

## Social Relationships, Inflammation Markers, and Breast Cancer Incidence in the Women's Health Initiative

### The Breast

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Supplemental Table 1. Associations between social relationship characteristics and dichotomous inflammation markers by cohort

Inflammation Marker Outcome	Social Relationship Characteristic	Observational Study			Clinical Trial		
		N	OR	95% CI	N	OR	95% CI
C-Reactive Protein (mg/L)	Social Network Size <sup>a</sup>	4,183	0.91	0.85, 0.98	8,108	0.99	0.94, 1.04
	Social Support <sup>a</sup>	4,085	1.00	0.98, 1.02	8,155	0.99	0.98, 1.01
	Social Strain <sup>a</sup>	4,047	1.07	1.02, 1.12	8,088	1.02	0.98, 1.05
	Social Support <sup>b</sup> Social Strain <sup>b</sup>	3,914	1.01	0.99, 1.03	7,888	0.99	0.98, 1.01
White Blood Cell Count (thousands of cells/uL)	Social Network Size <sup>a</sup>	73,231	0.79	0.75, 0.84	43,213	0.76	0.71, 0.82
	Social Support <sup>a</sup>	72,295	0.97	0.95, 0.99	45,585	0.98	0.96, 1.00
	Social Strain <sup>a</sup>	72,608	1.05	1.01, 1.09	45,607	1.08	1.03, 1.14
	Social Support <sup>b</sup> Social Strain <sup>b</sup>	71,114	0.97	0.96, 0.99	44,812	0.99	0.97, 1.01
			1.03	0.99, 1.07		1.07	1.02, 1.13

Dependent variable was C-Reactive Protein ( $\geq 3$  mg/L vs  $< 3$  mg/L) or White Blood Cell Count ( $\geq 10,000$  cells/uL vs  $< 10,000$  cells/uL). Social relationship variable was categorical Social Network Size (0-3), Social Support (0-9), and/or Social Strain (0-4). All models adjusted for age, race/ethnicity, education, age at menarche, age at menopause, parity, amount of time breastfeeding, and hormone therapy use. All variables were measured at baseline.

<sup>a</sup>Only social relationship variable in model.

<sup>b</sup>Model included both Social Support and Social Strain.

**Supplemental Table 2. Associations between social relationship characteristic and continuous inflammation markers by cohort**

Inflammation Marker Outcome	Social Relationship Characteristic	Observational Study				Clinical Trial			
		N	Beta	SE	P-value	N	Beta	SE	P-value
<b>C-Reactive Protein (mg/L)</b>	<b>Social Network Size<sup>a</sup></b>	4,183	-0.29	0.14	0.04	8,108	-0.19	0.08	0.03
	<b>Social Support<sup>a</sup></b>	4,085	0.02	0.04	0.6	8,155	-0.004	0.03	0.9
	<b>Social Strain<sup>a</sup></b>	4,047	0.34	0.09	<0.0001	8,088	0.18	0.06	0.002
	<b>Social Support<sup>b</sup> Social Strain<sup>b</sup></b>	3,914	0.07 0.40	0.04 0.10	0.1 <0.0001	7,888	0.01 0.18	0.03 0.06	0.6 0.004
<b>White Blood Cell Count (thousands of cells/uL)</b>	<b>Social Network Size<sup>a</sup></b>	73,231	-0.23	0.05	<0.0001	43,213	-0.23	0.06	0.0001
	<b>Social Support<sup>a</sup></b>	72,295	-0.03	0.02	0.05	45,585	-0.02	0.02	0.2
	<b>Social Strain<sup>a</sup></b>	72,608	0.10	0.03	0.003	45,607	0.07	0.04	0.07
	<b>Social Support<sup>b</sup> Social Strain<sup>b</sup></b>	71,114	-0.02 0.08	0.02 0.03	0.2 0.02	44,812	-0.01 0.06	0.02 0.04	0.4 0.1

Dependent variable was continuous CRP or WBC. Social relationship variable was categorical Social Network Size (0-3), Social Support (0-9), and/or Social Strain (0-4). All models adjusted for age, race/ethnicity, education, age at menarche, age at menopause, parity, amount of time breastfeeding, and hormone therapy use. All variables were measured at baseline.

<sup>a</sup>Only social relationship variable in model.

<sup>b</sup>Model included both Social Support and Social Strain.

