Accelerated telomere shortening in breast cancer survivors with a history of depression: A two-year longitudinal cohort study

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Introduction

- Cancer treatments are thought to accelerated biological aging, although this trajectory is highly variable.
- One risk factor for vulnerability in biological aging is depression history, with a nearly four-fold greater prevalence in breast cancer survivors
- Depression history in breast cancer survivors is associated with increased risk of morbidity and mortality.
- We hypothesized that a lifetime history of depression and cumulative lifetime number of depression episodes would exhibit an accelerated rate of biological aging as indexed by shortening of telomere length in a prospective cohort of breast cancer survivors carefully screened for lifetime depression history.

Methods

The Sleep Well and Thrive (STRIVE) Study is a population based, multiethnic prospective cohort study of non-depressed older breast cancer survivors enrolled between August 2013 and March 2015 who are members of Kaiser Permanente Southern California (KPSC), the largest integrated health care system in the state serving over 4.7 million individuals. Women were identified from the health plan's SEER (Surveillance Endpoints & End Results)-affiliated cancer registry.

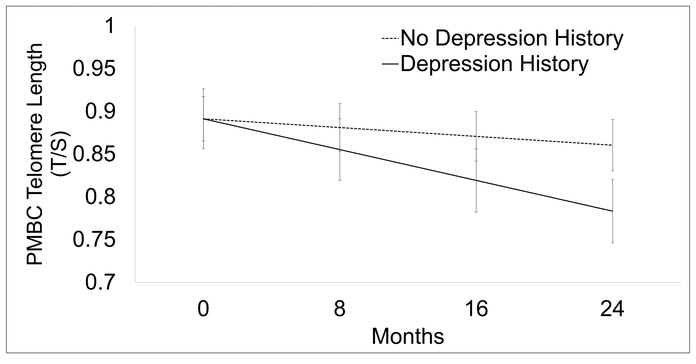
STRIVE study was designed to assess depression risk in breast cancer survivors who did not have a concurrent depressive episode and assess whether depression history affected biologic aging.

The inclusion criteria included women 55 to 85 years of age who had AJCC TNM Stages 0-II breast cancer diagnosed, were at least two years post-diagnosis, with no cancer recurrence, lived in Los Angeles County, no current major depressive disorder or major psychiatric disorder. Women were assessed for depression history by the structured clinical interview for diagnosis (SCID) using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria.

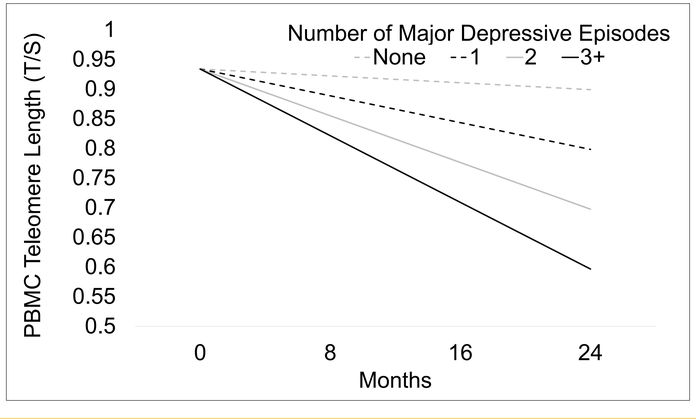
Participants (N=204) provided blood specimens at baseline and every 8 months over 24 months to measure peripheral blood mononuclear cell (PBMC) telomere length using standard qPCR method in the Aging Biology and Behavior Laboratory at UCLA. Reliability within and across plates was high with ICC > .98).

Results

Mixed linear models examined depression history and number of depression episodes on telomere length change, adjusting for age, race, education, income, years since dx, BMI, comorbidities, radiation, chemo, hormone, stage of cancer. Depression history predicted shortening of PBMC telomere length over 24 months (Beta[SE]=-.006[.002], p=.001).



A greater number of depressive episodes over the lifetime was associated with accelerated attrition of PBMC telomere length over 24 months (Beta[SE]=-.004[.001], p=.001).



Conclusion

- In breast cancer survivors without current depression, telomere shortening over 24 months was greatest in those with a lifetime depression history, particularly those with the greatest number of episodes of major depressive disorder over their lifetime.
- Depression history and its cumulative burden may contribute to accelerated biological aging, with implications for increased risk of morbidity and mortality in breast cancer survivors.

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Table 1. Descriptive statistics of STRIVE cohort by Depression History status.

