excess hazard.

DISCUSSION

We found strong independent effects of age and subtype on breast cancer-specific mortality. An overall J-shaped effect of age was observed with increased mortality among the youngest and even higher mortality among the elderly, compared to screening-aged women. Among young patients, tumor-associated factors, such as subtype, grade and stage, explained a large part of the survival disadvantage compared to screening-aged women. Contrary, among elderly patients stage and surgical treatment were more important, yet did not fully explain the increased mortality, indicating that other factors such as comorbidities may be driving the remaining poorer prognosis in the elderly.

Additionally, we found that young women with less aggressive luminal A-like subtype had increased breast cancer-specific mortality compared to screening-aged women also after adjustment for grade and stage, but there was no significantly increased mortality after

adjustment for surgery. Among all subtypes, old age (>70) was associated with increased mortality, also after adjustment for grade, stage and surgery, in particular for the more aggressive subtypes (TNBC, HER2-positive and luminal B-like HER2-positive). However, despite the size of the cohort, we did not detect an overall significant interaction between age and subtype.

We also found that the effect of subtype was strong in all age groups, where TNBC was associated with the highest breast cancer-specific mortality. It is important to acknowledge that, overall, the more aggressive subtypes contributed far more to mortality than the less aggressive subtypes.

Several smaller studies have assessed the effect of ER/PR status and subtype on breast cancer-specific mortality among young or very young patients, and found increased mortality in this patient group, in particular for luminal A-like tumors.[17, 19, 21-23] One large study assessed age effects within levels of clinical subtype using data from selected cancer centers,[25] and found increased mortality among youngest patient group, in particular for women with luminal tumors, but no association among elderly. However, this multicenter study was based on a much younger cohort than our population-based material, indicating that the older patients in that study were highly selected. A recent study found increased mortality among elderly patients for all clinical subtypes, but did not investigate mortality among the young age group.[27] The largest study ever to assess ER/PR status in relation to age and breast cancer-specific mortality, found similar J-shaped effects as our results in a population-based setting using SEER registry data.[20] The SEER data however did not include information on HER2. Our findings expand on these previous findings, by also including HER2 positive subtypes, and show that both age and subtype are

independent prognostic factors. HER2 targeted treatment has been available in some Norwegian hospitals since 2005,[37, 38] and was recommended in a national cost evaluation report in 2006 and included in national care guidelines since 2007.[39, 40]

Adjustment for tumor-associated factors (e.g. subtype, grade and stage) largely reduced the effect among the young, but not among the elderly women. Adjustment for surgical treatment reduced the associations in young, but more so among elderly. Further adjustment for planned adjuvant treatment did not change the associations. This indicates that the poorer survival in elderly women is likely driven by comorbidity or less intensive treatment possibly due to comorbidity.[41, 42] According to treatment guidelines for breast cancer in Norway, elderly patients should be given similar treatment as other age groups, but treatment decisions should also include comorbidity and life expectancy.[43, 44] Other explanations for the remaining survival deficit among elderly could be lack of organized screening in elderly or misclassified cause of death (which was to some extent confirmed in the relative survival analysis).

The poorer survival among young women with luminal A-like tumors is puzzling. Other studies have found similar results.[22-25] Luminal A-like tumors could be biologically different in young and old women.[42] It could also be that screening-aged women have less advanced luminal A-like tumors due to screening. Adjusting for stage reduced, but did not eliminate, the association among the young, which suggests that a screening effect contributes in part.

The strengths of the study include the population-based setting with essentially complete ascertainment of incident breast cancer cases and complete follow-up information via routine

databases. The information on subtype was of high quality and collected prospectively and routinely. A sensitivity analysis addressed the impact of the lack of subtype information among elderly women (>75) between 2005 and 2008, and confirmed the findings of the main analysis.

A limitation was the lack of adjustment for comorbidities, since there was no available information. In a relative survival analysis, which assessed excess all-cause mortality (including comorbidity-related) in the patients, we found reduced but still strong associations with old age. In addition, lack of screening adjustment is a potential problem, since the screening-aged women had a lower mortality likely driven by screening detection. Although adjustment for stage at diagnosis should capture most of this confounding effect, residual confounding cannot be ruled out. However, Partridge et al[25] adjusted their analysis for screening detection, which did not change their results. No adjustment for socioeconomic status was possible in our dataset. However, although socioeconomic status is related to age, opportunistic screening and survival and therefore could be a confounder, the healthcare system in Norway is characterized by equal access to diagnostics and treatment across the population, in addition to a national screening program for women aged 50-69. Any socioeconomic differences are unlikely to be large enough to substantially influence the observed association between age and survival in the present study.

In conclusion, we found strong and independent effects of age and subtype on breast cancer-specific mortality. Furthermore, we found that tumor-associated factors, such as subtype, grade and stage, explained a large part of the poorer prognosis among young patients, but did not explain the poorer prognosis among the elderly. Comorbidities and less intensive treatment could be possible explanations of the persisting increased breast cancer mortality among the elderly.

The higher mortality among elderly women is substantial, and suggests a possible benefit for increased screening age and treatment optimization. The higher mortality among young women with luminal A-like tumors warrants further research and suggests a need for even more aggressive treatment regimes in this young patient group with seemingly favorable tumors.

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Table 1. Year of diagnosis, tumour characteristics and treatments by age at diagnosis for study cohort.

