Supporting Statement A

The Sister Study PHASE 3:

Environmental and Genetic Risk Factors for Breast Cancer

(NIH/NIEHS)

REVISION

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Yellow highlights indicate changes since the last submission in 2012;

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Summary

The Sister Study is a prospective cohort study of the environmental and genetic risk factors for breast cancer and other diseases among 50,000 sisters of women who have had breast cancer. The long-term design allows us to also study the impact of environmental and genetic factors on survival and outcomes following a breast cancer diagnosis.

In the United States, more than 200,000 new cases of breast cancer are diagnosed each year. Breast cancer accounts for ~30% of all new cancer cases among women and ~15% of cancer deaths. The etiology of breast cancer is complex, with both genetic and environmental factors playing a role. Currently established breast cancer risk factors account for less than half the variation in breast cancer risk across the United States, and known breast cancer genes are found in fewer than 10% of breast cancer patients. Although the concordance rate for monozygotic twins is less than 20% (underscoring the importance of environmental contributors), sisters of women with breast cancer have, on average, a 2-fold increase in risk for breast cancer themselves. By focusing on a genetically susceptible group, more precise estimates of the contribution of environmental and other non-genetic factors to disease risk may be possible and the power to study gene by environment interactions will be greatly enhanced.

Between August 2003 and August 2009, we enrolled just over 50,000 at-risk volunteers into a prospective cohort study known as the Sister Study. Sister Study participants were recruited from across the United States and Puerto Rico. They were between ages 35 and 74 at enrollment and had at least one full or half sister who was diagnosed with breast cancer. Participants were recruited through a variety of means including the media, breast cancer advocacy groups, medical practitioners, community partners, and Sister Study participants themselves. Recruitment strategies were designed to enroll a cohort of sisters that is ethnically, geographically, and socioeconomically diverse. At enrollment, participants provided complete histories of personal and family health, reproductive health, diet, and environmental and lifestyle exposures. They completed a home exam in which height, weight, waist circumference, and blood pressure were measured by an examiner who also collected a blood sample. Whole blood, serum,

plasma, blood clots, blood spots, and cryopreserved lymphocytes were stored for future use. Participants also provided a first morning urine sample, toenail clippings, and household dust wipe samples.

Now in the long-term follow up phase of the Sister Study, the enrolled high-risk cohort is being followed actively for at least ten years for the development of breast cancer and other diseases. We anticipate, on average, 300 new cases of breast cancer to be diagnosed each year; thus after five years of follow-up we began to have sufficient cases and power to address hypotheses regarding gene-environment interactions, although for some hypotheses and for studies of gene-environment or gene-gene interactions, larger samples are required. Thus far ~2,900 incident cases of breast cancer have been reported by participants. Baseline data, banked blood, urine, and toenail samples, as well as banked environmental samples provide a rich resource for testing current and future hypotheses regarding risks for breast cancer and a wide range of other medical conditions.

Sister Study participants are contacted annually to track changes in their medical history. Every two to three years, participants are asked to provide more comprehensive health and exposure updates and to provide additional information on other factors that may affect disease risk and survival such as stress phenotype or diet. Over time, participants may be asked to provide additional biological or environmental samples and will be invited to participate in more focused clinical studies of specific outcomes.

During the course of the follow-up years, some participants are reported as deceased or permanently incapacitated due to physical or cognitive impairments. These women are likely to have experienced significant, unreported health changes prior to death and prior or subsequent to incapacitation. When a death or incapacitating event is reported, the Sister Study attempts to retrieve this missing health information, in the form of an Annual Update, in a timely manner through participants' next-of-kin or proxy.

[Conducted under Clinical Exemption CE 2009-09-004] Participants who develop breast cancer are asked to provide information about their diagnosis and treatment and asked to sign medical release forms allowing us to request medical records, additional details about diagnosis and treatment, and tumor tissue and/or diagnostic H&E slides from their health care providers. Pathology reports (only) are sought from

participants reporting other incident cancer (except non-melanoma skin cancer). Additional records may be sought to support specific future clinical studies. Similarly, additional information to allow disease confirmation or validation of self-reported diagnoses will be sought from participants who report other diseases of interest such as asthma, uterine fibroids, diabetes, thyroid disease, osteoporosis, rheumatoid arthritis and other autoimmune diseases, and neurodegenerative diseases.

