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Article

The Association Between Age, Comorbidities and Use of Radiotherapy in Women with Breast Cancer: Implications for Survival

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Abstract: Background: Radiotherapy plays an important role in the management and survival of patients with breast cancer. The aim of this study was to examine the association between age, comorbidities and use of radiotherapy in this population. **Methods:** Patients diagnosed with breast cancer from 2004–2013 were identified from the American College of Surgeons National Cancer Database (NCDB). Follow-up time was measured from the date of diagnosis (baseline) to the date of death or censoring. Adjusted hazard ratios (aHR) and 95% confidence intervals (95%CI) were used as the measure of association. **Results:** Independently of comorbidities and other important outcome-related factors, patients >65 years of age who received radiotherapy survived significantly longer than those who did not receive radiotherapy (aHR = 0.53, 95%CI = 0.52–0.54). However, as women aged, those with comorbidities were less likely to receive RT (adjusted *P*-trend by age <0.0001). **Conclusions:** The development of decision-making tools to assist clinicians, and older women with breast cancer and comorbidities, are needed to facilitate personalized treatment plans regarding RT. This is particularly relevant as the population ages and the number of women with breast cancer is expected to increase in the near future.

Keywords: breast cancer; comorbidities; older women; radiotherapy; survival

1. Introduction

Breast cancer is a disease of aging, predominately affecting women >65 years. [1,2] Over the next generation, the incidence of breast cancer in older women is expected to rise, influencing health service planning and delivery.[3] While there has been progress in the early detection and effective treatment of breast cancer, these gains are less evident in older women. [1,4] One out of two deaths from breast cancer occurs among women in this age group. [3]

Radiotherapy (RT) is an important treatment modality for patients with breast cancer. [5-8] However, misperceptions exist about its appropriateness and efficacy in older women. [1-3, 9-12] These include slower disease progression, less aggressive tumours and an assumption that mortality will be attributed to age-related comorbidities. [3] This paper explores the hypothesis that women >65 years of age with comorbidities are less likely to receive RT than women in younger age groups.

2. Materials and Methods

2.1 Data Source

Over 1,500 Commission on Cancer (CoC) accredited programs provide data to the National Cancer Database (NCDB), representing ~70% of incident cancer cases in the United States. [13] This database, which is maintained by the American College of Surgeons, is the largest cancer registry in the world and contains nearly 10 million cases. Participant hospitals must fulfil 35 benchmark criteria, applicable to the delivery of cancer care, to be accredited by the CoC. Every three years, hospitals are re-evaluated for adherence to these standards. Records in NCDB are de-identified. This study was considered exempt by the institutional review board (IRB) at the recipient NCDB member facility (Code of Federal Regulations 45 part 46.101(b)).

2.2 Eligibility

Patients who underwent surgical resection for primary, invasive breast cancer from 2004-2013 were included in the study. All tumours were pathologically confirmed. They were excluded if their tumors were in situ or advanced clinical stage IV. Patients receiving RT also were excluded if their dose was not within the range of 4000-6000 cGy or if the primary target was outside the breast, chest wall or lymph nodes. Sarcoma, lymphoma, and leukaemia histologies were not considered in the current analysis.

2.3 Definitions

Clinical and pathological stage were coded and assessed by each CoC facility using the American Joint Committee on Cancer (AJCC) TNM (Tumour, Nodes and Metastasis) system. [14] The majority of patients were staged according to the sixth and seventh editions of AJCC. Data were not converted from the lower TNM editions. Instead, a sensitivity analysis was performed by stratifying data by year of diagnosis, with the cut-off value based on the year when the seventh edition of AJCC was introduced (i.e., 2010). Payor type consisted of mutually exclusive categories and did not allow for multiple enteries for an individual patient (e.g., Medicare with supplemental insurance). Racial identity was self-reported. Age groups were categorised as <45, 45-65 and >65 years.