	20-39y		40-49y		50-59y		60-69y		70-79y		80-89y		Total	P-value[a]
	N	%	N	%	N	%	N	%	N	%	N	%	N	
Total (row %)	1494	5.5	4974	18.3	7688	28.4	8034	29.6	3137	11.6	1793	6.6	27120	
Year														
2005-2008	486	32.5	1730	34.8	2756	35.8	2529	31.5	609	19.4	0	0.0	8110	<0.001
2009-2012	547	36.6	1807	36.3	2679	34.8	2953	36.8	1270	40.5	1031	57.5	10287	
2013-2015	461	30.9	1437	28.9	2253	29.3	2552	31.8	1258	40.1	762	42.5	8723	
ER														
Neg	457	31.7	828	17.2	1177	15.7	981	12.5	434	14.1	236	13.4	4113	<0.001
Pos	984	68.3	3996	82.8	6313	84.3	6855	87.5	2634	85.9	1526	86.6	22308	
Missing	*53*	*3.5*	*150*	*3.0*	*198*	*2.6*	*198*	*2.5*	*69*	*2.2*	*31*	*1.7*	*699*	
PR														
Neg	635	44.3	1324	27.6	2523	33.8	2494	32.1	1036	34.0	590	33.7	8602	<0.001
Pos	798	55.7	3480	72.4	4931	66.2	5287	67.9	2015	66.0	1162	66.3	17673	
Missing	*61*	*4.1*	*170*	*3.4*	*234*	*3.0*	*253*	*3.1*	*86*	*2.7*	*41*	*2.3*	*845*	
HER2														
Neg	1008	72.5	3722	80.8	5876	84.5	6374	87.4	2526	87.6	1416	88.8	20922	<0.001
Pos	382	27.5	883	19.2	1077	15.5	918	12.6	356	12.4	178	11.2	3794	
Missing	*104*	*7.0*	*369*	*7.4*	*735*	*9.6*	*742*	*9.2*	*255*	*8.1*	*199*	*11.1*	*2404*	
Subtype														
LumA	545	40.8	2799	62.3	4113	60.4	4489	62.8	1734	61.2	957	61.0	14637	<0.001
LumB HER2-	132	9.9	372	8.3	1017	14.9	1212	17.0	495	17.5	290	18.5	3518	
LumB HER2+	248	18.6	609	13.6	665	9.8	603	8.4	232	8.2	117	7.5	2474	
HER2+	122	9.1	246	5.5	371	5.5	286	4.0	112	4.0	58	3.7	1195	
TNBC	288	21.6	466	10.4	638	9.4	557	7.8	260	9.2	146	9.3	2355	
Missing	*159*	*10.6*	*482*	*9.7*	*884*	*11.5*	*887*	*11.0*	*304*	*9.7*	*225*	*12.5*	*2941*	
Grade														
Low grade (I)	103	7.7	704	15.4	1701	23.9	2014	26.9	546	19.3	243	16.5	5311	<0.001
Medium grade (II)	491	36.7	2215	48.4	3460	48.6	3759	50.2	1483	52.5	824	56.0	12232	
High grade (III+IV)	745	55.6	1656	36.2	1954	27.5	1716	22.9	794	28.1	405	27.5	7270	
Missing	*155*	*10.4*	*399*	*8.0*	*573*	*7.5*	*545*	*6.8*	*314*	*10.0*	*321*	*17.9*	*2307*	
TNM stage														
I	414	29.9	1677	36.0	3768	51.0	4444	57.4	1134	38.9	347	25.8	11784	<0.001
II	689	49.7	2188	46.9	2731	36.9	2487	32.1	1246	42.7	657	48.8	9998	
III	237	17.1	654	14.0	676	9.1	572	7.4	373	12.8	266	19.8	2778	
IV	45	3.2	144	3.1	217	2.9	236	3.0	162	5.6	76	5.6	880	
Missing	*109*	*7.3*	*311*	*6.3*	*296*	*3.9*	*295*	*3.7*	*222*	*7.1*	*447*	*24.9*	*1680*	
Surgery														
Mastectomy	977	65.5	2581	51.9	2846	37.0	2668	33.2	1570	50.1	977	54.6	11619	<0.001

BCS	466	31.2	2254	45.3	4612	60.0	5086	63.3	1264	40.3	303	16.9	13985	
No surgery	49	3.3	138	2.8	229	3.0	278	3.5	301	9.6	511	28.5	1506	
Missing	*2*	*0.1*	*1*	*0.0*	*1*	*0.0*	*2*	*0.0*	*2*	*0.1*	*2*	*0.1*	*10*	
Planned adjuvant treatment														
None	111	12.7	332	10.5	508	11.2	610	14.3	300	22.5	340	49.0	2201	<0.001
RT alone	204	23.3	928	29.2	1850	40.7	2073	48.5	492	36.8	112	16.1	5659	
CT alone	31	3.5	49	1.5	75	1.7	78	1.8	35	2.6	27	3.9	295	
RT, CT	98	11.2	271	8.5	356	7.8	239	5.6	81	6.1	12	1.7	1057	
HT alone	1	0.1	13	0.4	60	1.3	119	2.8	111	8.3	140	20.2	444	
RT, HT	16	1.8	52	1.6	316	7.0	544	12.7	192	14.4	52	7.5	1172	
CT, HT	69	7.9	223	7.0	184	4.0	77	1.8	30	2.2	7	1.0	590	
RT, CT, HT	345	39.4	1306	41.1	1196	26.3	533	12.5	95	7.1	4	0.6	3479	
Missing	*619*	*41.4*	*1800*	*36.2*	*3143*	*40.9*	*3761*	*46.8*	*1801*	*57.4*	*1099*	*61.3*	*12223*	

Percentages (%) calculated over total (excluding missing). Missing percentages (%) calculated over total.
[a] Pearson Chisquare test.

Table 2. Associations between age, subtype, grade, stage, surgery and breast cancer-specific mortality.