Nested case-control or case-cohort studies will be carried out among sisters who develop cancer or other clinical outcomes of interest and a sample of those who do not, to assess specific gene-environment interactions or other hypotheses. Patients who develop breast cancer during the follow-up period for the Sister Study are followed to study the role of environment and genes in survival following breast cancer diagnosis. Add-on studies may collect serial biological samples from informative subgroups to evaluate preclinical biomarkers and assess changes in biomarkers over time.

The Sister Study completed enrollment in August 2009, concluding contact with the public at large, and discontinued the data collection using Sister Study enrollment questionnaires and materials previously approved by OMB. Follow-Up I (biennial) was completed in 2012; Follow-Up II (triennial) was completed in 2014.

This application is to request a REVISION for the ongoing long-term follow-up of the enrolled cohort. Approval is requested for 3 years. Annual Update form (ATTACHMENT 1A) used yearly is submitted here with minor changes for continued approval. Detailed Follow-Up II forms have been modified and are submitted here for continued use in Follow-Up *III* (triennial; ATTACHMENT 2A).

A. Justification

A.1. Circumstances Making the Collection of Information Necessary

The National Institute of Environmental Health Sciences (NIEHS) is responsible for conducting research on chemical, physical, and biological factors in the environment that affect human health. The **Sister Study**, with its focus on potential environmental causes of breast cancer, is supported by the mandate of NIEHS as defined by US Code Title 42, Chapter 6A, Subchapter III, Part A, Section 281, as amended by the Health Research Extension Act of 1985, which is "the conduct and support of research, training,

health information dissemination, and other programs with respect to factors in the environment that affect human health, directly or indirectly."

Breast cancer is the most common cancer among women in developed countries. In the United States, more than 230,000 new cases of invasive breast cancer are anticipated in 2015. Many of the best-understood risk factors are endogenous or are related to lifestyle choices that are not easily modified. Family history of breast cancer is one of the most well established risk factors for the disease with an approximate 2-fold increase in risk in first-degree relatives. No known genetic or environmental breast cancer risk factor or combination of risk factors has high enough relative risks to account for the observed association with family history.

The etiology of breast cancer is complex, with genetic and environmental factors likely playing a combined role. Identifying gene-environment or gene-gene interactions will be important in understanding breast cancer etiology and identifying prevention strategies. A number of genes already have been identified as candidates for study. Large-scale studies are needed to confirm reported gene-environment interactions and to test new biologically based hypotheses as both technology and our understanding of mechanisms improve over time. The Sister Study offers a unique opportunity to gather important epidemiological data that will make a difference in understanding the multi-factorial etiology of breast cancer.

There is suggestive evidence, including studies of disease patterns in migrants, to support a role of the environment in breast cancer risk, although specific environmental factors have not been clearly elucidated. With the exception of earlier studies of organochlorine pesticides, recent provocative studies of other endocrine disrupting chemicals, and earlier studies of irradiated populations, little work has been done in the area of non-lifestyle environmental factors. In part, this may be due to the difficulty of retrospectively measuring most environmental exposures. Few studies have examined occupational exposures among women, although there is evidence that some may play a role in breast cancer etiology. The National Toxicology Program has identified at least 35 mammary carcinogens, many of which have not been evaluated in human studies. Agents on this list include pesticides and fumigants, chemicals used

in manufacturing rubber, vinyl, polyurethane foams, benzene-based dyes, and some pharmaceuticals, as well as solvents.

The Sister Study was designed to investigate the independent and joint effects of genetic susceptibility and environmental, biological and lifestyle factors on the risk of breast cancer and other diseases in a cohort of sisters of women with breast cancer. In addition, we have the opportunity to efficiently assess risks for other diseases with similar risk factor profiles or which are otherwise important causes of morbidity in women, such as cardiovascular disease, autoimmune disease, osteoporosis, and diabetes.