Breast cancers were subtyped into four groups on the basis of hormone receptor (HR) and epidermal growth factor receptor status (HER2). Comorbidities were categorized using the Charlson (Deyo) Comorbidity Index (CCI). Patients with no comorbidities were assigned a score of 0. The highest score of 2 indicates the presence of multiple comorbidities. [15,13]

2.4 Statistical analysis

Categorical variables were denoted as frequencies and percentages, while continuous variables were reported as medians and interquartile ranges (IQR). Statistical significance for categorical variables was tested using the chi-square (χ^2) procedure and the Kruskal-Wallis H test for continuous variables. Trends across categories were assessed using a Cochran-Armitage trend test with *P* values computed using a likelihood ratio procedure. [16] Follow-up time was measured from the date of diagnosis (baseline) to the date of death or censoring. Adjusted odds ratios (aOR) and hazard ratios (aHR) were estimated using logistic and Cox regression models, respectively. Survival probabilities at 2, 5, 8, and 10 years were computed using the product-limit method. The parallel-hazards assumption was not violated in our models.

Unless indicated otherwise, the reference group for binary variables was the complement of the indicated category. Other variables were categorized according to NCDB definitions. A multistage-iterative expectation-maximization (EM) algorithm was used to account for missing values. [17] Statistical significance was defined as $P \leq .05$. SAS Version 9.4 (SAS Institute, Cary, NC, USA) was used to analyze the data.

3. Results

The median age of women at diagnosis was 59 years (N=980,381; IQR=20) (Table 1). Over half of patients lived more than 9 miles from their treatment facility, which in most cases was a comprehensive community cancer center (49%). The majority of women were white (84%), had private health insurance (56%), and presented with clinical stage I-II disease (69%). Among women >65 years of age, 75% had well or moderately differentiated tumours and only 16% had lymph node invasion. Most tumours in this age group were ≤2 cm (67%). Approximately 17% of older women had the more aggressive triple negative breast cancer (HR-/HER2-).

The majority of patients received RT (61%), with a median dose of 5000 cGy (IQR=440 cGy) (Table 2). Among those receiving radiation, treatment was administered prior to surgery in ~1.8% of cases. Women >65 years, independent of biologic subtype, were less likely to receive RT (53%) and to have their lymph nodes treated (17%). Compared with younger women ≤ 65, they were more likely to receive lower doses of radiation, with a greater percentage falling within the 4000-4500 cGy range. This older age group also was less likely to receive neoadjuvant chemotherapy (NACT). When they did receive NACT, their pathologic complete response rate was the lowest of all age groups (11%). Fewer women >65 years received mastectomy (36%) and chemotherapy (24%).

As women aged, those with more comorbidities were less likely to receive RT (Table 3). For example, the odds ratio associated with not receiving RT (corresponding to CCI level II vs level 0), increased across age groups (Age <45 years: aOR=1.1, 95%CI=.91-1.3; Age 45-65 years: aOR=1.3, 95%CI=1.26-1.41; Age >65 years: aOR=1.6, 95%CI=1.5-1.7; adjusted P-trend by age<.0001). Women >65 years with CCI=2 were 2.2-fold (95%CI=2.1-2.3) less likely to receive RT than those who were <45 with CCI=0.

In addition to the odds ratio, a linear trend with respect to CCI was observed within the age categories of 45-65 and >65 years (adjusted P<.0001); as hypothesised, this trend was less evident among women aged <45 years (adjusted P=.020). A noticeably higher, 1.9-fold aOR (CCI level II vs level 0; 95%CI=1.5-1.9) was observed among women aged >65 with HR-/HER2+ tumours compared with other hormone receptor categories. In contrast, women in the same age group with tumour type HR-/HER2- had a 1.3-fold aOR (95%CI=1.2-1.5). Even when women aged >65 years with comorbidities (CCI, I and II combined) did receive RT, they were more likely to receive lower doses in the 4,000-4,500 cGy range than younger women with comorbidities (>65 years, 28%; 45-65 years, 22%; <45 years, 17%; adjusted P-trend <.0001).

