

## Background

U.S. military beneficiaries differ from the U.S. general population with regards to access to health care as care is provided at no or much lower cost in the military health system. Other differences also exist. Many of these differences are known factors affecting invasive breast cancer outcomes. Thus it is desirable to conduct a comparative analysis of breast cancer outcomes between these two populations to find out whether there is any outcome difference, and if yes what the contributing factors are.

## Methods

This study drew from a pool of invasive breast cancer patients enrolled from the Clinical Breast Care Project at the Walter Reed National Military Medical Center (CBCP-WR). Breast cancer Research Data 1973-2010 of the Surveillance, Epidemiology, and End Results (SEER) Program were downloaded from <http://seer.cancer.gov/data/>.

We restricted our analysis to patients who were diagnosed between 2001 and 2010. We compared overall survival (OS), disease-specific survival (DSS), and 5-year OS and DSS rates in breast cancers between 418 patients from CBCP-WR and 1,000 sets of 1,672 matched patients from SEER. Each CBCP-WR patient was randomly matched to 4 SEER patients on 3 demographic variables (age at diagnosis in 5-year groups, diagnosis year, and race). Cox proportional hazards regression model was used to calculate hazard ratio (HR) after adjusting for the 3 demographic variables (age, diagnosis year, and race). Four additional tumor characteristics variables (ER, PR, AJCC stage, and grade) were added to and adjusted in the model to assess their contribution to the survival difference. Kaplan-Meier estimate and Wald test were used to generate and compare survival curves, respectively. To compare 5-year survival rates, *P*-values were calculated assuming normal distribution of the rates and using the difference of the two survival rates and their standard errors.

## Results

### Patient characteristics

**Table 1** shows the characteristics of CBCP-WR patients and their matched SEER patients. After matching for the 3 demographic variables, CBCP-WR and SEER patients still significantly differed from each other in many tumor characteristics, including ER, PR, stage, and grade. Therefore in the following comparative analyses, the 3 demographic variables were first adjusted in the survival model; then 7 variables were adjusted after adding these 4 tumor characteristics variables to the model.

**Table 1.** Characteristics of the CBCP-WR and SEER cohorts

Variable	CBCP-WR patients (n=418) No. (%)	Matched SEER patients (n=1,672)	
		Mean <sup>o</sup> (%)	Mean <i>P</i> -value <sup>o</sup>
Age at diagnosis, mean (years)(STD)	59.16(13.07)	58.67(13.07)	0.4707
Race			1.0000
White	302(72.25%)	1208(72.25%)	
Black	93(22.25%)	372(22.25%)	
Asian/Pacific islander	21(5.02%)	84(5.02%)	
American Indian/Alaska native	2(0.48%)	8(0.48%)	
Unknown	0(0%)	0(0%)	
ER			0.0001
Positive	305(72.97%)	1160(69.38%)	
Negative	99(23.68%)	352(21.05%)	
N/A	14(3.35%)	160(9.57%)	
PR			<0.0001
Positive	236(56.46%)	940(58.13%)	
Negative	167(39.95%)	514(30.74%)	
N/A	15(3.59%)	186(11.12%)	
AJCC stage			<0.0001
I	211(50.48%)	721(43.12%)	
II	147(35.17%)	568(33.97%)	
III	46(11.0%)	221(13.22%)	
IV	14(3.35%)	77(4.61%)	
N/A	0(0%)	85(5.08%)	
Grade			<0.0001
I	146(34.93%)	304(18.18%)	
II	145(34.69%)	629(37.62%)	
III	123(29.43%)	602(36.0%)	
Unknown	4(0.96%)	137(8.19%)	
Pre-menopausal	67(16.03%)	N/A	N/A
Post-menopausal	351(83.97%)		
Her2			
Positive	35(8.37%)	N/A	N/A
Negative	363(86.84%)		
N/A	20(4.78%)		
Ki67			
Positive	154(36.84%)	N/A	N/A
Negative	239(57.18%)		
N/A	25(5.98%)		
Median follow-up time (months)	54	51.63	0.6090

<sup>o</sup> Mean value of 1000 comparisons. *P*-value <0.05 is in red.