By focusing on sisters, the study has several unique advantages. Not only are the sisters of women with breast cancer at greater risk for breast cancer themselves (about a two-fold risk based on other studies and borne out in preliminary analysis of incidence in the Sister Study), they will have a higher prevalence of any genes that prove to be related to breast cancer risk and they should have a higher frequency of some risk factors due to behaviors and experiences they share with their sisters who have already developed breast cancer. The study is especially well suited to address hypotheses related to shared childhood and prenatal exposures, in addition to factors later in life. Our study will have greater statistical power than a similarly sized general population cohort (see **Sections B**). Furthermore, based on current experience, sisters of women with breast cancer continue to be highly motivated to participate in breast cancer research. Participation and retention rates are higher than in other studies and the quality of data is high. For example, ten years after study inception, the response rate to annual questionnaires remains over 91%. These features will enhance both validity and statistical power to detect associations. The study is large enough to have begun investigating gene-environment interactions. Less common genes and rare exposures can be studied with continued follow-up of the cohort.

The prospective design offers several advantages over the retrospective case-control studies that have been most widely used to assess gene-environment interactions. The most often cited advantage of the case-control design is efficiency; in order to accrue the same number of cases in a population-based cohort, a substantially larger number of women must be studied. However, in retrospective studies,

exposures must be ascertained after the occurrence of disease. Although certain exposures can be studied retrospectively using questionnaires or, occasionally, using occupational or medical records, numerous potential biases can limit the ability to make causal inferences. In the Sister Study, we ascertain exposures and collected biological and environmental samples prior to the onset of disease. By banking samples for later analysis, we minimize the costs of measuring exposure, since only new cases and a sub-sample of non-cases will be analyzed.

We enrolled a cohort of just over 50,000 high-risk women (ages 35 to 74) who were the cancer-free sisters of women who had breast cancer. This cohort is being followed annually for at least ten years. Comprehensive baseline questionnaire data, fasting blood, first morning urine, household dust and toenail samples were collected. Study questionnaires were designed to collect information on known, suspected, and speculative risk factors in order to maximize the chance of detecting environmental risk factors of concern to women. In order to address new hypotheses, it was necessary to also collect comprehensive data on currently –known risk factors, to be able to account for these factors in other analyses. In contrast to previous cohort studies where environmental exposures are either ignored or addressed superficially, we aimed to collect sufficient data so that environmental risks can be conclusively identified, or in the event that risks are not confirmed, we can say that we have thoroughly investigated the possibility. Brief **Annual Updates** record changes in contact information, residence location and health. Less frequent, more detailed **Follow-Up** questionnaires address new hypotheses that arise and collect details on changes in health and exposures. Our study assesses hypotheses that derive from the scientific literature, but we also collect data on poorly studied exposures of concern to women. The incident cases that develop over time are followed for the duration of the study, allowing us to also study the role of lifestyle, environmental exposures, and genes in prognosis and survival among women with cancer.

The Sister Study is an NIEHS intramural study designed to allow for trans-NIH and extramural collaboration. The study was developed in response to the heightened concern expressed by numerous women's and environmental groups about the possibility of increased breast cancer risk due to environmental causes, and the perceived lack of serious attention paid to such concerns. In addition to

consulting with scientific colleagues both within the government and at universities, we solicited the input of groups such as the National Breast Cancer Coalition and other advocacy and interest groups and consumers as we planned the Sister Study and assessed its feasibility. Our Steering Committee and Scientific Advisory Board are diverse groups of professionals in the various areas of this complex effort. They include experts in epidemiology, long-term cohort retention, breast cancer, biological specimen management, laboratory science, as well as representatives from various organizations focused on minorities, breast cancer support, and women.

A.2. Purpose and Use of the Information Collection

Information collected in this study is used to further scientific understanding of the effects of environmental exposures by studying women with enhanced susceptibility to breast cancer and to address questions of concern to all women at risk for breast cancer. Epidemiologists and biostatisticians at NIEHS and their collaborators at other institutions are responsible for testing the hypotheses of interest and disseminating results through the scientific literature. Results are published in medical and epidemiologic journals as well as basic science journals when appropriate. Results are presented at scientific meetings and at meetings of breast cancer advocates and other interested groups. Data are used to assess current hypotheses regarding risk factors for breast cancer, to generate new hypotheses for subsequent analyses in the Sister Study, and specifically to identify preventable risk factors or combinations of risk factors. In addition to scientists and clinicians who use this information in developing prevention strategies and to advise their patients, analysis results are reported to the women who participate in the study and to other women through the media, our website, and other Sister Study publications and newsletters. Results of the study may figure in future risk assessments and evaluations of the carcinogenicity of specific environmental agents and could be used in the development of exposure guidelines or standards, should important environmental risks be uncovered. Thus the results are and will be of use to Public Health officials, other scientists, physicians, elected and appointed officials, and women and their families.