	No patients		No Deaths	Model includes age, year	Model includes age, year, subtype	Model includes age, year, subtype, grade	Model includes age, year, subtype, grade, stage	Model includes age, year, subtype, grade, stage, surgery
	N	%	N	HR[a] [95% CI]	HR[b] [95% CI]	HR[c] [95% CI]	HR[d] (95% CI)	HR[e] [95% CI]
Age								
20-39	1139	5.3	109	2.26 [1.81,2.82]	1.77 [1.42,2.22]	1.51 [1.21,1.89]	1.31 [1.05,1.64]	1.22 [0.97,1.52]
40-49	3975	18.6	233	1.30 [1.10,1.55]	1.32 [1.11,1.58]	1.21 [1.01,1.44]	0.99 [0.83,1.18]	1.00 [0.84,1.19]
50-59	6205	29.0	277	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
60-69	6524	30.5	269	0.99 [0.84,1.18]	1.03 [0.87,1.22]	1.07 [0.91,1.27]	1.19 [1.01,1.41]	1.15 [0.97,1.36]
70-79	2448	11.5	186	2.25 [1.87,2.71]	2.29 [1.90,2.76]	2.22 [1.84,2.68]	2.05 [1.70,2.47]	1.92 [1.58,2.31]
80-89	1093	5.1	148	5.19 [4.21,6.41]	5.22 [4.23,6.44]	4.96 [4.02,6.13]	3.92 [3.17,4.85]	2.78 [2.23,3.46]
Subtype								
LumA	13120	61.4	464		1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
LumB HER2-	3062	14.3	218		2.03 [1.72,2.38]	1.78 [1.51,2.10]	1.69 [1.44,1.99]	1.68 [1.42,1.97]
LumB HER2+	2165	10.1	137		1.82 [1.50,2.21]	1.28 [1.05,1.56]	1.02 [0.84,1.25]	0.99 [0.82,1.21]
HER2+	1007	4.7	105		2.99 [2.41,3.69]	1.71 [1.37,2.14]	1.37 [1.10,1.72]	1.32 [1.06,1.65]
TNBC	2030	9.5	298		4.22 [3.64,4.89]	2.39 [2.02,2.82]	3.17 [2.69,3.74]	3.12 [2.64,3.68]
Grade								
Low grade (I)	4581	21.4	63			1.00 [ref]	1.00 [ref]	1.00 [ref]
Medium grade (II)	10597	49.6	486			3.00 [2.30,3.90]	1.69 [1.30,2.21]	1.75 [1.34,2.28]
High grade (III+IV)	6206	29.0	673			5.76 [4.39,7.56]	2.93 [2.22,3.85]	3.14 [2.38,4.13]
TNM stage								
I	10070	47.1	119				1.00 [ref]	1.00 [ref]
IIA	2697	12.6	202				2.28 [1.80,2.88]	2.09 [1.65,2.65]
IIB	4514	21.1	179				4.48 [3.47,5.79]	3.75 [2.89,4.86]
II (SEER summary)	1311	6.1	123				6.65 [5.28,8.39]	5.39 [4.25,6.82]
IIIA	6	0.0	1				9.45 [7.41,12.05]	7.52 [5.85,9.68]
IIIB	1404	6.6	161				14.43 [11.33,18.38]	10.14 [7.88,13.05]
III (SEER summary)	856	4.0	166				26.36 [3.65,190.11]	12.10 [1.67,87.71]
IV	526	2.5	271				73.46 [58.81,91.77]	30.00 [23.11,38.93]
Surgery								
Mastectomy	8999	42.1	729					1.00 [ref]
BCS	11884	55.6	252					0.62 [0.53,0.73]

No surgery	501	2.3	241		4.01 [3.30,4.86]

[a] Model including age and year.
[b] Model including age, year and subtype.
[c] Model including age, year, subtype and grade.
[d] Model including age, year, subtype, grade and stage.
[e] Model including age, year, subtype, grade, stage and surgery.

Table 3. Associations between age, subtype and breast cancer-specific mortality, with/without adjustment for surgery and adjuvant treatment. Restricted to subset of patients with information on planned adjuvant treatment (n=11,934, 56% of study cohort).

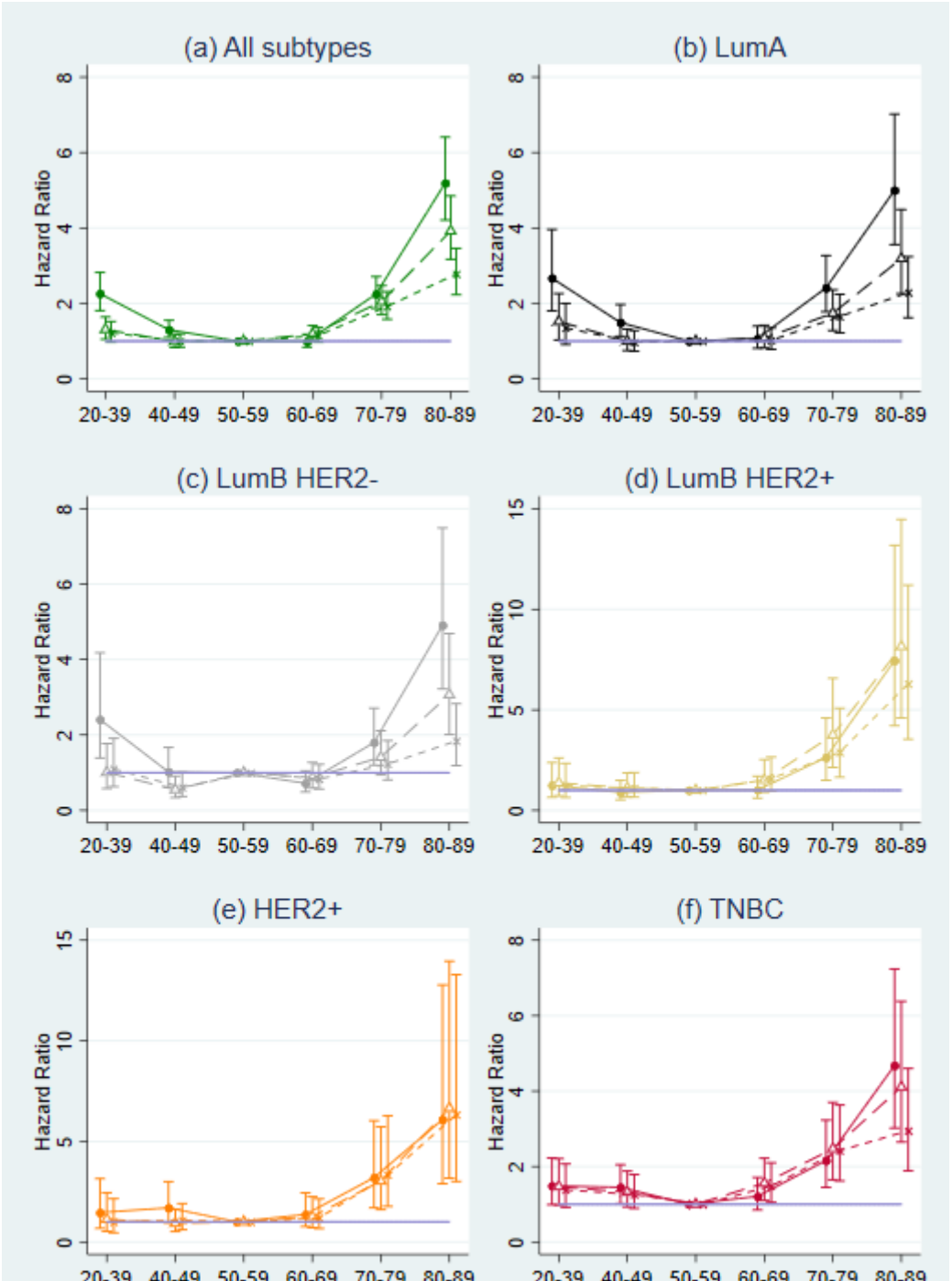
	No Patients	No deaths	Model includes age, year, subtype, grade, stage	Model includes age, year, subtype, grade, stage, surgery	Model includes age, year, subtype, grade, stage, surgery, adjuvant treatm.
	N	N	HR[a] [95% CI]	HR[b] [95% CI]	HR[c] [95% CI]
Age					
20-39	687	71	1.37 [1.03,1.82]	1.33 [1.00,1.77]	1.31 [0.98,1.74]
40-49	2577	140	0.89 [0.70,1.11]	0.87 [0.69,1.09]	0.86 [0.68,1.08]
50-59	3664	156	1.00 [ref]	1.00 [ref]	1.00 [ref]
60-69	3454	143	1.24 [0.99,1.56]	1.18 [0.94,1.49]	1.19 [0.95,1.51]
70-79	1073	92	2.25 [1.73,2.92]	2.05 [1.57,2.67]	2.10 [1.60,2.76]
80-89	479	68	4.34 [3.20,5.88]	3.40 [2.49,4.63]	3.48 [2.51,4.84]
Subtype					
LumA	7502	266	1.00 [ref]	1.00 [ref]	1.00 [ref]
LumB HER2-	1710	128	1.67 [1.34,2.06]	1.66 [1.34,2.06]	1.69 [1.36,2.09]
LumB HER2+	1292	78	0.91 [0.70,1.18]	0.93 [0.71,1.20]	0.93 [0.71,1.21]
HER2+	462	46	1.28 [0.92,1.77]	1.29 [0.93,1.78]	1.40 [0.99,1.96]
TNBC	968	152	2.97 [2.38,3.72]	2.95 [2.36,3.69]	3.25 [2.54,4.16]