Adjusted survival probabilities (2, 5, 8, and 10 years) for older women who received radiation, were consistently greater than those not receiving RT (aHR=.53, 95%CI=.52-.54) (Table 4). For example, the probability of surviving 5 years was 91% among women who received radiation, compared with 83% for those who did not receive radiation. Independently of comorbidities and other important outcome-related factors, RT was associated with improved survival overall and for all biologic subtypes.

4. Discussion

Comorbidities are common among older breast cancer patients although, the two do not always coexist. [11,18] A common belief or misperception among health care providers is that breast cancer progresses more slowly in older women and the patient is more likely to die from comorbidities. [3,19]. Life expectancy may be underestimated even though many older women with comorbidities are living longer due to better management of their conditions. [19,20] While age and comorbidities should be considered, they should never alone be a barrier to standard treatment. This includes the benefits of RT for older women. [19-23]

In this study, as women aged, those with more comorbidities were less likely to receive RT. Furthermore, overall survival was consistently greater for older women who received RT.

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4.1 RT survival and local control

Similar to our findings, several studies have reported that older women are less likely to receive RT than younger women and when RT was administered to this group they generally had better local and regional control and improved survival. [24-29] An analysis of 4,836 women (50-89 years) reported that as women aged, RT was more likely to be omitted (26% for women aged ≥75 years compared with 7% of the time for women aged 50-64 years). RT omission was associated with significantly reduced local control, breast cancer specific survival (BCSS) and overall survival (OS). Women aged ≥75 had lower 5-year OS and BCSS when RT was omitted. [28]

Another study of 44,731 patients with triple negative breast cancer (TNBC) (aged 19-90 years) found that RT was associated with improved OS for women of all ages. Approximately 40% of patients aged 76-80 years, who might have benefitted from RT, did not receive it (although the median expected survival was greater than 10 years for this age group). [24] Our findings are again confirmed by a large study (n=27,399) of women with early stage breast cancer, many who had one or more comorbidities, reported increasing survival with age among those receiving RT. [27] However, in a longitudinal study of 636 women aged ≥70 who received breast conserving surgery (BCS) and Tamoxifen, 98% vs. 90% were free from local and regional recurrence if they received RT but RT was not associated with improved BCSS and OS. [26]

In a subset analysis focusing on inflammatory breast cancer (IBC), older women with more comorbidities were less likely to receive trimodality treatment including RT and had poorer OS, than younger women with fewer comorbidities. [30] The authors suggested that treatment delivery bias may account for younger healthier patients more frequently receiving aggressive, guideline-compliant therapy.

4.2 O*mission of RT*

In some cases, it may be reasonable to omit RT in those with a low chance of recurrence (e.g., ≤2 cm with clear margins, negative axillary lymph nodes, HR^+), or when risk of toxicity, advancing age and comorbidities outweigh the risk of recurrence. [10,21-23,5,31] Older women with a life expectancy less than 5 years and breast cancer may not derive a survival benefit from RT. [12]

An unwarranted fear of toxicity can lead to RT omission even though RT is not considered to be more toxic in older women. [10,11,20,21] RT also may be omitted because of difficulty attending regular clinic visits (e.g., inadequate transportation, accommodation or carer availability), perceived non-compliance with instructions, and limited upper limb mobility (when positioning a patient during RT). [20,3,1]

4.3 RT and comorbidities

While there are valid reasons for omitting RT in older women with breast cancer, comorbidities alone should not be the main reason to forgo this therapy. As suggested by several reports in the literature, RT may be considered for most older women when their comorbidities are well managed. [20,12,24] However, in our study, older women with comorbidities were less likely to receive RT than their younger counterparts.

