Measuring Stress in the Sister Study

Outline of the Sister Study Behavioral and Psychological Health Questionnaire
1.   Perceived stress (past 30 days)
2.   State depression (past week)
3.   Anxiety (past week)
4.   Traumatic life events and experiences (lifetime)
5.   Fear of being a victim of violence (lifetime)
6.   Personal safety/terrorism (current)
7.   Job stress (current or recently held job)
8.   Harassment on the job (lifetime)
9.   Experience of discrimination based on race, ethnicity, age, or sex (lifetime and past 5 years)
10-11.   Family care giving (past 12 months)
12-14.   Role strain (past 12 months)
15-16.   Social support (current and childhood)
17.   Coping (current)
18-20.   Religion/spirituality (current)
21.   Optimism (current)
22.   Impact of breast cancer (past week)
23-25.   Beliefs about breast cancer and cancer prevention (current)

Definition of stress
Stress can be thought of as real or perceived threats to homeostasis, the physiological processes that maintain equilibrium and survival. Stress may be considered to include the environmental stimuli that result in psychological and biological changes, the perception of the threat posed by these changes, and the changes themselves. The assessment of stress can, therefore, involve measurements at all these levels. Environmental conditions or events, themselves, may lead to physiological changes. However, to some extent, it is the subjective perception of these stimuli that determine whether they are stressful.

Methods for assessing stress in the Sister Study
Several aspects of psychological stress and vulnerability will be assessed using data from the baseline and follow-up questionnaires. These include environmental stressors such as chronic stress (job strain, caregiver stress), traumatic life events (e.g., violence), as well as perceived stress, coping, social networks, and mental health (history of depression and anxiety disorders). The following provides an overview of data available in the baseline questionnaire and what will be included in the follow-up questionnaire.

Baseline questionnaire
Environmental stressors Data collected at baseline could be used to create objective categorization of life events and chronic stress. Data on major life events include loss of a loved one (death of a parent or sibling) and pregnancy loss (stillbirth, miscarriage). There are previous examples of linking job history data with occupation-title data from U.S. National Surveys on occupational stress [1], though few examples exist that would point towards the validity of this method specifically among women or using contemporary occupational title data (see discussion of occupational strain in follow-up questionnaire).

One somewhat unique stressful experience of the participants in the Sister Study may be the diagnosis of their sister with breast cancer. The acute impact and extended worry associated with this experience may be reflected, in part, by factors measured in the baseline questionnaire, including: number of affected relatives, age at sister's diagnosis, mortality, genetic testing, mammography frequency, and personal history of cancer or other breast conditions. However, the relationship between these characteristics and

chronic stress from cancer worry is likely to be complex and be modified by other factors such as coping style, social networks, and personality.

Perceived Stress The baseline questionnaire included a well-known series of questions on perceived stress in the past 30 days, the Perceived Stress Scale (PSS) [2]. This is a commonly used, well-validated instrument that provides a good cross-sectional snapshot of stress and has been linked to a number of outcomes, including infections [3,4] and response to vaccination [5], cortisol levels [6], telomere shortening [7], and coronary heart disease [8]. Data obtained from the PSS can be viewed as either a main exposure or a modifier.

Follow-up questionnaire
The choice of instruments for inclusion in the follow-up questionnaire is influenced by a number of considerations: 1) feasibility – time for administration; 2) comparability with other studies existing or in the field; 3) association with physiological changes/health outcomes in other studies; and 4) meaningfulness – timing relative to disease onset, chronic vs. acute, severe vs. mild.

1. Perceived stress (past 30 days)
Perceived Stress Scale (PSS) [2]. (see description on baseline questionnaire). No modifications were made to this scale. A trajectory of stress over time can also be obtained through administering the PSS in the follow-up questionnaire, which will be of use in establishing a pattern of chronic stress perception in some participants. The PSS was also included as part of the baseline CATI for the Sister Study.

2. State depression (past week)
Center for Epidemiological Studies Depression Scale (CES-D). To reduce participant burden, we have chosen to adopt a shorter form of the CESD, the CES-D10, that includes 10 of the 20 questions in the full scale, rated on 4-point scale [9]. No modifications were made to this scale. Depression may reflect both the response to past or present stress and may also lead to physiological changes similar to stress [10-14]. One prospective study has shown an association of having experienced chronic depression with severe episodes and risk of breast cancer twenty years later [15]. The CES-D has been in use since 1977, and was developed specifically for self-administered use in studies of the epidemiology of depressive symptomatology in the general population. It has excellent internal consistency and test-retest reliability, and has been evaluated for subsets of the original population including persons older than 64 and African Americans (http://www.musc.edu/dfm/RCMAR/DepressionTools.html). Data generated by the CESD-10 will allow us to examine depressive symptoms as a primary endpoint or determinant, but equally importantly will be considered potential confounder or modifier of other data collected in the follow-up questionnaire in that depressive mood may color response to other questionnaire items.