The type and amount of information we collected at baseline before women develop breast cancer, and at subsequent follow-up collections, fulfill many scientific and clinical needs. For breast cancer,

many of the exposures of interest, including endogenous hormone levels, micronutrients, and even some environmental exposures, are measured most accurately in biological samples collected before the onset of disease or treatment and their associated symptoms and biological and lifestyle changes. The cohort design allows us to collect data on exposures, including biological exposure measures, diet and lifestyle, before the onset of disease.

Brief Annual Update forms **(ATTACHMENT 1A; correspondence in ATTACHMENT 1B; web screenshots in ATTACHMENT 1C)** are used annually to update changes in contact information and health status. Follow-Up III (triennial) forms **(ATTACHMENT 2A; correspondence in ATTACHMENT 2B; telephone script in ATTACHMENT 2C; web screenshots in ATTACHMENT 2D)** record changes in health, lifestyle, occupational and environmental exposures and address new hypotheses. As technology for self-collected environmental samples improves, women may be asked to provide such samples (for example, using in-home water test kits) as part of cohort follow-up.

Women who develop breast cancer or other conditions of interest during the course of follow-up are asked to allow us to obtain medical records and tissue samples from their health care providers. [Conducted under Clinical Exemption CE 2009-09-004]

Since the last Revision, participants have completed Annual and Follow-Up II updates according to schedule with average response rates remaining over 90%. In addition, several reports have been published, describing factors under investigation **(ATTACHMENT 9)**.

A.3. Use of Information Technology and Burden Reduction

Web-based and Computer Assisted Telephone Interviews (CATI) completion of Annual Updates and Follow-Up forms are available along with the option for self-administered hardcopy forms. The three modes are integrated in the data system so that data collected through multiple means can be seamlessly combined. The Web-based and CATI technologies offer advantages over the traditional pencil and paper method:

- Less paper is required.
- There is no “mail wait” when offering forms to or retrieving data from participants.

- The Web-based approach offers more convenience to participants who prefer to work on mobile or PC devices.
- The telephone interview requires little reading for the participant, an important factor for individuals with low reading comprehension or poor eyesight.
- Data extraction is more efficient because skip patterns are automated and response inconsistencies can be queried at the time of the interview.

At enrollment (*now completed*), name, address, phone numbers, email address, Social Security number, date of birth, and medical information were collected. Personally identifiable information (PII) is stored encrypted and separate from all other data. Contact information is used to deliver Annual Update and Follow-Up materials. A Privacy Impact Assessment was completed for the Sister Study information management system.

A.4. Efforts to Identify Duplication and Use of Similar Information

The information we collect is not available from other sources. There is little consensus in the scientific community on how environment impacts breast cancer. While some studies have addressed environmental factors such as diet, pesticides, and electromagnetic fields, no conclusive evidence exists because of limits in sample size and/or study design. Although there are cohort studies, such as Harvard's Nurses Health Study, that do address risk factors for breast cancer, none of these cohorts has collected substantial information on environmental and occupational exposures, and none includes biological and environmental samples for all participants. All of the existing cohorts focus on diet and other lifestyle factors. Large-scale prospective studies such as the Sister Study are needed to validate some of the already reported gene-environment interactions and to test new biologically-based hypotheses as both the technology and our understanding of synergistic mechanisms improve over time.

As noted above, there are important advantages to the Sister Study design. First, these sisters are at increased risk of breast cancer, likely due to shared genetic and environmental factors. Their family history increases the expected number of new cancers, the frequency of relevant gene polymorphisms, and the frequency of relevant exposures, making the study efficient compared to unenriched cohort

designs. Second, because the study is prospective, blood samples and risk factor information were collected prior to diagnosis. A third advantage is that sisters are highly motivated, which has proven to benefit data quality and completeness and reduce loss to follow-up.