Older women with breast cancer often have been excluded from clinical trials, resulting in a paucity of evidence about the influence of comorbidities on treatment decisions regarding RT. [1,9-12,20-22] Therapeutic options for older women may not be evidence based, resulting in under treatment with suboptimal outcomes. [1,9,11,20,21] Future studies to assess the effectiveness of RT in patients with comorbidities will benefit by including a representative sample of older women. [9,11,12,21] Analyses of secondary and linked data also can help inform study design. [9]

4.4. Decision making tools

To our knowledge, there is a lack of validated decision-making tools to help clinicians identify which older women will benefit from RT and to assist them in making treatment decisions. [22,32]

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While some instruments, such as the Comprehensive Geriatric Assessment tool, are useful to measure comorbidities and functional/mental status, they are limited in predicting survival rates in older women with breast cancer. [20,21] An appropriate decision tool should consider the benefits of RT, especially in the context of tumour biology, toxicity, life expectancy, patient preference, quality of life and comorbidities. [11,23,33] Tools that assist older women with breast cancer to make decisions regarding RT also would be valuable.

4.5 Strengths and limitations

Little is known about breast cancer and ageing, especially in the context of RT, comorbidities, and biologic subtypes. By using the NCDB, a large national sample encompassing ~70% of incident cases, we were able to analyse the data by these important characteristics. In comparison, only 25% of new cases are identified through the Surveillance, Epidemiology, and End Results (SEER) program. [34] To our knowledge, this is the first study to simultaneously address trends in RT by age, comorbidity status, and breast cancer biologic subtypes.

There is no consensus in the literature regarding the age cut-off point for older women, limiting comparison of our results with other studies.[35] Although NCDB is the most comprehensive collection of breast cancer data in the United States, it may underrepresent priority populations such as those lacking comprehensive health insurance. [36] The CCI was reported as three broad categories in the NCDB, which may have limited specificity of our results. [37]

Selection bias may be present as women with more comorbidities may not have progressed to surgery. However, the bias was likely towards the null. Some patients may have refused RT because their tumors were rapidly progressing. While this information was unavailable in NCDB, our analyses were adjusted for factors associated with tumor severity, thus minimizing selection bias. Information on specific systemic therapy also was not available. Again, this limitation likely did not impact results as we were able to stratify analyses by biological subtype, with treatment specificity within these groups.

Cardiovascular comorbidities tend to occur with greater frequencies in older patients and potentially may be exacerbated by RT. However, improvements in RT delivery, which restricts the dose received to the heart, and the long delay between RT and cardiovascular side effects, have minimised this concern.

Although NCDB is one of the most comprehensive data source for breast cancer in the world, some data fields are unavailable or contain missing values. For example, information on exact comorbidities and their severity is not available in NCDB and consequently we were unable to assess their impact on treatment decisions regarding RT. The NCDB also did not collect data on disease specific survival. To account for missing data, we use a multistage EM algorithm. Furthermore, variability exists in how data was reported across NCDB sites, limiting the generalizability of our results. Given the large number of comparisons in our study, we cannot rule out that our findings may be attributable to chance.

5. Conclusions

After adjusting for key clinical and demographic factors, we observed that older women with breast cancer and more comorbidities were less likely to receive RT. However, OS was consistently greater for older women who received RT. This was true even in the presence of comorbidities and when the analysis was stratified by biological subtypes. Future studies are needed to better understand the relationship between age, comorbidities and RT treatment decisions and how this impacts on patient outcomes. The personalization of treatment plans regarding RT for older women also is warranted, with emphasis on developing tools to assist clinicians and patients in this process. The aetiology of treatment non-compliance and delivery bias are multifactorial in nature. [30] Increasing community, educational, and social efforts aimed at minimizing barriers to RT represents other important steps for future consideration. Additionally, research of older women with breast cancer will benefit from targeted strategies aimed at mitigating the impact of comorbidities in this population. [38]

Author Contributions: JTE, SH, SJ, SC, CJ, and TB contributed to the conception and design of the study. JTE and CJ created the formatted analysis database and performed the statistical analysis. JTE, SH, SC, SJ, CJ, and TB wrote the first draft of the manuscript. All authors contributed to the manuscript revision and approved the submitted version.