**Supplemental Table 3. Associations between inflammation markers and time from baseline to breast cancer diagnosis by cohort**

Breast Cancer Outcome	Inflammation Marker	<u>Observational Study</u>				<u>Clinical Trial</u>			
		N Cases	N Non-Cases	HR	95% CI	N Cases	N Non-Cases	HR	95% CI
<b>Invasive</b>	<b>C-Reactive Protein</b>	125	3,653	0.84	0.58, 1.23	269	7,286	1.13	0.87, 1.46
	<b>White Blood Cell Count</b>	2,707	65,679	1.01	0.78, 1.31	1,621	39,062	1.15	0.83, 1.59
<b><i>In Situ</i></b>	<b>C-Reactive Protein</b>	31	3,631	0.83	0.40, 1.75	69	7,232	1.11	0.67, 1.85
	<b>White Blood Cell Count</b>	625	65,100	1.42	0.89, 2.27	424	38,694	2.03	1.23, 3.37

Dependent variable was time from baseline to breast cancer diagnosis, censored at 10 years after baseline. Inflammation marker was C-Reactive Protein ( $\geq 3$  mg/L vs  $< 3$  mg/L) or White Blood Cell Count ( $\geq 10,000$  cells/uL vs  $< 10,000$  cells/uL). All models adjusted for age, race/ethnicity, education, age at menarche, age at menopause, parity, amount of time breastfeeding, hormone therapy use, body mass index, smoking, caregiving, negative life events, physical activity, and sleep quality. Models of invasive breast cancer excluded those who developed *in situ* breast cancer, and vice versa. Inflammation markers and confounders were measured at baseline.

**Supplemental Table 4. Associations between social relationship characteristics and time to breast cancer diagnosis, with and without adjustment for inflammation markers, by cohort**

Breast Cancer Outcome	Social Relationship Characteristic	Inflammation Marker Mediator	Observational Study				Clinical Trial				
			N Cases	N Non-Cases	HR	95% CI	N Cases	N Non-Cases	HR	95% CI	
<b>Invasive</b>	<b>Social Support</b>	<b>None</b>	2,712	65,410	1.01	0.99, 1.02	1,606	38,397	1.00	0.98, 1.01	
		<b>CRP</b>	123	3,532	0.96	0.91, 1.02	265	7,103	0.99	0.95, 1.04	
		<b>WBC</b>	2,660	64,354	1.00	0.99, 1.02	1,606	38,367	1.00	0.98, 1.01	
	<b>Social Strain</b>	<b>None</b>	2,731	65,700	0.99	0.96, 1.02	1,589	38,436	0.99	0.95, 1.03	
		<b>CRP</b>	122	3,502	1.01	0.88, 1.15	257	7,051	1.06	0.96, 1.16	
		<b>WBC</b>	2,676	64,643	0.99	0.96, 1.02	1,589	38,406	0.99	0.95, 1.03	
	<b>Social Network Size</b>	<b>None</b>	2,748	66,400	0.98	0.93, 1.02	1,610	38,789	1.02	0.97, 1.08	
		<b>CRP</b>	123	3,623	0.93	0.76, 1.14	268	7,216	1.06	0.93, 1.21	
		<b>WBC</b>	2,693	65,333	0.97	0.93, 1.02	1,610	38,759	1.02	0.97, 1.08	
	<b><i>In Situ</i></b>	<b>Social Support</b>	<b>None</b>	625	64,837	1.03	1.00, 1.06	413	38,032	1.02	0.99, 1.06
			<b>CRP</b>	30	3,511	0.96	0.85, 1.08	68	7,051	1.03	0.95, 1.13
			<b>WBC</b>	614	63,785	1.03	1.00, 1.06	412	38,002	1.02	0.99, 1.06
<b>Social Strain</b>		<b>None</b>	628	65,121	0.94	0.88, 1.00	419	38,069	0.98	0.91, 1.06	
		<b>CRP</b>	30	3,482	0.85	0.64, 1.11	67	6,997	1.04	0.86, 1.25	
		<b>WBC</b>	617	64,068	0.93	0.87, 1.00	418	38,039	0.98	0.91, 1.06	
<b>Social Network Size</b>		<b>None</b>	633	65,819	1.03	0.94, 1.13	424	38,421	1.11	0.99, 1.24	
		<b>CRP</b>	31	3,601	0.69	0.45, 1.04	68	7,163	1.26	0.96, 1.65	
		<b>WBC</b>	622	64,756	1.03	0.94, 1.13	423	38,391	1.11	1.00, 1.24	

Dependent variable was time from baseline to breast cancer diagnosis, censored at 10 years after baseline. Social relationship variable was categorical Social Network Size (0-3), Social Support (0-9), or Social Strain (0-4). All models adjusted for age, race/ethnicity, education, age at menarche, age at menopause, parity, amount of time breastfeeding, hormone therapy use, body mass index, smoking, caregiving, negative life events, physical activity, and sleep quality. Models further adjusted for inflammation marker included CRP ( $\geq 3$  mg/L vs  $< 3$  mg/L) or WBC ( $\geq 10,000$  cells/uL vs  $< 10,000$  cells/uL). Models of invasive breast cancer excluded those who developed *in situ* breast cancer, and vice versa. Social relationship characteristics, inflammation markers, and confounders were measured at baseline.

CRP=C-Reactive Protein, WBC=White Blood Cell Count