We are unaware of any duplication of this project with any other project now underway at other organizations. Several prospective cohort studies—for example, The Nurses' Health Study, Canadian National Breast Screening Study, New York University Women's Health Study, Iowa Women's Health Study—have investigated breast cancer in women, but none have focused primarily on the gene-environment link, especially in terms of the broader external environment.

A.5. Impact on Small Businesses or Other Small Entities

None.

A.6. Consequences of Collecting the Information Less Frequently

Annual updates take approximately 10 minutes, and Follow-Up self-administered questionnaires are 40 minutes or less. Annual contact cannot be done less frequently because the analysis relies on exposure and health-status changes over time, and ascertaining cases close to the time of diagnosis is important. A participant's recall diminishes greatly with time, and death may occur. Annual contact is necessary to preserve reliability and completeness and will facilitate maintenance of the cohort and tracing of those few who are lost to follow-up.

A.7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

There are no special circumstances relating to the guidelines of 5 CFR 1320.5 and the project fully complies.

A.8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside Agency

The proposed information collection was published in the Federal Register on 02 December 2015, Vol. 80, page 75465 and allowed 60-days for public comment. No public comments were received.

Early discussions were held with special interest groups to gain information on to what extent women who are at higher risk of developing breast cancer were willing to participate in a new longitudinal study requiring a long-term commitment and intense initial data collection. These meetings involved advocacy

groups including cancer-free sisters, breast cancer survivors, Latina women, African-American women, lesbian women, and other minorities. Support for this study was overwhelmingly enthusiastic and the majority of comments were favorable. These discussions gave us specific and valuable feedback that was incorporated into our study protocol.

Efforts to consult both within and outside NIEHS at the time the Study was first developed are summarized in **ATTACHMENT 3**. Numerous researchers both within the NIH and in the extramural community were consulted during the planning of this study.

Our study was and continues to be formally reviewed within the NIEHS intramural community, NIEHS Board of Scientific Counselors, and externally by federal and academic experts (see **ATTACHMENT 3**). Many continue to serve the Sister Study in an advisory capacity. The archived data and samples facilitate collaborations both within the NIH and in the extramural community.

Advisory to the study investigators in *ad hoc* meetings are the Sister Study Steering Committee, composed of NIEHS research staff Honglei Chen PhD (919-541-3782), Jack Taylor MD PhD (919-541-4631) and Christine Parks PhD (919-541-2577); UNC Assistant Professor Hazel Nichols PhD (919-966-7456), with SSS Sister Study senior staff.

A.9. Explanation of Any Payment or Gift to Respondents

During enrollment, participants received a prepaid 120-minute phone card valued at less than five dollars as an incentive to complete the interviews and specimen collection at enrollment. While this amount was not equivalent to the value of the effort required of participants, it helped to convey our appreciation of that effort.

Other tokens such as newsletters, greeting cards, and health event diaries with the study logo are provided periodically to enhance participation and retention. Increasing response rates and retention improve the quality of the scientific data we are collecting by minimizing response bias. Monetary and other incentives have been shown to significantly increase response rates and reduce the overall costs of follow-up.

A.10. Assurance of Confidentiality Provided to Respondents

Procedures to protect the confidentiality of respondents and the data collected include the following:

- The data constitute a system of records under the NIH Privacy Act System #09-25-**0200**: Clinical, Basic and Population-based Research Studies of the National Institutes of Health (NIH), HHS/NIH/OD. Published in the Federal Register September 26, 2002 (Vol. 67, No. 187, Pages 60742 - 60784)
- Each participant was assigned a study ID number. The ID alone is used to identify biological samples and all data forms. Only the ID number is entered into the database and used in the analysis of data. Subjects' names and addresses are stored separately.
- Information linking ID number to participant name is kept in locked physical files or password-protected, restricted access electronic files at the North Carolina office of the NIEHS Epidemiology Branch Support Services Contractor.
- Contractor employees undergo background checks, ethics training and sign a Pledge of Confidentiality **(ATTACHMENT 4)**.
- Only Sister Study research personnel have access to study data.
- Study results are published in summary form only — no individual results are published or shared.
- Shared samples and data are provided without identifiers and study ID numbers will be scrambled to prevent accidental identification of participants.
- A **Certificate of Confidentiality** has been secured for this study **(ATTACHMENT 5)**.