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Table 1: Patient characteristics (N=980,381, 2004-2013)[§]

Characteristic	Age (Years)			P value[†]
	<45 n (%) Median [IQR]	45-65 n (%) Median [IQR]	>65 n (%) Median [IQR]	
Overall (n)	127786	517614	334981	
Demographics				
Facility type				
Academic/research	52964 (41)	156816 (30)	82258 (25)	<.0001
Community	7229 (6)	55352 (11)	44994 (13)	
Comprehensive community	59156 (46)	248486 (48)	172210 (51)	
Integrated network	8437 (7)	56960 (11)	35519 (11)	
Great circle distance (miles)	10 [14]	9 [15]	8 [12]	<.0001
Hispanic	14507 (11)	37636 (7)	15665 (5)	<.0001
Insurance				
Medicaid	14356 (11)	44324 (9)	6985 (2)	<.0001
Medicare	2736 (2)	49652 (10)	280882 (84)	
Other government	1624 (1)	6614 (1)	1092 (<1)	
Private	103805 (81)	403061 (78)	44565 (13)	
None	5265 (4)	13963 (3)	1457 (<1)	
Income (US $)				
<38,000	17817 (14)	74639 (14)	52688 (16)	<.0001
38,000-47,999	25131 (20)	107224 (21)	78190 (23)	
48,000-62,999	34099 (27)	139865 (27)	93572 (28)	
63,000 +	50739 (40)	195886 (38)	110531 (33)	
Race				
Black	18933 (15)	60820 (12)	29177 (9)	<.0001
White	99832 (78)	432056 (83)	296153 (88)	
Other	9021 (7)	24738 (5)	9651 (3)	
Clinical				
Clinical stage (AJCC)				
I	41433 (32)	224219 (43)	162074 (48)	<.0001
II	41488 (32)	130998 (25)	76745 (23)	
III	44865 (35)	162397 (31)	96162 (29)	
Charlson/Deyo score				
0	120259 (94)	455787 (88)	265192 (79)	<.0001
1	6818 (5)	52573 (10)	55730 (17)	
2	709 (1)	9254 (2)	14059 (4)	
Differentiation (Grade)				
Well (I)	15599 (12)	108904 (21)	85473 (26)	<.0001
Moderately (II)	51151 (40)	234551 (45)	164743 (49)	
Poorly (III)	60257 (47)	171836 (33)	83680 (25)	
Non (IV)	779 (1)	2323 (<1)	1085 (<1)	
Biologic subtype				
HR^+/HER_2^-	52857 (41)	251859 (49)	176543 (53)	<.0001
HR^+/HER_2^+	18547 (15)	75850 (15)	47845 (14)	
HR^-/HER_2^+	24493 (19)	89104 (17)	52700 (16)	
HR^-/HER_2^-	31889 (25)	100801 (19)	57893 (17)	
Histology (ICD-O-3)				
Infiltrating duct carcinoma, NOS (8500/3)	104416 (82)	395108 (76)	239639 (72)	<.0001
Infiltrating/invasive lobular carcinoma (8520/3, 8522/3)	11443 (9)	73191 (14)	54353 (16)	
Infiltrating duct mixed (8523/3)	3782 (3)	16010 (3)	12236 (4)	
Other	8145 (6)	33305 (6)	28753 (8)	
Lymph node invasion	37148 (29)	112473 (22)	55017 (16)	<.0001
Margins (positive)	6490 (5)	22287 (4)	16612 (5)	<.0001
Tumour size (cm)				
≤2	66117 (52)	326887 (63)	223751 (67)	<.0001
>2-5	50259 (39)	159876 (31)	94927 (28)	
>5	11410 (9)	30851 (6)	16303 (5)	

[§]Clinical stage I-III, pathologically confirmed, primary breast cancer. [†]Chi-square (categorical) or Kruskal-Wallis H (continuous) test. AJCC: American Joint Committee on Cancer. cm=centimetre. HER=Human epidermal growth factor receptor. HR=Hormone receptor. ICD-O-3: International Classification of Diseases for Oncology, Third Edition. IQR=Interquartile range. NOS: not otherwise specified. US=United States.

