



Original article

Social relationships, inflammation markers, and breast cancer incidence in the Women's Health Initiative

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ABSTRACT

Objectives: Previous research has reported associations between social relationships and carcinogenesis. Inflammation is a potential mediator of these associations. To clarify these links for one tumor site, we examined associations between social relationships, circulating inflammation markers, and breast cancer incidence.

Materials and Methods: Among 132,262 participants from the prospective Women's Health Initiative, we used linear and logistic regression to evaluate associations between social relationship characteristics (social support, social strain, social network size) and inflammation markers of C-reactive protein (CRP) and white blood cell count (WBC). Cox regression was used to evaluate associations between inflammation markers and breast cancer incidence, as well as associations between social relationship characteristics and breast cancer incidence with and without adjustment for inflammation markers.

Results: Larger social networks were associated with lower continuous CRP (beta = -0.22, 95% CI -0.36, -0.08) and WBC (beta = -0.23, 95% CI -0.31, -0.16). Greater social strain was associated with higher continuous CRP (beta = 0.24, 95% CI 0.14, 0.33) and WBC (beta = 0.09, 95% CI 0.04, 0.14). When WBC was dichotomized at 10,000 cells/uL, high WBC was associated with greater hazards of *in situ* breast cancer (HR = 1.65, 95% CI 1.17, 2.33) but not invasive breast cancer. Social relationship characteristics were not associated with incidence of invasive or *in situ* breast cancer.

Conclusion: Larger social networks were associated with lower inflammation and greater social strain was associated with higher inflammation. Higher inflammation might be associated with development of *in situ* breast cancer, but this appeared to be due to factors other than social relationships.

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1. Introduction

Social gradients in health and illness have been widely documented [1]. Recent research in the social epidemiology of chronic disease has increasingly linked characteristics of social relationships, such as social networks and social strain, to cancer outcomes including quality of life [2] and survival [3-7]. Relatively little research has examined associations between social relationships and cancer incidence, although one study reported no association

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Abbreviations

Abbreviation definition

CRP	C-Reactive Protein
CT	Clinical Trial
OS	Observational Study
WBC	White Blood Cell Count
WHI	Women's Health Initiative

between caregiving stress and breast cancer incidence [8], while work on the related topic of job stress and risk of cancer has found inconsistent results [9–11]. Moreover, critical gaps remain in our understanding of the mechanisms underlying links between social relationships and cancer.

Social relationships have been linked to inflammation [12,13], which is a potential mediator of associations between social relationships and cancer, providing one possible mechanism through which social interactions might “get under the skin” to influence health. Social isolation, lack of social support, and high social strain have each been associated with higher systemic, low-grade, chronic inflammation [14–16]. Inflammation is also one major indicator of innate immunity and physiological stress response in the pathways to cancer [17]. In turn, chronic inflammation can contribute to different stages of carcinogenesis, including tumor initiation [18].

We evaluated the potential role of inflammation markers as mediators of associations between social relationships and breast cancer incidence in the Women's Health Initiative (WHI). Breast cancer is an important tumor site in which to investigate these kinds of associations because of its high incidence and mortality, with over 250,000 new cases and 40,000 deaths expected in the United States in 2017 [19]. Previous WHI work has evaluated associations between characteristics of social relationships and breast cancer, but has not evaluated the role of inflammation [4,20,21]. We hypothesized that smaller social networks, lower social support, and higher social strain would each be associated with higher circulating concentrations of inflammation markers, that higher inflammation would be associated with greater hazards of subsequent diagnosis with breast cancer, and that associations between social relationships and breast cancer incidence would be attenuated after adjusting for inflammation markers.

2. Materials and methods

2.1. Study population

WHI has been described previously [22]. Briefly, WHI is a large longitudinal study of United States women's health ($n = 161,808$) including Observational Study (OS; $n = 93,676$) and Clinical Trial (CT; $n = 68,132$) cohorts (CT registration identification number NCT00000611). Women aged 50–79 at baseline were enrolled during 1993–98. Those ineligible for the CT, typically due to prior health conditions or unwillingness to participate in a trial, were offered the opportunity to participate in the OS.

Starting from the overall WHI sample of 161,808, we applied the following exclusions sequentially: 1) self-reported history at baseline of any cancer except non-melanoma skin cancer (16,255 excluded), and 2) CT participants assigned to receive a hormone therapy intervention of either unopposed estrogen or a combination of estrogen and progesterone (13,291 excluded). CT participants assigned as controls in hormone therapy trials were not excluded. The final study sample for this analysis was 132,262

participants.

Procedures to ascertain incident breast cancer cases during the WHI observation period have been described [23,24]. Briefly, documents such as operative or oncology consultation reports were sent from the diagnosing clinic to the central WHI Clinical Coordinating Center, where trained coders working under the supervision of a physician and epidemiologist reviewed and coded the diagnostic information according to Surveillance, Epidemiology, and End Results Program coding guidelines [23]. Each participant was categorized as a case or non-case, with cases further subdivided into invasive and *in situ* cases.

2.2. Measures of social relationship characteristics

Social relationship characteristics included social network size, social support, and social strain as assessed by self-report at baseline. We measured social network size on a scale of 0–3, the sum of three dichotomous indicators (0 = no, 1 = yes) for marital status, religious attendance in the past month, and social club or group attendance in the past month. Marital status was coded as “yes” if the participant indicated being presently married or in a marriage-like relationship, and “no” if widowed, divorced, separated, or never married. Social support was based on a previously validated measure rescaled to a range of 0–9, the sum of nine dichotomous indicators (0 = no, 1 = yes) for the availability of someone for the participant to talk to in various circumstances, for example, when she needed someone to listen or give good advice [25]. Social strain was based on a previously validated measure rescaled to a range of 0–4, the sum of four dichotomous indicators (0 = no, 1 = yes) for the presence of other people in the participant's life who got on her nerves, asked too much, excluded her, or asked her to do things she did not want to do [26].

2.3. Inflammation markers

Blood concentrations of inflammation markers were measured at baseline as continuous variables. High-sensitivity C-reactive protein (CRP; units: mg/L) was measured at the University of Minnesota (Minneapolis, MN) using an immunoturbidimetric assay on a Roche/Hitachi Modular P Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). Total white blood cell count (WBC; units: thousands of cells/uL) was measured using automated clinical hematology cell counters following standardized quality assurance procedures. Among the 132,262 participants eligible for this analysis, CRP was measured in 14,375 participants (11%) and WBC in 130,844 (99%).

2.4. Covariates

Based on the Berkman-Glass conceptual model of social networks on health outcomes [27], we created a directed acyclic graph (Fig. 1) to identify potential sources of confounding of the associations of interest [28]. We identified three clusters of covariates: 1) demographic factors, including age (continuous), race (non-Hispanic white, other), education (0–12, 13 + years in school), and WHI enrollment (OS, CT); 2) reproductive factors, including hormone therapy use (ever, never), age at menarche (9 or less, 10, 11, 12, 13, 14, 15, 16, 17+), parity (0, 1, 2, 3, 4, 5 + term pregnancies), months breastfed (never, 1–6, 7–12, 13–23, 24+), and age at menopause (continuous); and 3) lifestyle and behavioral factors, including body mass index (continuous), smoking status (current, former, or never), caregiving (times a week: 0, <1, 1–2, 3–4, 5+), number of negative life events (0–11), physical activity (any, none), and level of sleep disturbance (0–20). Measurements of all covariates were taken at baseline.

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