The proposal was initially reviewed by the NIEHS Institutional Review Board on 3/14/2002 and Copernicus Group IRB on 12/12/2006. Attached is documentation from the most recent Continuing Reviews **(2015; ATTACHMENTS 6 & 7)**. Informed consent was obtained at enrollment (***Phase 1***) spelled out the steps taken to protect privacy.

The biological and environmental samples collected will be stored indefinitely in a secure building for future testing and may be disposed of at any time at the Principal Investigator's discretion. Specimens

are labeled with ID number only. These and related issues were explained in the Informed Consent documents. Specimens shared with outside researchers are assigned a new identification number; the code linking the new and the old identification number is known only to the NIEHS contractor responsible for the Sister Study field work. This new identification number is not linked to any identifying information. Identifying information, such as name, Social Security number, or address will not be shared with researchers outside of the Sister Study protocol. Samples will only be shared for scientifically valid studies that meet approved scientific and ethical standards. Samples and data that are shared can be used only for the specific research described in an approved research proposal and may not be used for other purposes without approval from the Sister Study investigators.

Participants may elect to leave the study at any time. As explained in the Informed Consent documents, no new data will be collected from patients who elect to drop out, but the data already provided will continue to be used in some analyses unless a written request to destroy remaining/unused data and specimens is received. Screening data on women who are found to be ineligible were not retained by the Sister Study.

A.11. Justification for Sensitive Questions

Breast cancer is a complex disease likely caused by many factors. Follow-Up *II* (triennial) questions addressing sensitive and personal issues such as personal experience with violence, physical and psychological abuse, discrimination, and stress related to the sister's breast cancer diagnosis are not being readministered in Follow-Up *III*. In order to carry out a comprehensive analysis of stress, some questions on social support, personality traits, and depression *are* repeated in Follow-Up *III*. The justification for each of these scales and their source and derivation is fully described in **ATTACHMENT 8**. As described in **ATTACHMENT 8**, stress may play an important direct or indirect role in risk for breast cancer and other health outcomes. It is likely that the relationship is complex and a comprehensive approach, including assessing acute and chronic stress at different time periods and accounting for factors that modify response to stress, is required. In addition to compelling scientific evidence, we learned through our early focus groups that many women believe that stress plays a role in risk for breast cancer and other diseases,

and we have been urged, by the various constituencies that have endorsed the Sister Study, to study this topic of high interest to women.

Information is collected directly from participants. Participation is voluntary, and respondents can withdraw from the study at any time. Participants may refuse to answer specific individual questions, including those they find to be too sensitive or personal. All information is kept confidential to the extent provided by law. At no time will any individualized genetic results be given out. We have a Certificate of Confidentiality in place for this study.

A.12.1 Estimated Annualized Burden Hours

For the remainder of the study, women will be contacted once each year to update contact information and health status (~10 minutes per response); and asked to complete more comprehensive updates (~40 minutes total) every three years. Contact of next-of-kin/proxies for deceased or incapacitated participants is included in the burden budget for Annual Update. The annual reporting burden is as follows: *Estimated Number of Respondents:* 50,884 – 2,561 deceased/incapacitated/dropped = 48,323 study participants or next-of-kin/proxies. *Estimated Number of Responses per Respondent:* See annualized table below:

Estimated Annualized Burden Hours

Activity	Annual Number of Respondents	Number of Reponses per Respondent	Average Burden per response(hours)	Total Burden Hours per year
Annual Update	32,215	1	10/60	5,369
Follow-Up III (triennial)	16,108	1	40/60	10,739
Follow-Up III Telephone Prompting Script	*4,832**	1	3/60	242
TOTAL per year	**48,323**	**53, 155**		**16,350**

**These Respondents are* included *in the* 16,108 *for Follow-Up III, thus not added into TOTAL Respondents per year*.

Average Annual Burden Hours Per Response: ~20 minutes; and *Estimated Total Annual Burden Hours Requested:* **16,350**.