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Table 2: Treatment variables by age (N=980,381, 2004-2013)[§]

Treatment	Age (Years)			P value
	<45 n (%) Median [IQR]	45-65 n (%) Median [IQR]	>65 n (%) Median [IQR]	
Chemotherapy	98703 (77)	292645 (57)	80891 (24)	<.0001
Endocrine therapy	78852 (62)	350597 (68)	213620 (64)	<.0001
Immunotherapy (only for HER_2^+)	2469 (6)	6839 (4)	2235 (2)	<.0001
Neoadjuvant therapy				
No	120641 (94)	500969 (97)	330098 (99)	<.0001
Yes	7145 (6)	16645 (3)	4883 (1)	
Response				<.0001
NR	1541 (22)	4146 (25)	1602 (33)	
pCR	1412 (20)	2736 (16)	557 (11)	
RD	4192 (59)	9763 (59)	2724 (56)	
Radiotherapy				
No	53048 (42)	175492 (34)	158469 (47)	<.0001
Yes	74738 (58)	342122 (66)	176512 (53)	
Type				<.0001
Photon	74027 (58)	328099 (63)	164955 (49)	
Proton	12 (<1)	48 (<1)	36 (<1)	
Other	55747 (42)	189467 (37)	169990 (51)	
Dose (cGy)	5001 [360]	5000 [440]	5000 [540]	<.0001
4000-4500	11341 (15)	75801 (22)	51860 (29)	<.0001
>4500-5000	26024 (35)	116998 (34)	55799 (32)	
>5000-5500	36053 (48)	143804 (42)	66139 (37)	
>5500-6000	1320 (2)	5519 (2)	2714 (2)	
Lymph nodes treated	25353 (34)	76095 (22)	30014 (17)	<.0001
Surgery				
Lumpectomy/Partial	55062 (43)	309460 (60)	213094 (64)	<.0001
Mastectomy	72724 (57)	208154 (40)	121887 (36)	
Contralateral	31007 (43)	57412 (28)	11020 (9)	<.0001

[§]Clinical stage I-III, pathologically confirmed, primary breast cancer. [†]Chi-square (categorical) or Kruskal-Wallis H (continuous) test. cGy=centigray NR=No response. HER=Human epidermal growth factor receptor. HR=Hormone receptor. IBC=Inflammatory breast cancer. IQR=Interquartile range. pCR=pathologic Complete response. RD=Residual disease.

Table 3. Percentage of patients receiving radiation therapy by age group, comorbidity level and hormone receptor status (N=980,381, 2004-2013)[§]