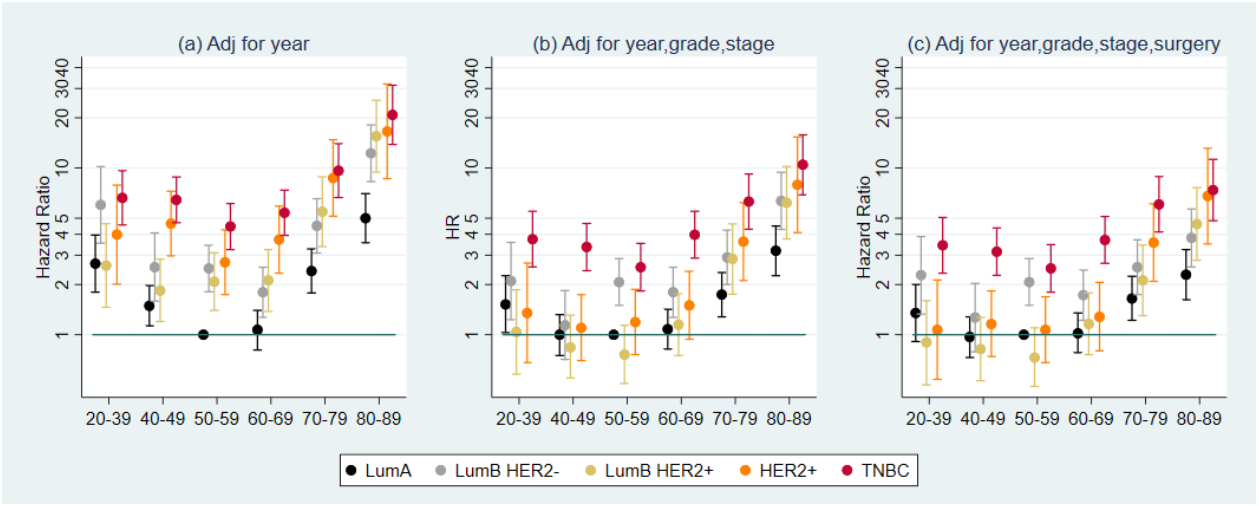
[a] Model including age, year, subtype, grade and stage.
[b] Model including age, year, subtype, grade, stage and surgery.
[c] Model including age, year, subtype, grade, stage, surgery and planned adjuvant treatment.

FIGURE LEGENDS

Figure 1. Associations between age at diagnosis and breast cancer-specific mortality (a) for all subtypes, and within levels of subtype: (b) Luminal A-like, (c) Luminal B-like HER2 negative, (d) Luminal B-like HER2-positive, (e) HER2-positive and (f) TNBC. From models adjusting for year (solid line); year, subtype, grade and stage (long dashed line); year, subtype, grade, stage and surgery (short dashed line). Estimates in Supplementary Table S1.

Figure 2. Associations between age, subtype and breast cancer-specific mortality compared to overall reference group (Lum A, age 50-59y) from models adjusting for (a) year, (b) year, grade and stage, (c) year, grade, stage and surgery. Y-axis is on log-scale. Likelihood ratio test for interaction between age and subtype in each panel (a) p=0.1286, (b) p=0.1005, (c) p=0.0606. Estimates in Supplementary Table S2.