A.12-2 Annualized Cost to respondents

Table A12-2. Annual Cost to Respondent

Type of Respondent	Number of Respondents	Total Annual Burden Hours	Wage Rate*	Respondent Cost
Individual	48,323	20/60	$25.24	$406,565.92

*National average hourly wage rate http://www.bls.gov/news.release/empsit.t19.htm.

The estimated total annualized cost to respondents is $406,565.92 (using $25.24 Bureau of Labor Statistics 12/2015 National average hourly wage X 16,350 hours). There are no capital, operating, or maintenance costs.

A.13. Estimate of Other Total Annual Cost Burden to Respondents or Recordkeepers

There is no other total annual cost burden to respondents or recordkeepers.

A.14. Annualized Cost to the Federal Government

Over the next 3 years, the annualized cost to the Federal Government is expected to be $4,156,725 per year, totaling $12,470,175 over 3 years.

Annualized Cost to the Federal Government

Contractor Costs	Salary	Fringe Rate	% Effort	Annualized Cost
18 Subcontracted Staff for Data Collection	$57,486	39%	1800%	$1,438,292
Operational Costs for Data Collection (Non-labor)				$908,091
Other Contractual Costs for Data Collection (Non-labor)				$1,013,520
Travel Costs Associated with Data Collection				$0
Other Costs (Non-labor)				$796,822
Total Contractor Costs				**$4,156,725**

Federal Staff	Grade/ Salary (Percent FTE or effort)	Federal Staff Costs
NIH Senior Investigators	$233,241 (10%)	$23,324
NIH Technical Information Specialist	$111,814 (5%)	$5,591
Total Federal Staff Cost		**$ 28,915**

A.15. Explanation for Program Changes or Adjustments

Changes in burden and annualized cost merely reflect the anticipated progress and the next scheduled phases of the longitudinal study. Total burden request changes from 26,856 hours per year for 3 years (for 2012 revision) to 16,350 hours per year for the next 3 years. This reflects a reduction of the number of questions in the detailed Follow-Up to reduce participant burden, and the expected attrition in the cohort due to death, incapacitation or refusal to continue; it **does not** however represent a change in Protocol. *Changes* to the Annual Update and Follow-Up forms are summarized here; *additions* are highlighted in blue on the *attached* forms (**ATTACHMENTS 1A AND 2A**):

Summary of Changes to Forms

	Annual Health Update
	• #2-7: Added questions to update menstrual/menopause, smoking, and hormone replacement status.
	Follow-Up *III* Health & Medical History
General Health	• #2: Added question about ultrasound of ovaries • #7: Re-worded to round height to nearest inch • *Deleted questions on cold sores, colds, and flu*
Family Medical History	• #9: Added question about total number of full or half sisters ever diagnosed with breast cancer • #12-17: Added questions about which grandparent(s) have been diagnosed with cancer and at what age
Personal Medical History	• #33-34: Changed question to specify type of cancer for older cancers as well as more recent • #45-46: Added questions about spine and rib fractures • *Deleted questions about any other broken bones, other major injuries requiring hospitalization* • #48e: Added question about other medications for diabetes • #52: Added question about tooth loss • #86: Added question about detached retina • *Deleted questions about chronic bronchitis, migraine headaches, endometriosis, other kidney disease, and hearing loss* • #91-95: Added detailed questions added about endometriosis, incontinence, pelvic prolapse
Surgeries	• #99: Added questions about sneezing or runny nose; dizzy, or weak; getting up regularly at night to pass urine; unexplained pains; dribbling of saliva • *Deleted questions about heartburn and acid regurgitation/reflux* • *Deleted questions about doctor's recommendation following an abnormal screening; cyst drained or removed; needle, surgical or excisional biopsy* • #114: Added question about benign breast disease • *Deleted a question about mastitis; any other major health conditions*
Reproductive History and Hormones	• *Deleted questions related to inability to become pregnant, fertility medications, and mastitis* • #137-140: Added part C question to specify the reason for taking certain medications • #138: Added question about ospemifene or osphena
Symptoms of Menopause or Pre-Menopause	• *Deleted questions on other excessive sweating; pain with intercourse; irregular menstrual bleeding; bladder problems; depression, anxiety, or emotional distress; and insomnia*
Medications	• #155a: Added question about angina medications

