

## BACKGROUND

The relationship between age at diagnosis and mortality from breast cancer remains unclear. Prior studies categorized patients into biologically arbitrary groups such as decades which risks loss of granularity and statistical information.

## OBJECTIVE

To examine the relationship between age at diagnosis and risk of breast cancer-specific mortality (BC-SM) with rigorous statistical methodology.

## METHODS

Retrospective population analysis of adult women with invasive breast cancer in the SEER database from 2010-2015. Multivariable Cox cause-specific hazards model was used to evaluate the association of age at diagnosis with risk of BC-SM. Functional relationship of age was assessed using residual diagnostics (cumulative sums of Martingale residuals and the supremum test). Analyses were performed using SAS v9.4 (Cary, NC). A p-value of <0.05 was considered statistically significant.

## RESULTS

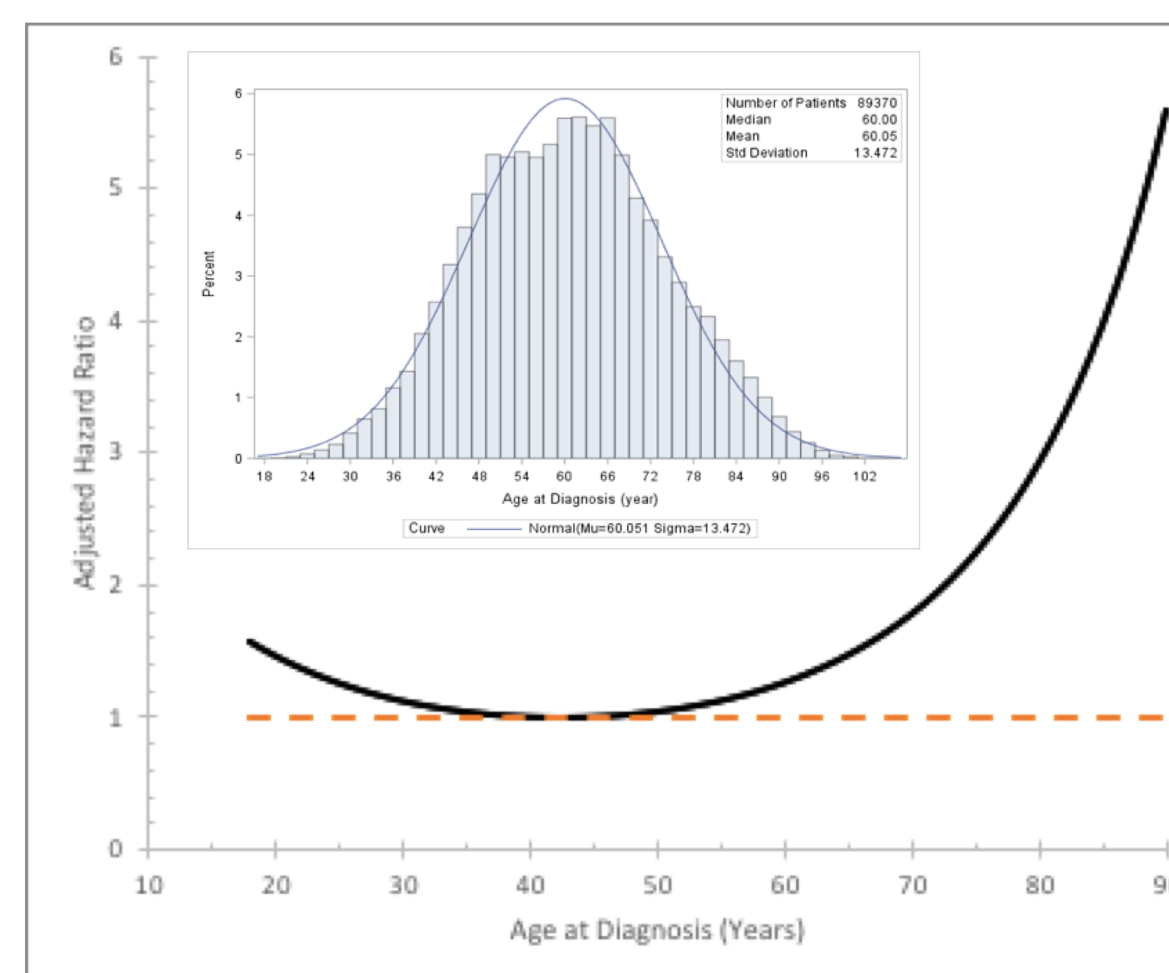
Table 1. Demographic and clinical characteristics of the total population of 89,370 women.

Variable	Statistic or Category	Value/Frequency	Percent
Age at diagnosis (years)	Mean (standard deviation)	60.1 (13.5)	
	Median (interquartile range)	60 (50-69)	
Race	White	68704	76.9
	Black	9888	11.1
	Other/Unknown	10778	12.1
Grade	I	21599	24.2
	II	38676	43.3
	III	28926	32.4
	IV	169	0.2
ER status	Negative	14838	16.6
	Positive	73762	82.5
	Unknown	770	0.9
PR status	Negative	24085	27.0
	Positive	64415	72.1
	Unknown	870	1.0
HER2 status	Negative	72489	81.1
	Positive	13181	14.8
	Unknown	3700	4.1
Subtype	HR+ / HER2+	9216	10.3
	HR- / HER2+	3945	4.4
	HR+ / HER2-	62833	70.3
	Triple Negative	9580	10.7
T stage	Unknown	3796	4.3
	T1	52760	59.0
	T2	27113	30.3
	T3	5674	6.4
N stage	T4	3419	3.8
	Unknown	404	0.5
	N0	60561	67.8
	N1	21179	23.7
Overall stage	N2	4593	5.1
	N3	2727	3.1
	Unknown	310	0.4
	I	45708	51.1
Year of diagnosis	II	30083	33.7
	III	9602	10.7
	IV	3977	4.5

Table 2. Final Cox's cause-specific hazards models for BC-SM.