Biologic Subtype	Radiation	Charlson/Deyo Comorbidity Index (CCI)														P[†‡] Trend by Age
		Age<45 Years					Age 45-65 Years					Age >65 Years				
		0 n (%)	I n (%)	II n (%)	P[†] Trend	aOR[†‡] (95%CI) II vs 0	0 n (%)	I n (%)	II n (%)	P[†] Trend	aOR[†‡] (95%CI) II vs 0	0 n (%)	I n (%)	II n (%)	P[†] Trend	aOR[†‡] (95%CI) II vs 0	
All	N	49692 (41)	3054 (45)	302 (43)	.020	1.1 (.91-1.3)	151604 (33)	19849 (38)	4039 (44)	<.0001	1.3 (1.26-1.41)	120090 (45)	29713 (53)	8666 (62)	<.0001	1.6 (1.5-1.7)	<.0001
	Y	70567 (59)	3764 (55)	407 (57)			304183 (67)	32724 (62)	5215 (56)			145102 (55)	26017 (47)	5393 (38)			
HR^+ HER_2^-	N	19793 (40)	1327 (44)	140 (42)	.0029	1.2 (.92-1.6)	67842 (31)	9350 (35)	1899 (40)	<.0001	1.4 (1.2-1.5)	59307 (43)	15160 (50)	4498 (59)	<.0001	1.6 (1.5-1.7)	<.0001
	Y	29698 (60)	1705 (56)	194 (58)			152403 (69)	17519 (65)	2846 (60)			79394 (57)	15041 (50)	3143 (41)			
HR^+ HER_2+	N	7066 (41)	448 (43)	48 (44)	.57	1.1 (.70-1.8)	22001 (33)	2919 (37)	580 (43)	<.0001	1.4 (1.2-1.7)	16677 (44)	4240 (53)	1248 (62)	<.0001	1.8 (1.6-2.0)	<.0001
	Y	10329 (59)	594 (57)	62 (56)			44690 (67)	4903 (63)	757 (57)			21131 (56)	3778 (47)	771 (38)			
HR^- HER_2^+	N	9595 (41)	521 (45)	45 (46)	.03	1.4 (.87-2.4)	28064 (35)	3363 (42)	722 (50)	<.0001	1.4 (1.2-1.6)	20581 (49)	4777 (58)	1371 (67)	<.0001	1.9 (1.5-1.9)	<.0001
	Y	13648 (59)	631 (55)	53 (54)			51622 (65)	4621 (58)	712 (50)			21861 (52)	3439 (42)	671 (33)			
HR^- HER_2^-	N	13238 (44)	758 (48)	69 (41)	.71	.80 (.55-1.2)	33697 (38)	4217 (43)	838 (48)	.0011	1.3 (1.1-1.4)	23525 (51)	5536 (60)	1549 (66)	<.0001	1.3 (1.2-1.5)	<.0001
	Y	16892 (56)	834 (52)	98 (59)			55468 (62)	5681 (57)	900 (52)			22716 (49)	3759 (40)	808 (34)			

[§]Clinical stage I-III, pathologically confirmed, primary breast cancer. [†]Adjusted for chemotherapy, hormone/endocrine therapy, immunotherapy, lymph node invasion, margins, race, surgery type, tumour size. [‡]Likelihood ratio trend test. aOR=adjusted odds ratio. HER2=human epidermal growth factor receptor 2. HR=hormone receptor. N=no. Y=yes.

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Table 4. Overall survival and hazard ratios by hormone receptor status for women >65 years, (N=334,981, 2004-2013)[§]

Biologic Subtype	Radiation	Overall Survival (%)				Hazard Ratio (95% CI)	
		Years				Univariable	Multivariable[†]
		2	5	8	10		
All	N	94	83	73	67	.45 (.441-.454)	.53 (.52-.54)
	Y	98	91	85	80		
HR^+ HER_2^-	N	95	85	76	71	.41 (.40-.42)	.49 (.48-.51)
	Y	98	93	87	84		
HR^+ HER_2+	N	94	85	77	74	.40 (.39-.42)	.47 (.45-.49)
	Y	98	93	88	84		
HR^- HER_2^+	N	93	81	72	67	.47 (.46-.49)	.54 (.52-.56)
	Y	98	91	84	80		
HR^- HER_2^-	N	92	81	70	63	.54 (.52-.55)	.62 (.60-.64)
	Y	96	89	81	75		

[§]Clinical stage I-III, pathologically confirmed, primary breast cancer. [†]Adjusted for Carlson/Deyo Comorbidity Index, chemotherapy, hormone/endocrine therapy, immunotherapy, lymph node invasion, margins, race, surgery type, tumour size. HER2=human epidermal growth factor receptor 2. HR=hormone receptor. N=no. Y=yes.