3. Anxiety (past week)
Hospital Anxiety and Depression Scale (HADS). Only the anxiety subscale has been included, as the depression subscale would be redundant with the CES-D. The original response categories for this scale vary from item to item, but the questions lend themselves readily to a uniform set of categories; so the response categories were modified in order to make them uniform across all the questions in this scale, and to match the categories used in the CES-D. This was done for the purpose of making the instrument more user-friendly for the respondent. Anxiety disorder is another mood disorder that may have effects similar to that of depression[14]. The HADS has been found to perform well in assessing the severity of symptoms, as well as identifying anxiety disorders in psychiatric patients, primary care patients, and the general population (Bjelland et al, 2002). The limitation of this instrument to the past week captures the construct of "state" anxiety, a transitory emotional response, rather than "trait" anxiety, a personality trait of reacting generally to stressors with a particular emotional response. Similar to depression, the HADS will allow examination of anxiety symptoms as a primary endpoint or determinant, and also as potential

confounder or modifier of other data collected in the follow-up questionnaire in that anxious mood may influence the responses to other questionnaire items.

4. Traumatic life events and experiences (lifetime)

Revised Brief Betrayal Trauma Survey (BBTS). This was originally a 14-item questionnaire which has been modified to include a total of 23 items. The original instrument had respondents report "yes" or "no" for each item, for three different age ranges (before age 12, age 12 through 17, and age 18 and older). Our revised layout has the respondent report her experiences for the same age ranges, but also provides a means for her to mark if the experience occurred in the past 12 months. In addition, for each event that she has experienced (regardless of when it happened), she is asked a follow-up question (how much distress or anxiety has this caused you in the past 4 weeks). This reference period is based on the time frame found in the 7-item Post-Traumatic Stress Disorder (PTSD) Screener (Breslau, Peterson, et al. 1999). Although we do not ask the specific PTSD screener questions, this follow-up question allows us to gain an understanding of whether past traumatic experiences may contribute to current PTSD.

The limitations of previously widely used "life events" indices (such as the Holmes-Rahe Social readjustment scale) include the usual focus on events in the past year, as well as the inclusion of events that might differentially be experienced as stressful depending on an individual's perspective (e.g., divorce, job loss). As such, this approach does not represent the state of the art in assessing the impact of potentially stressful life events. In contrast, the experience of a real or perceived threat to one's life from exposure to violence can be an extreme stressor for most individuals that may lead to psychological and physiological changes. Such a stressor, even if experienced during childhood or in developmentally sensitive periods, can have long lasting and profound effects [16, 17]. Thus, we decided to adapt the Revised Brief Betrayal Trauma Survey (BBTS) (Goldberg and Freyd, 2004; http://dynamic.uoregon.edu~jif/btts/), which includes 14 traumatic events before and after the age of 18, including natural disasters, accidents, and interpersonal traumas with and without betrayal.

5. Fear of being a victim of violence (lifetime)

This is a brief set of questions developed specifically for the Sister Study aimed at assessing not only the experience of violence (as in the BBTS), but rather, the extent of any ongoing, chronic *fear of, or concern about* being a victim of violence.

6. Personal safety/terrorism (current)

These three questions are related to #5 above, and deal specifically with fear for personal safety with regard to terror strikes. They are taken from the 2004 Melamed et al. article "Association of Fear of Terror With Low-Grade Inflammation Among Apparently Healthy Employed Adults."

7. Job stress (current or recently held job)

Karasek Job Content Questionnaire. The scale is unmodified, but the instructions were clarified so that respondents who do not currently hold a job are instructed to answer with regard to their most recently held job. The Job Content Questionnaire has been applied in diverse national and international settings, and shows good reliability and consistency across populations [18].

Work stress is one of the most commonly used models of chronic stress. The Karasek Demand-Control model [19] combines two features of the work environment: "Job demands" refer to the tasks required or workload, while "decisional control" refers to the ability to control work activities and make important decisions at work. In this model, a job that involves both high demands and low control will lead to greater job strain. Job strain has frequently been linked with the development of hypertension and heart disease in men, but data in women is less abundant and findings have been inconsistent [20-23].