(a) All subtypes
(b) LumA
(c) LumB HER2-
(d) LumB HER2+
(e) HER2+
(f) TNBC
Hazard Ratio
20-39
40-49
50-59
60-69
70-79
80-89


(a) Adj for year
(b) Adj for year,grade,stage
(c) Adj for year,grade,stage,surgery
Hazard Ratio
HR
1
2
3
4
5
10
20
30
40
20-39
40-49
50-59
60-69
70-79
80-89
LumA
LumB HER2-
LumB HER2+
HER2+
TNBC

SUPPLEMENTAL MATERIAL

Table S1. Associations between age and breast cancer-specific mortality within levels of subtype. These numbers correspond to Figure 1.

	No patients		No deaths	Model includes age, year, subtype	Model includes age, year, subtype, grade	Model includes age, year, subtype, grade, stage	Model includes age, year, subtype, grade, stage, surgery
	N	%	N	HR[a] [95% CI]	HR[b] [95% CI]	HR[c] [95% CI]	HR[d] [95% CI]
LumA							
20-39	480	3.7	33	2.67 [1.80,3.96]	2.03 [1.36,3.01]	1.52 [1.03,2.26]	1.35 [0.91,2.00]
40-49	2512	19.1	99	1.49 [1.13,1.97]	1.31 [0.99,1.73]	1.00 [0.75,1.32]	0.97 [0.73,1.28]
50-59	3810	29.0	99	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
60-69	4140	31.6	107	1.07 [0.81,1.40]	1.10 [0.84,1.45]	1.08 [0.82,1.42]	1.02 [0.78,1.35]
70-79	1518	11.6	73	2.41 [1.78,3.27]	2.21 [1.63,2.99]	1.74 [1.28,2.36]	1.65 [1.22,2.24]
80-89	660	5.0	53	5.00 [3.56,7.02]	4.47 [3.18,6.28]	3.19 [2.26,4.49]	2.29 [1.62,3.24]
Total	13120	100.0	464				
LumB HER2-							
20-39	112	3.7	16	2.41 [1.39,4.18]	1.69 [0.97,2.94]	1.01 [0.58,1.77]	1.10 [0.63,1.91]
40-49	319	10.4	21	1.02 [0.62,1.67]	0.85 [0.52,1.39]	0.55 [0.34,0.91]	0.61 [0.37,1.01]
50-59	924	30.2	60	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
60-69	1100	35.9	48	0.72 [0.49,1.05]	0.77 [0.53,1.12]	0.87 [0.59,1.27]	0.83 [0.57,1.22]
70-79	416	13.6	38	1.80 [1.20,2.71]	1.78 [1.18,2.67]	1.41 [0.94,2.11]	1.23 [0.81,1.85]
80-89	191	6.2	35	4.91 [3.22,7.49]	4.80 [3.14,7.32]	3.07 [2.01,4.69]	1.84 [1.19,2.83]

Total	3062	100.0	218				
LumB HER2+							
20-39	208	9.6	13	1.25 [0.65,2.38]	1.13 [0.59,2.14]	1.37 [0.72,2.61]	1.22 [0.64,2.34]
40-49	527	24.3	26	0.89 [0.53,1.49]	0.85 [0.51,1.43]	1.11 [0.66,1.87]	1.12 [0.66,1.88]
50-59	601	27.8	32	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
60-69	545	25.2	27	1.02 [0.61,1.70]	1.08 [0.65,1.81]	1.51 [0.90,2.53]	1.58 [0.95,2.65]
70-79	198	9.1	20	2.63 [1.50,4.59]	2.74 [1.56,4.79]	3.75 [2.14,6.57]	2.89 [1.65,5.08]
80-89	86	4.0	19	7.45 [4.21,13.18]	7.24 [4.09,12.82]	8.15 [4.59,14.47]	6.29 [3.54,11.20]
Total	2165	100.0	137				
HER2+							
20-39	93	9.2	9	1.46 [0.68,3.15]	1.40 [0.65,3.01]	1.13 [0.53,2.45]	1.00 [0.46,2.15]
40-49	204	20.3	24	1.70 [0.97,3.00]	1.67 [0.95,2.94]	0.93 [0.52,1.63]	1.08 [0.61,1.91]
50-59	322	32.0	24	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
60-69	254	25.2	22	1.37 [0.77,2.44]	1.34 [0.75,2.39]	1.26 [0.71,2.25]	1.20 [0.67,2.14]
70-79	92	9.1	16	3.20 [1.70,6.03]	3.01 [1.60,5.67]	3.03 [1.61,5.73]	3.33 [1.77,6.28]
80-89	42	4.2	10	6.09 [2.90,12.78]	5.71 [2.72,11.98]	6.65 [3.17,13.96]	6.33 [3.01,13.29]
Total	1007	100.0	105				

TNBC							
20-39	246	12.1	38	1.49 [0.99,2.23]	1.40 [0.93,2.09]	1.47 [0.98,2.21]	1.38 [0.92,2.07]
40-49	413	20.3	63	1.45 [1.02,2.05]	1.39 [0.98,1.98]	1.32 [0.93,1.88]	1.26 [0.89,1.79]
50-59	548	27.0	62	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
60-69	485	23.9	65	1.21 [0.85,1.71]	1.25 [0.88,1.77]	1.56 [1.10,2.22]	1.48 [1.05,2.10]
70-79	224	11.0	39	2.16 [1.45,3.23]	2.26 [1.51,3.38]	2.47 [1.65,3.70]	2.42 [1.62,3.63]
80-89	114	5.6	31	4.68 [3.02,7.24]	4.77 [3.08,7.39]	4.11 [2.65,6.38]	2.95 [1.89,4.60]
Total	2030	100.0	298				

[a] Model including age, year and subtype. Interaction term between age and subtype included.
[b] Model including age, year, subtype and grade. Interaction term between age and subtype included.
[c] Model including age, year, subtype, grade and stage. Interaction term between age and subtype included.
[d] Model including age, year, subtype, grade, stage and surgery. Interaction term between age and subtype included.

Table S2. Associations between age, subtype and breast cancer-specific mortality with common reference group (LumA, 50-59 y) from interaction models. These numbers correspond to Figure 2.