**Table 2.** Comparisons of DSS between CBCP-WR and matched SEER populations

Population	Patient count		Adjusted for 3 variables			Adjusted for 7 variables		
	CBCP-WR	SEER	HR <sup>o</sup>	<i>P</i> -value <sup>o</sup>	Counts ( <i>P</i> <0.05) <sup>#</sup>	HR <sup>o</sup>	<i>P</i> -value <sup>o</sup>	Counts ( <i>P</i> <0.05) <sup>#</sup>
All	418	1672	0.558	0.007	991	0.587	0.025	872
Age <50 years	130	520	1.021	0.713	0	0.747	0.381	86
Age ≥50 years	288	1152	0.388	0.001	1000	0.463	0.020	896
Black	93	372	0.572	0.124	244	0.432	0.040	793
White	302	1208	0.592	0.048	682	0.694	0.231	101
ER-	99	352	0.719	0.287	29	0.567	0.123	399
ER+	305	1160	0.494	0.030	836	0.674	0.265	89
Stages I & II	358	1289	0.578	0.127	220	0.623	0.205	99
Stages III & IV	60	298	0.686	0.184	129	0.555	0.066	616

**Table 3.** Comparisons of 5-year DSS rates between CBCP-WR and matched SEER populations

Population	Adjusted for 3 variables				Adjusted for 7 variables			
	CBCP-WR	SEER <sup>o</sup>	<i>P</i> -value <sup>o</sup>	Counts ( <i>P</i> <0.05) <sup>#</sup>	CBCP-WR	SEER <sup>o</sup>	<i>P</i> -value <sup>o</sup>	Counts ( <i>P</i> <0.05) <sup>#</sup>
All	0.934	0.885	0.004	997	0.923	0.886	0.021	893
Age <50 years	0.936	0.936	0.730	0	0.935	0.919	0.402	67
Age ≥50 years	0.956	0.891	0.0001	1000	0.940	0.893	0.012	953
Black	0.894	0.821	0.098	407	0.894	0.818	0.046	763
White	0.943	0.905	0.036	795	0.930	0.907	0.202	223
ER-	0.850	0.798	0.279	90	0.851	0.781	0.100	527
ER+	0.961	0.923	0.017	924	0.947	0.928	0.257	152
Stages I & II	0.970	0.949	0.097	442	0.968	0.950	0.166	256
Stages III & IV	0.722	0.625	0.178	166	0.731	0.614	0.064	644

<sup>o</sup> Mean value of 1000 comparisons. Mean *P*-value <0.05 is in red.

<sup>#</sup> Counts significantly greater than the expected 50 occurrences (*P*-value <0.05 by exact binomial tests) are in blue.

**Table 4.** 5-Year DSS rate differences (CBCP-WR – SEER)

Population	Adj3 <sup>o</sup>		Adj7 <sup>o</sup>		(Adj3 - Adj7) / Adj3 <sup>#</sup>		<i>P</i> -value
	Median	Median	Median	Median	95% CI		
All	0.0488	0.0372	0.2386	0.2310	(0.2310, 0.2461)	<0.0001	
Age <50 years	-8.67E-05	0.0155	0.2459	(-0.0622, 0.5550)		0.1147	
Age ≥50 years	0.0646	0.0467	0.2794	(0.2728, 0.2859)		<0.0001	
Black	0.0725	0.0764	-0.0749	(-0.0926, -0.0576)		<0.0001	
White	0.0379	0.0231	0.3933	(0.3817, 0.4050)		<0.0001	
ER-	0.0523	0.0698	-0.3757	(-0.4075, -0.3453)		<0.0001	
ER+	0.0382	0.0193	0.4991	(0.4879, 0.5104)		<0.0001	
Stages I & II	0.0210	0.0181	0.1449	(0.1363, 0.1535)		<0.0001	
Stages III & IV	0.0962	0.1168	-0.2424	(-0.2656, -0.2198)		<0.0001	

<sup>o</sup> Adj3, adjusted for 3 variables; Adj7, adjusted for 7 variables.

<sup>#</sup> Pair-wise comparison calculating the relative contribution of the additional tumor variables to the DSS rate difference between CBCP-WR and SEER.