Very little data exists to the possible effect of chronic stress from job strain and physiological changes possibly on pathway to cancer, e.g., allostatic load [24], oxidative DNA damage [25]. Job strain might be related to behavioral risk factors for cancer, but few studies have directly examined this question [26, 27]. Few human studies have reported on job strain and cancer risk, and one prospective study provides little evidence that job strain contributes to risk of breast cancer. After up to eight years follow-up in the Nurses Health Study: compared with low job strain (low demand, low control), high job strain (high demand, low control) was not associated with risk of breast cancer (relative risk, RR=0.87; 95% CI 0.73, 1.04). However, women with active jobs (high demands, high control), however, had a significantly lower incidence of breast cancer (RR = 0.83, 95 percent confidence interval: 0.69, 0.99). Data collected in the Sister Study will allow examination of job strain across a wider variety of occupations and industries to determine whether these associations can be replicated.

8. Harassment on the job (lifetime)
This brief set of questions revises a "Workplace Bullying" assessment provided by Dr. Gary Namie. The original version asked about the respondent's experience of mistreatment in the past 12 months, in the last 5 years, and ever. We have simplified this to "in the past 12 months" and "at any other time in your working life." We have also re-phrased the final part of the question to be more specific.

Recently awareness is growing of the role of bullying and harassment on the job; bullying can be considered a type social stress at work. Being bullied at work was associated with increased risk of heart disease and depression, as well as being overweight in one study of mostly female staff in a hospital [28], and has also been related to increased anxiety, decreased social support, and altered cortisol response [29].

9. Experience of discrimination based on race, ethnicity, age, or sex (lifetime and past 5 years)
These are based on a set of questions regarding perceived racism developed by Dr. Glinda Cooper (NIEHS) and used in the Carolina Lupus Study to assess recent and past experience of perceived discrimination. The experience of discrimination is another potential chronic stressor which may lead to physiological changes associated with cancer, e.g., allostatic load [24], oxidative DNA damage [25].

10-11. Family care giving (past 12 months)
These are adapted from a set of questions used in the Nurses' Health Study.
Caregiver stress also represents a form of chronic stress, and has been included in a number of studies on cancer, cardiovascular disease, and immune function [30-34]. Women, in particular, often bear the majority of family caregiving responsibilities outside of their paid employment. This may be a particular burden and source of chronic stress among women who routinely provide care to children living at home or an ill or ageing family member.

The Nurses Health Study asked about hours of informal caregiving (unrelated to participants' paid work as nurses) and self-reported caregiving stress. In 1992 and 1996, Nurses' Health Study participants were asked about non-occupational experience with caregiving, which was then examined with respect to breast cancer after 4-8 years follow-up. High levels of self-reported stress from caring for a child were unrelated to breast cancer outcome. However, high levels of self-reported stress associated with adult care were related to a borderline lower incidence of breast cancer (hazard ratio = 0.82, 95 percent confidence interval: 0.68, 1.00). No significant interactions were found between caregiving and other psychosocial variables.

12-14. Role strain (past 12 months)
Two questions were adapted from the NIOSH 2002 Quality of Worklife module section D, and one new question was added. The only modification to the other questions was to add the reference period "in the past 12 months."

"Role strain" refers to the conflict between demands of work and family life, and represents another contributor to chronic stress. Given the age range of participants in the Sister Study, a good proportion of women may be both working and caring for children or parents. The intersection of these experiences may be informative. The NIOSH General Social Survey includes two questions, "How often do the demands of your job interfere with your family life" and visa versa (rated often, sometimes, rarely, and never), which has been adapted for use in the Sister Study questionnaire. More detailed questions related to this construct were used in the National Study of Midlife Development (MIDUS), and were independently associated with mental health status in women in a cross-sectional study in three different industrialized countries [35].

15-16. Social support (current and childhood)
These questions were adapted from selected Social Networks questions from the California Teachers' Cohort. Certain items from the Abbreviated Childhood Trauma Questionnaire that capture emotional support during childhood were revised and added to this social networks scale.

Social support may provide a buffer between stress and illness by modulating stress appraisal or enabling reappraisal, which reduces the threat or stress response to threat [36]. This may, in turn, eliminate or reduce the physiological response to external stressors. Social networks have been consistently associated with various health outcomes: the impact of social integration on overall age-adjust mortality is comparable to behavioral and physiological risk factors (e.g., smoking, cholesterol)[37]. There is little evidence that social networks are directly related to the incidence of cancer, but literature suggests that cancer screening behaviors may be affected by the structural qualities of social networks [38, 39].