	No patients		No deaths	Model includes age, year, subtype	Model includes age, year, subtype, grade	Model includes age, year, subtype, grade, stage	Model includes age, year, subtype, grade, stage, surgery
	N	%	N	HR[a] [95% CI]	HR[b] [95% CI]	HR[c] [95% CI]	HR[d] [95% CI]
20-39							
LumA	480	42.1	33	2.67 [1.80,3.96]	2.03 [1.36,3.01]	1.52 [1.03,2.26]	1.35 [0.91,2.00]
LumB HER2-	112	9.8	16	6.01 [3.54,10.20]	3.62 [2.13,6.17]	2.10 [1.23,3.58]	2.28 [1.33,3.88]
LumB HER2+	208	18.3	13	2.60 [1.46,4.63]	1.54 [0.86,2.76]	1.04 [0.58,1.86]	0.90 [0.50,1.60]
HER2+	93	8.2	9	3.99 [2.01,7.89]	2.10 [1.06,4.18]	1.35 [0.68,2.69]	1.07 [0.54,2.13]
TNBC	246	21.6	38	6.62 [4.55,9.63]	3.28 [2.23,4.82]	3.74 [2.55,5.50]	3.44 [2.34,5.05]
	1139	100.0	109				
40-49							
LumA	2512	63.2	99	1.49 [1.13,1.97]	1.31 [0.99,1.73]	1.00 [0.75,1.32]	0.97 [0.73,1.28]
LumB HER2-	319	8.0	21	2.54 [1.59,4.08]	1.82 [1.13,2.91]	1.14 [0.71,1.84]	1.27 [0.79,2.03]
LumB HER2+	527	13.3	26	1.84 [1.20,2.84]	1.17 [0.75,1.80]	0.84 [0.55,1.31]	0.82 [0.53,1.27]
HER2+	204	5.1	24	4.64 [2.97,7.25]	2.51 [1.59,3.95]	1.10 [0.70,1.74]	1.16 [0.74,1.83]
TNBC	413	10.4	63	6.44 [4.70,8.83]	3.28 [2.36,4.55]	3.36 [2.42,4.65]	3.15 [2.27,4.37]
	3975	100.0	233				
50-59							
LumA	3810	61.4	99	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]

LumB HER2-	924	14.9	60	2.50 [1.81,3.44]	2.14 [1.55,2.95]	2.07 [1.50,2.86]	2.07 [1.50,2.86]
LumB HER2+	601	9.7	32	2.08 [1.40,3.10]	1.37 [0.92,2.05]	0.76 [0.51,1.14]	0.73 [0.49,1.10]
HER2+	322	5.2	24	2.72 [1.74,4.25]	1.50 [0.95,2.36]	1.19 [0.76,1.87]	1.07 [0.68,1.69]
TNBC	548	8.8	62	4.46 [3.24,6.12]	2.35 [1.69,3.26]	2.54 [1.83,3.53]	2.50 [1.80,3.47]
	6205	100.0	277				
60-69							
LumA	4140	63.5	107	1.07 [0.81,1.40]	1.10 [0.84,1.45]	1.08 [0.82,1.42]	1.02 [0.78,1.35]
LumB HER2-	1100	16.9	48	1.80 [1.27,2.54]	1.65 [1.17,2.33]	1.80 [1.27,2.54]	1.73 [1.22,2.44]
LumB HER2+	545	8.4	27	2.12 [1.38,3.24]	1.49 [0.97,2.28]	1.15 [0.75,1.76]	1.16 [0.76,1.78]
HER2+	254	3.9	22	3.72 [2.34,5.91]	2.01 [1.26,3.21]	1.50 [0.94,2.40]	1.28 [0.80,2.06]
TNBC	485	7.4	65	5.39 [3.94,7.37]	2.94 [2.13,4.06]	3.98 [2.88,5.50]	3.70 [2.68,5.12]
	6524	100.0	269				
70-79							
LumA	1518	62.0	73	2.41 [1.78,3.27]	2.21 [1.63,2.99]	1.74 [1.28,2.36]	1.65 [1.22,2.24]
LumB HER2-	416	17.0	38	4.50 [3.09,6.55]	3.81 [2.62,5.54]	2.91 [2.00,4.24]	2.54 [1.74,3.71]
LumB HER2+	198	8.1	20	5.47 [3.38,8.86]	3.75 [2.31,6.09]	2.85 [1.75,4.62]	2.12 [1.30,3.45]
HER2+	92	3.8	16	8.71 [5.14,14.78]	4.52 [2.65,7.72]	3.62 [2.11,6.19]	3.57 [2.09,6.10]
TNBC	224	9.2	39	9.64 [6.65,13.99]	5.31 [3.63,7.77]	6.29 [4.29,9.21]	6.05 [4.13,8.88]
	2448	100.0	186				
80-89							

LumA	660	60.4	53	5.00 [3.56,7.02]	4.47 [3.18,6.28]	3.19 [2.26,4.49]	2.29 [1.62,3.24]
LumB HER2-	191	17.5	35	12.26 [8.29,18.13]	10.28 [6.95,15.21]	6.35 [4.28,9.42]	3.81 [2.55,5.68]
LumB HER2+	86	7.9	19	15.52 [9.45,25.48]	9.94 [6.04,16.36]	6.19 [3.76,10.20]	4.61 [2.79,7.62]
HER2+	42	3.8	10	16.58 [8.62,31.90]	8.56 [4.43,16.56]	7.93 [4.10,15.33]	6.79 [3.50,13.14]
TNBC	114	10.4	31	20.84 [13.84,31.36]	11.22 [7.40,17.01]	10.47 [6.90,15.89]	7.38 [4.83,11.26]
	1093	100.0	148				

[a] Model including age, year and subtype. Interaction term between age and subtype included (test for interaction p-value 0.1286).
[b] Model including age, year, subtype and grade. Interaction term between age and subtype included.
[c] Model including age, year, subtype, grade and stage. Interaction term between age and subtype included (test for interaction p-value 0.1005).
[d] Model including age, year, subtype, grade, stage and surgery. Interaction term between age and subtype included (test for interaction p-value 0.0606).