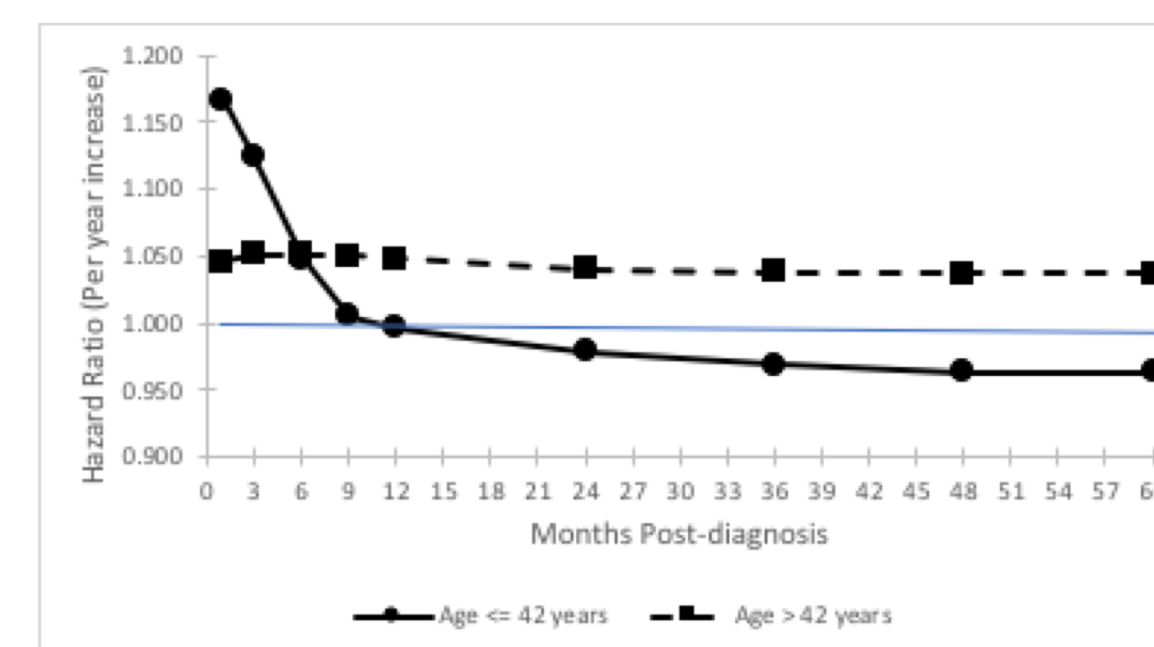
Parameter	Comparison	P-value	Hazard Ratio	95% Confidence Interval
Age	Per year increase	<0.0001	0.94	0.93-0.95
	Per unit increase	<0.0001	1.00	1.00-1.00
Grade	II versus I	<0.0001	1.51	1.33-1.73
	III versus I	<0.0001	2.61	2.29-2.99
	IV versus I	<0.0001	3.74	2.52-5.53
	Stage	II versus I	<0.0001	3.94
Stage	III versus I	<0.0001	15.27	13.52-17.25
	IV versus I	<0.0001	81.67	72.52-91.97
	Race	Black versus White	<0.0001	1.26
Race	Other versus White	0.0001	0.81	0.73-0.90
	ER status	Negative versus Positive	<0.0001	1.57
Unknown versus Positive		0.1547	1.60	0.84-3.07
PR status	Negative versus Positive	<0.0001	1.77	1.63-1.92
	Unknown versus Positive	0.0633	1.80	0.97-3.35
HER2 status	Negative versus Positive	<0.0001	1.74	1.61-1.89
	Unknown versus Positive	<0.0001	1.78	1.52-2.08
Year of diagnosis	Per year increase	0.1932	0.99	0.96-1.01

Figure 1. The functional relationship between age at diagnosis and breast cancer-specific mortality is quadratic.



- During a median follow-up of 33 months, 7,047 women (7.9%) died, of which 4,523 (5.1% of the total population) died of breast cancer.
- The unadjusted cumulative incidence of BC-SM at five years was 8.6% (95% CI 8.3-8.8%).

Figure 2. Risk of BC-SM over time stratified by age.



## DISCUSSION

Relative to women diagnosed with breast cancer in their early 40s, younger women and, to a greater magnitude, older women have disproportionately high rates of BC-SM. Further studies to elucidate the biological underpinnings of this observation are needed.

This is the largest study to demonstrate a quadratic relationship between age at diagnosis and risk of BC-SM, and the first to report a vertex corresponding to lowest risk at age 42.

## CONCLUSIONS

The relationship between age at diagnosis and adjusted risk of BC-SM is complex. With the growing appreciation for breast cancer as a heterogeneous disease, it is essential to address age accurately as a prognostic risk factor in predictive models.

## REFERENCES

1. Rosenberg et al. *Breast Cancer Res Treat.* 2005;89(1):47-54.
2. Tai et al. *BMC Cancer.* 2005;5:130.
3. Brandt et al. *World J Surg Oncol.* 2015;13:33.