17. Coping (current)
Nine items were adapted from the Brief COPE Inventory. The Brief COPE consists of 28 items which cover 14 subscales; we have incorporated items that reflect nine of these: positive re-framing, use of emotional support, behavioral disengagement, active coping, denial, self-blame, venting, acceptance, and humor. The subscales that we have not included are: self-distraction, substance abuse, use of instrumental support, planning, and religion. The religion aspect is covered in the next item.

Coping strategies represent the behavioral and cognitive responses taken to reduce or eliminate psychological distress or stressful situations. Coping may mediate the impact of personality traits, e.g., optimism, on distress [40]. One critique of coping scales is that coping often is situational and is generally not predictive of health outcomes (Cohen, personal communication). Some investigators have used a subset of the brief COPE (e.g., NHS; Wright, personal communication). Data collected on coping will be used primarily as effect modifiers or potential confounders, and will be grouped into sets of traits (for example, Active/positive reframing/use of emotional support; 2) Denial/behavioral disengagement; 3)Humor/positive reframing. Groupings may be driven by the data or informed by the literature.

18-20. Religion/spirituality (current)
Selected questions were adapted from the Study of Women's Health Across the Nation (SWAN). Religion is among the most common coping mechanisms, and is an especially important response to stress in some populations. Religion and spirituality are especially important in the African American community.

21. Optimism (current)
Two different scales have been combined: the revised Life Orientation Test (LOT-R) which is being used in its entirety; and the DS14: Standard Assessment of Negative Affectivity, Social Inhibition, and Type D Personality, from which we have dropped two items ("I often find myself worrying about something", and "I find it hard to start a conversation").

It can be argued that various aspects of personality might modify or perhaps explain some, if not all, of the relationship of health outcomes with coping, social networks, and perceived stress.

The appeal of assessing personality includes its relative stability across situations. Personality features such as optimism, as measured by the Life Orientation Test (LOT-R), may be both associated with active coping or health behaviors and health outcomes. For example, optimism has been associated with slower progression of atherosclerosis in healthy women [41] and with pulmonary function in older men [42], while pessimism has been linked with both coping style and psychological outcomes in breast cancer patients [43]. Optimism measured in the elderly has also been linked with overall survival [44], but was not associated with longevity when optimism was measured during childhood [45].

22. Impact of breast cancer (past week)

The Impact of Event Scale is being used in its entirety, with instructions for the respondent to think about her overall experience with breast cancer in her family as the referent event whose impact is being assessed.

One potentially stressful life event shared by all the participants in the Sister Study may be the diagnosis of their sister with breast cancer. The Impact of Event Scale (IES, 15 items) has been widely used in studying the impact of life threatening illness, included cancer, and has been reported to be a valid and reliable instrument in women with an increased risk of hereditary breast cancer [46]. Included in the IES are three sets of symptoms (intrusion, arousal, and avoidance) that are also used to characterize post traumatic stress disorder (PTSD). In a study of 73 women with a sister or mother with breast cancer who were attending a high risk clinic, 4% reported symptoms consistent with PTSD and 7% reported sub-clinical PTSD based on responses to the IES-R [47]. In a subset of these women who also completed the State Trait Anxiety Index (STAI; n=55), nearly half scored above the clinical cute point for the STAI trait measure, indicating significant symptoms of anxiety, and nearly a third reported symptoms of depression using the Center for Epidemiological Studies Depression Scale (CES-D). Time since relative's diagnosis was associated with the IES-R intrusion scale, with a higher intrusion level for recent (<11 years) than distant (11-20 yrs) time since diagnosis. Number of relatives diagnosed, age at interview, and other demographic factors were not related to IES-R scores, but it should be noted that the group was fairly young on average (43 years, range 19-77), white (80%), and highly educated. These findings also reflect a highly selected group, and may be more extreme compared with a community-based sample or participants in the Sister Study.

It bears noting that, although the diagnosis of breast cancer in a sister may represent a single traumatic event or set of experiences, the increased and perceived risk of cancer in the unaffected sibling is an ongoing threat and in that respect may also be viewed as a potential source of chronic stress.

23-25. Beliefs about breast cancer and cancer prevention (current)

The two questions regarding perceived risk of breast cancer come from Appleton [48]. The remaining questions regarding beliefs about what factors influence risk of breast cancer were developed for the Sister Study, derived from a prior study showing racial differences between white and African-American women in breast cancer risk attribution[49]. For example, African-American women were more likely to attribute risk of cancer to a "blow to the breast" or personal factors, while whites were more likely to attribute risk of cancer to environment or heredity. While risk attribution in women with a family history of breast cancer is not directly related to etiological hypotheses in the Sister Study, collecting these data will offer a unique opportunity to examine these factors in a broad sample of women and in relation to environmental determinants and participant characteristics.

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