Table S3. Associations between subtype and breast cancer-specific mortality within age groups.

	No patients		No deaths	Model includes age, year, subtype	Model includes age, year, subtype, grade	Model includes age, year, subtype, grade, stage	Model includes age, year, subtype, grade, stage, surgery
	N	%	N	HR[a] [95% CI]	HR[b] [95% CI]	HR[c] [95% CI]	HR[d] [95% CI]
20-39							
LumA	480	42.1	33	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
LumB HER2-	112	9.8	16	2.25 [1.24,4.09]	1.79 [0.98,3.25]	1.38 [0.76,2.51]	1.69 [0.93,3.08]
LumB HER2+	208	18.3	13	0.97 [0.51,1.85]	0.76 [0.40,1.45]	0.68 [0.36,1.30]	0.67 [0.35,1.27]
HER2+	93	8.2	9	1.49 [0.71,3.12]	1.04 [0.50,2.17]	0.89 [0.42,1.86]	0.79 [0.38,1.67]
TNBC	246	21.6	38	2.48 [1.56,3.96]	1.62 [1.01,2.59]	2.45 [1.53,3.94]	2.55 [1.59,4.09]
Total	1139	100.0	109				
40-49							
LumA	2512	63.2	99	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
LumB HER2-	319	8.0	21	1.71 [1.07,2.74]	1.39 [0.87,2.22]	1.15 [0.72,1.84]	1.31 [0.81,2.10]
LumB HER2+	527	13.3	26	1.24 [0.81,1.91]	0.89 [0.58,1.38]	0.85 [0.55,1.31]	0.84 [0.55,1.30]
HER2+	204	5.1	24	3.12 [2.00,4.87]	1.92 [1.22,3.01]	1.11 [0.70,1.74]	1.20 [0.76,1.88]
TNBC	413	10.4	63	4.33 [3.16,5.94]	2.50 [1.81,3.47]	3.37 [2.44,4.66]	3.25 [2.35,4.50]
Total	3975	100.0	233				

50-59							
LumA	3810	61.4	99	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
LumB HER2-	924	14.9	60	2.50 [1.81,3.44]	2.14 [1.55,2.95]	2.07 [1.50,2.86]	2.07 [1.50,2.86]
LumB HER2+	601	9.7	32	2.08 [1.40,3.10]	1.37 [0.92,2.05]	0.76 [0.51,1.14]	0.73 [0.49,1.10]
HER2+	322	5.2	24	2.72 [1.74,4.25]	1.50 [0.95,2.36]	1.19 [0.76,1.87]	1.07 [0.68,1.69]
TNBC	548	8.8	62	4.46 [3.24,6.12]	2.35 [1.69,3.26]	2.54 [1.83,3.53]	2.50 [1.80,3.47]
Total	6205	100.0	277				
60-69							
LumA	4140	63.5	107	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
LumB HER2-	1100	16.9	48	1.69 [1.20,2.37]	1.50 [1.06,2.11]	1.67 [1.18,2.35]	1.69 [1.20,2.38]
LumB HER2+	545	8.4	27	1.98 [1.30,3.03]	1.35 [0.88,2.06]	1.07 [0.70,1.63]	1.13 [0.74,1.74]
HER2+	254	3.9	22	3.48 [2.20,5.51]	1.83 [1.15,2.91]	1.39 [0.87,2.23]	1.25 [0.78,2.01]
TNBC	485	7.4	65	5.05 [3.71,6.87]	2.67 [1.94,3.67]	3.69 [2.68,5.09]	3.62 [2.63,5.00]
Total	6524	100.0	269				
70-79							
LumA	1518	62.0	73	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
LumB HER2-	416	17.0	38	1.86 [1.26,2.76]	1.73 [1.17,2.56]	1.67 [1.13,2.48]	1.54 [1.04,2.28]
LumB HER2+	198	8.1	20	2.27 [1.38,3.72]	1.70 [1.04,2.79]	1.63 [0.99,2.68]	1.28 [0.78,2.11]

HER2+	92	3.8	16	3.61 [2.10,6.21]	2.05 [1.19,3.54]	2.08 [1.20,3.60]	2.16 [1.25,3.74]
TNBC	224	9.2	39	4.00 [2.71,5.90]	2.41 [1.62,3.57]	3.61 [2.42,5.38]	3.66 [2.46,5.46]
Total	2448	100.0	186				
80-89							
LumA	660	60.4	53	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
LumB HER2-	191	17.5	35	2.46 [1.60,3.76]	2.30 [1.50,3.53]	1.99 [1.29,3.06]	1.66 [1.08,2.56]
LumB HER2+	86	7.9	19	3.11 [1.84,5.25]	2.22 [1.31,3.77]	1.94 [1.15,3.29]	2.01 [1.19,3.42]
HER2+	42	3.8	10	3.32 [1.69,6.53]	1.92 [0.97,3.79]	2.49 [1.26,4.91]	2.96 [1.50,5.87]
TNBC	114	10.4	31	4.17 [2.68,6.50]	2.51 [1.60,3.94]	3.28 [2.09,5.16]	3.22 [2.05,5.07]
Total	1093	100.0	148				

[a] Model including age, year and subtype. Interaction term between age and subtype included.
[b] Model including age, year, subtype and grade. Interaction term between age and subtype included.
[c] Model including age, year, subtype, grade and stage. Interaction term between age and subtype included.
[d] Model including age, year, subtype, grade, stage and surgery. Interaction term between age and subtype included.

Table S4. Associations between age, subtype and breast cancer-specific mortality over periods 2005-2008 (ER/PR/HER2 available for age 20-79) and 2009-2015 (ER/PR/HER2 available for age 20-89).