### Survival comparisons

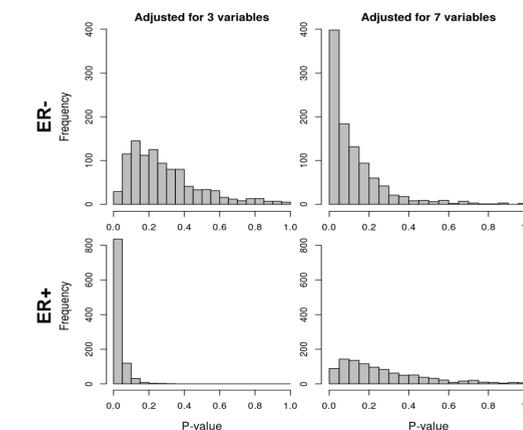
- In general, CBCP-WR patients showed statistically significant survival advantage (HR<1) over SEER patients, which was supported by the low average *P*-value and the significantly higher number of significant comparisons than expected (**Table 2**).
- CBCP-WR patients also had significantly higher 5-year DSS rates than SEER patients (**Table 3**). For example, for the whole population the absolute differences in 5-year DSS rates were 4.9% (93.4% vs. 88.5%) and 3.7% (92.3% vs. 88.6%) after adjusting for 3 and 7 variables, respectively.
- The adjustment of the additional tumor characteristics variables contributed differently to the survival differences in different subpopulations (**Tables 2, 3 & 4**). Such adjustment yielded more significant survival advantage in CBCP-WR for younger (<50 years), black, ER-, and stages III and IV patients; whereas it reduced the survival superiority in CBCP-WR for the whole population, as well as older (≥50 years), white, ER+, and stages I and II patients. As an example, **Figure 1** shows the enrichment and reduction of significant comparisons in ER- and ER+ patients, respectively, after such adjustments in the survival model.
- Similar results were obtained in OS comparisons but not showed here.

## Conclusions

- CBCP-WR patients demonstrated significantly better DSS, OS (not shown), and 5-year survival rates compared to civilian patients in SEER.
- Tumor characteristics contributed in opposite directions to the survival difference in patients with more- and less-aggressive phenotypes.
- These results warrant further analyses of other contributing factors, such as health care access, treatments, additional pathologic characteristics, and socioeconomic statuses, to this outcome disparity.

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**Figure 1.** Example histograms of *P*-values in Table 2

## Survival comparative analysis of patients with invasive breast cancer treated by a military medical center and matched patients of the US general population

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### BACKGROUND

U.S. military beneficiaries differ from the U.S. general population with regards to access to health care as care is provided at no or much lower cost in the military health system. Other differences also exist. Many of these differences are known factors affecting invasive breast cancer outcomes. Thus it is desirable to conduct a comparative analysis of breast cancer patient outcomes between these two populations to find out whether there is any outcome difference, and if yes what the contributing factors are.

### METHODS

We compared overall survival (OS), disease-specific survival (DSS), and 5-year OS and DSS rates in breast cancers between 399 patients from the Clinical Breast Care Project at the Walter Reed National Military Medical Center (CBCP-WR) and 1,000 sets of 1596 matched patients from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. All patients were diagnosed between 2001 and 2010. Each CBCP-WR patient was randomly matched to four SEER patients on six demographic and clinicopathologic variables (age at diagnosis in 5-year groups, race, diagnosis year, estrogen receptor (ER), progesterone receptor, and AJCC stage).

### RESULTS

The CBCP-WR cohort had better survival than the SEER population. At the whole cohort level, the mean hazard ratios (HRs) from 1,000 matched comparisons for OS and DSS were 0.774 and 0.708, with mean log-rank *P*-values of 0.124 and 0.125. The numbers of 175 and 141 comparisons showing a log-rank *P*-value <0.05 out of the 1,000 tests were significantly higher than what would be expected from a random distribution of these *P*-values (*P*<0.00001, exact binomial test). By stratifying the cohorts we identified that this survival disparity was mainly contributed by patients with a diagnosis age  $\geq 50$  years (for DSS, mean HR=0.550, mean *P*=0.049, and 642 of 1,000 tests showed a *P*<0.05; for OS, mean HR=0.713, mean *P*=0.081, and 377 of 1,000 tests showed a *P*<0.05), but not by patients with a diagnosis age <50 years. The absolute differences in 5-year DSS rates were 4.4% (94.6% in CBCP-WR vs. 90.2% in SEER; mean *P*=0.010) for all matched patients and 4.8% (95.2% vs. 90.4%; mean *P*=0.015) for patients diagnosed at an age  $\geq 50$  years. Again there was no significant difference for patients diagnosed at an age <50 years. When stratified by race, ER, stage or grade, most of the patient subpopulations showed favorable 5-year OS and DSS rates in the CBCP-WR cohorts.

### CONCLUSION

Overall, these results suggested that breast cancer patients, especially older patients seen in the CBCP-WR, carried more favorable outcomes than those from the general population. The findings warrant further analyses of the contributing factors, such as health care access, treatments, population characteristics, additional pathologic characteristics, and socioeconomic statuses, to this outcome disparity.

The views expressed in this article are those of the author and do not reflect the official policy of the Department of Defense, or U.S. Government.