	Follow-Up *III* Lifestyle & Quality of Life
	• #4a: Added question on current smoking status • #4c: Added question asking if at least 10 cigarettes had been smoked since Jan 1, 2012 • #6a-d: Added questions on e-cigarette usage • #13-20: Added questions on drinking caffeinated or decaffeinated coffee, tea, or soft drinks • *Deleted questions about swimming in pools; hobbies* • #27-27a: Added questions about gray hair • #31: Added question about usage of chemical products for fleas or ticks on pets • #32: Consolidated 4 questions about being outdoors in daylight to 1 question • *Deleted questions about sunscreen and protective clothing; number of household pets; air fresheners; relatives or friends they feel close to; hours providing care for children, ill or disabled; behaviors* • #63a-d: Added questions about having little interest in doing things, feeling depressed, feeling nervous or anxious, and worrying • *Deleted questions about employment; restless leg syndrome* • #82a-l: Added questions about sleeping habits • Reworded: The alternative practices of spirituality/meditation/prayer and deep breathing exercises changed to meditation/deep breathing exercises • #112: Added question about vegan diet • #114: Added question about gluten-free diet • *Deleted questions about some supplements; alternative practices; diets ; food allergies, lactose intolerance, cereal, milk, and other various food intakes*

A.16. Plans for Tabulation and Publication and Project Time Schedule

The primary goal of the study is to identify environmental and familial risk factors for breast cancer and other diseases by studying a cohort of sisters of women who have had breast cancer. The Sister Study is not designed around one particular *a priori* hypothesis, but is designed to allow us to address a number of hypotheses regarding gene-environment interactions and risk for breast cancer. Current hypotheses regarding environment-gene interactions will be addressed in the early years of the study. The reports generated from this study will include the risk factors that may be influenced by the action of genes with known polymorphisms (A.16-1 below). Clearly, as enough cases accrue, scientific understanding of biologic mechanisms and genes will advance considerably. A prospective study such as the Sister Study is designed to respond to new hypotheses as they emerge.

A.16-1

Factor	Genetic Marker of Interest
Cigarette smoke	CYP1A2, NAT2, GSTM1, CYP1A1, DNA repair polymorphisms, CYP2A6, CYP2C9
Exogenous hormones	CYP17, CYP1A2, CYP1A1, estrogen receptor polymorphisms
Hormonal risk factors	CYP17, aromatase, hormone receptor polymorphisms
Oxidative stress	Genes involved in oxidative stress
Melatonin	Polymorphism screening
Nutritional and dietary factors	Vitamin D metabolism and receptor polymorphisms, CYP1A2, NAT2
Grilled meat consumption	GSTM1
Alcohol	ADH, ALDH, CYP2E1
Sunlight exposure	Vitamin D metabolism and polymorphisms
Calcium, calcium channel blockers	Vitamin D metabolism receptor, estrogen metabolism and receptor polymorphisms

A.16-2

Project Time Schedule

Activity	Time Schedule
Began vanguard phase of enrollment	August 2003
Began nationwide enrollment	October 2004
Completed Enrollment questionnaires and collect specimens on 50,000 women	August 2009
Annual Update	Began June 2005
Follow-Up I (biennial)	Began March 2008
Follow-Up II (triennial)	Began January 2012
Follow-Up III (triennial)	*current*
Analyses	Began mid-2007
Publication	Began 2007

A.17. Reason(s) Display of OMB Expiration Date is Inappropriate

We again request continued approval to display the OMB control number without the expiration date on printed forms. This request is based on the precedent (see OMB No. 0935-0104: Medical Expenditure Panel Survey: Survey About Your Diabetes Care) that this is a longitudinal study scheduled to last for 14 or more years, and for which individual follow-up activities span across a number of years, thus across OMB expiration dates. Annual Update forms, as well as two of the three Follow-Up forms, will be used throughout the length of the study. Therefore, the cost of multiple printing cycles, merely to change OMB date, rather than taking advantage of cost savings realized with larger batch printing of approved materials, totaling hundreds of thousands of pages, that undergo little or no contextual change is inordinately costly to the government. Nonetheless, these items continue to be included in each 3-year revision package sent to OMB for continuation of approval.

A.18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to certification for this submission.