	2005-2008 N=5866			**2009-2015** N=15518		
	HR[a] [95% CI]	**HR[b] [95% CI]**	**HR[c] [95% CI]**	**HR[a] [95% CI]**	**HR[b] [95% CI]**	**HR[c] [95% CI]**
Age						
20-39	2.40 [1.78,3.25]	1.65 [1.21,2.24]	1.40 [1.03,1.90]	2.11 [1.52,2.92]	1.20 [0.87,1.67]	1.10 [0.79,1.53]
40-49	1.39 [1.10,1.76]	1.33 [1.05,1.69]	1.06 [0.83,1.34]	1.21 [0.93,1.57]	0.88 [0.67,1.14]	0.91 [0.70,1.18]
50-59	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]	1.00 [ref]
60-69	1.06 [0.84,1.34]	1.14 [0.91,1.44]	1.24 [0.98,1.56]	0.93 [0.73,1.18]	1.13 [0.89,1.44]	1.11 [0.87,1.41]
70-79	1.90 [1.40,2.59]	1.87 [1.37,2.54]	1.63 [1.20,2.23]	2.42 [1.89,3.08]	2.29 [1.79,2.92]	2.05 [1.60,2.62]
80-89	N/A	N/A	N/A	5.05 [3.99,6.39]	3.80 [2.99,4.83]	2.72 [2.12,3.50]
Subtype						
Lum A		1.00 [ref]	1.00 [ref]		1.00 [ref]	1.00 [ref]
Lum B HER2-		1.95 [1.54,2.48]	1.82 [1.43,2.31]		1.59 [1.27,1.99]	1.53 [1.22,1.91]
Lum B HER2+		1.01 [0.74,1.40]	0.90 [0.65,1.24]		1.09 [0.85,1.40]	1.06 [0.83,1.36]
HER2+		1.77 [1.28,2.44]	1.57 [1.14,2.16]		1.25 [0.91,1.71]	1.28 [0.93,1.75]
TNBC		2.07 [1.60,2.66]	2.74 [2.13,3.54]		3.63 [2.92,4.51]	3.59 [2.89,4.46]

[a] Model including age and year.
[b] Model including age, year, subtype, grade and stage.
[c] Model including age, year, subtype, grade, stage and surgery.

N/A=not available.

Table S5. Associations between age, subtype and breast cancer-specific mortality restricted to women with stage I-III.

	Stage I-III N=20858		
	HR[a] [95% CI]	**HR[b] [95% CI]**	**HR[c] [95% CI]**
Age			
20-39	2.67 [2.10,3.40]	1.42 [1.11,1.81]	1.33 [1.04,1.70]
40-49	1.42 [1.16,1.72]	1.09 [0.89,1.32]	1.04 [0.85,1.26]
50-59	1.00 [ref]	1.00 [ref]	1.00 [ref]
60-69	0.94 [0.77,1.14]	1.10 [0.91,1.34]	1.11 [0.91,1.35]
70-79	2.30 [1.86,2.85]	2.10 [1.69,2.60]	1.96 [1.58,2.44]
80-89	5.83 [4.59,7.40]	4.21 [3.31,5.35]	3.06 [2.38,3.93]
Subtype			
Lum A		1.00 [ref]	1.00 [ref]
Lum B HER2-		1.82 [1.51,2.19]	1.75 [1.46,2.11]
Lum B HER2+		1.06 [0.84,1.34]	1.00 [0.79,1.27]
HER2+		1.43 [1.12,1.84]	1.39 [1.08,1.78]
TNBC		3.02 [2.51,3.62]	2.86 [2.38,3.43]

[a] Model including age and year.
[b] Model including age, year, subtype, grade and stage.
[c] Model including age, year, subtype, grade, stage and surgery.

Table S6. Associations between age, subtype and breast cancer death using cause-specific mortality approach and relative survival approach.

	No patients N=21,384	N Deaths due BC N=1,222	N Deaths All causes N=2,052	**Cause-specific mortality Cox regression[a] HR [95% CI]**	**Cause-specific mortality FPM[b] HR [95% CI]**	**Relative Survival FPM[c] EHR [95% CI]**
Age						
20-39	1139	109	135	1.22 [0.97,1.52]	1.22 [0.97,1.52]	1.25 [1.01,1.54]
40-49	3975	233	284	1.00 [0.84,1.19]	1.00 [0.84,1.19]	0.93 [0.79,1.11]
50-59	6205	277	406	1.00 [ref]	1.00 [ref]	1.00 [ref]
60-69	6524	269	496	1.15 [0.97,1.36]	1.15 [0.97,1.36]	1.16 [0.98,1.38]
70-79	2448	186	382	1.92 [1.58,2.31]	1.92 [1.59,2.32]	1.99 [1.64,2.41]
80-89	1093	148	349	2.78 [2.23,3.46]	2.78 [2.23,3.46]	2.34 [1.83,3.00]
Subtype						
Lum A	13120	464	947	1.00 [ref]	1.00 [ref]	1.00 [ref]
Lum B HER2-	3062	218	360	1.68 [1.42,1.97]	1.68 [1.42,1.97]	1.60 [1.36,1.88]
Lum B HER2+	2165	137	201	0.99 [0.82,1.21]	0.99 [0.81,1.21]	0.85 [0.69,1.04]
HER2+	1007	105	147	1.32 [1.06,1.65]	1.32 [1.06,1.66]	1.23 [0.98,1.54]
TRN	2030	298	397	3.12 [2.64,3.68]	3.12 [2.65,3.68]	2.96 [2.51,3.49]

[a] Cox regression model for cause-specific mortality (death due to breast cancer), model includes age, subtype, year, grade, stage and surgery. Same as model e in Table 2.
[b] Flexible parametric model (FPM) for cause-specific mortality (death due to breast cancer), model includes age, subtype, year, grade, stage and surgery; yielding similar results as Cox regression.
[c] Flexible parametric model for excess hazard mortality rates (death due to all causes in patients versus general population), model includes age, subtype, year, grade, stage and surgery; yielding slightly lower excess hazard ratio (HER) for women aged 80-89 compared to HR in cause-specific models; while no difference in the other age groups.

The relative survival analysis compared all-cause mortality in the patient cohort to all-cause mortality in an age- and year-matched Norwegian reference population, estimating the direct and indirect excess mortality associated with cancer, irrespective of cause of death classification. Excess hazard rate ratios compared the excess mortality by exposure levels. EHRs should be similar to HRs from a Cox model if no misclassification of cause of death is present.