	Distribution by Lifetime History of Depression Status				
	Yes		No		
Demographic/Clinical Variables	N	% Mean (SD)	N	% Mean (SD)	P-value
Age (Years)	73	68.6 (5.6)	133	71.0 (6.2)	.007
White	58	80%	94	71%	0.36
Black or African-American	12	16%	29	22%	
Asian	3	4%	10	8%	
BMI <30	56	78%	94	71%	0.31
BMI 30+	16	22%	38	29%	
Education					
College or above	45	69%	79	64%	0.71
Some college	11	17%	27	22%	
High School or below	9	14%	17	14%	
Unknown/Missing					
Years since BC diagnosis					
Number of years	73	5.4 (3.3)	34	6.2 (4.0)	
Radiation					
No (with and w/o Chemo)	37	51%	61	46%	0.064
Yes (without Chemo)	21	29%	57	43%	
Yes (with Chemo)	15	21%	15	11%	
Hormonal					
No	43	59%	64	48%	0.14
Yes	30	41%	69	52%	
Chemotherapy					
No	50	69%	95	71%	0.66
Yes	23	31%	38	29%	
Initial stage at BC diagnosis					
Stage 0 (DCIS)	15	21%	24	18%	0.64
Stage I	36	50%	61	46%	
Stage II	21	29%	47	36%	
Charlson Co-Morbidity Index					
0	19	26%	39	29%	0.68
1-2	32	44%	50	38%	
3+	22	30%	44	33%	

Table 2. Mixed linear model testing role of depression history in predicting 24 months PBMC telomere length change

	Model 0	**Model 1** Age, Years since dx, Race, Education, Income, Baseline TL	**Model 2** Model 1 covariates, BMI, Comorbidities	**Model 3** Model 1 & 2, Radiation, Chemotherapy, Hormonal Therapy, Stage of Breast Cancer
Covariates		Beta (SE), P Value	Beta (SE), P Value	Beta (SE), P Value
Baseline telomere length	.685 (.033), <.001	.682 (.033), <.001	.683 (.033), <.001	.683 (.033), <.001
Age		-.004 (.002), .024	-.004 (.002), .029	-.004 (.002), .039
Years since diagnosis		.009 (.002), .002	.009 (.003), .004	.008 (.003), .012
Race, White/Non-White		-.049 (.023), .037	-.049 (.023), .037	-.050 (.024), .037
Education		.001 (.004), .78	.001 (.004), .78	.0004 (.004), .93
Income ($K)		-.0002 (.0002), .39	-.0002 (.0002), .40	-.0002 (.0002), .40
BMI			-.0003 (.0025), .92	.0001 (.003), .99
Comorbidities			-.001 (.005), .85	-.002 (.006), .75
Radiation				-.021 (.021), .33
Chemotherapy				-.001 (.027), .98
Hormonal Therapy				-.005 (.023), .83
Stage of BC				.007 (.017), .70
Predictor				
Time	-.007 (.001), <.001	-.007 (.001), <.001	-.007 (.001), <.001	-.007 (.001), <.001
Lifetime History of Depression	.055 (.028), .052	.055 (0.028), .053	.055 (.029), .056	.053 (.029), .068
Time X Lifetime History of Depression	-.006 (.002), .001	-.006 (.002), .001	-.006 (.002), .001	-.006 (.002), .001
Predictor				
Time	-.002 (.001), .022	-.002 (.001), .029	-.002 (.001), .029	-.001 (.001), .18
Number of MDD Episodes	.023 (.013), .073	.029 (.014), .035	.029 (.014), .029	.039 (.020), .048
Time X Number of MDD Episodes	-.002 (.001), .008	-.002 (.001), .009	-.002 (.001), 009	-.004 (.001), .001

Table 3. Mixed linear model testing role of insomnia and depressive symptoms in predicting 24 months PBMC telomere length

	Model 2 Controlling for Model 1 and Insomnia or Depressive Symptoms	**Model 3** Cumulative Insomnia or Cumulative Depressive Symptoms	**Model 4** Interaction of Insomnia or Depressive Symptoms
Covariates	Beta (SE), P Value	Beta (SE), P Value	Beta (SE), P Value
Age	-.008 (.004), .033	-.008 (.004), .047	-.008 (.004), .046
Years since diagnosis	.003 (.006), .63	.003 (.006), .62	.003 (.006), .53
Baseline telomere length	.413 (.069), <.001	.413 (.069), <.001	.413 (.069), <.001
Predictors			
Lifetime History of Depression	-.109 (.048) .024	-.096 (.047) .043	-.144 (.060), .017
Baseline Insomnia, ISI 8+	.055 (.048), .26		
Baseline Depressive Symptoms, PHQ8 >8	-.072 (.085), .40		
Cumulative Insomnia, ISI 8+		.047 (.069), .50	
Cumulative Depressive Symptoms, PHQ8		-.166 (.125), .19	
Moderation			
Depression Hx X BI Insomnia			.127 (.093), .18
Depression Hx X BI Depressive symptoms			.076 (.136), .58
Depression Hx X Cum. Insomnia			.021 (.135), .88
Depression Hx X Cum. Depressive symptoms			-.354 (.223), .12