

SF 424 R&R and PHS-398 Specific Table of Contents

SF 424 R&R Face page.....	2
Research & Related Other Project Information	3
Project Summary/Abstract	4
Project Narrative	5
Facilities and Other Resources	6
PHS 398 Cover Page Supplement.....	8
PHS 398 Research Plan	10
Specific Aims	11
Research Strategy	12
Protection of Human Subjects.....	18
Inclusion of Women and Minorities	19
Targeted/Planned Enrollment Table.....	20
Inclusion of Children	21

PI: Boggs, Deborah A.	Title: Bilateral oophorectomy and cancer risk and mortality in African American women	
	FOA: PAR08-237	
	FOA Title: SMALL GRANTS PROGRAM FOR CANCER EPIDEMIOLOGY (R03)	
1 R03 CA162103-01		
	Organization: BOSTON UNIVERSITY MEDICAL CAMPUS	
<i>Senior/Key Personnel:</i>		
	<i>Organization:</i>	<i>Role Category:</i>
Deborah Boggs	Trustees of Boston University, BUMC	PD/PI
Lynn Rosenberg	Trustees of Boston University, BUMC	Co-Investigator

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? Yes No

1.a If YES to Human Subjects

Is the Project Exempt from Federal regulations? Yes No

If no, is the IRB review Pending? Yes No

2. * Are Vertebrate Animals Used? Yes No

3. * Is proprietary/privileged information included in the application? Yes No

4a. * Does this project have an actual or potential impact on the environment? Yes No

5. * Is the research performance site designated, or eligible to be designated, as a historic place? Yes No

6. * Does this project involve activities outside of the United States or partnerships with international collaborators? Yes No

PROJECT SUMMARY/ABSTRACT

Hysterectomy is one of the most common surgical procedures in the U.S. About 600,000 U.S. women undergo hysterectomy each year, and about half of these women also undergo bilateral oophorectomy. There is concern that some of these procedures are not medically indicated. African American women are much more likely than white women to have gynecologic surgery, particularly at younger ages. Bilateral oophorectomy results in abrupt loss of ovarian function. Evidence suggests that hysterectomy may lead to impaired ovarian function. Little is known about the long-term effects of bilateral oophorectomy and hysterectomy on health outcomes. Based on limited epidemiologic data, bilateral oophorectomy has been associated with a reduced risk of breast cancer but an increased risk of colorectal cancer, lung cancer, cancer mortality, and all-cause mortality. The effect of hysterectomy with retention of one or both ovaries on long-term health outcomes is less clear. Studies to date on the relation of oophorectomy and hysterectomy to cancer incidence and mortality have included few African American women, and none has reported separately on this population group. We will use data from the Black Women's Health Study (BWHS), an ongoing cohort study of 59,000 African American women, to address the hypothesis that bilateral oophorectomy and hysterectomy influence cancer incidence and mortality. Specifically, we propose to prospectively examine the relation of bilateral oophorectomy and hysterectomy with retention of one or both ovaries to incidence of the most common cancers in women (breast, colorectal, and lung) and to cancer mortality and all-cause mortality. Women were enrolled in the BWHS in 1995 and have been followed biennially by mailed questionnaire. History of gynecologic surgery has been ascertained at baseline and on each follow-up questionnaire. An estimated 1,925 breast cancer cases, 370 colorectal cancer cases, 360 lung cancer cases, 855 cancer deaths, and 2,425 total deaths will contribute to analyses in follow-up from 1995-2011. Given that loss of ovarian function earlier in life may have a more considerable effect on long-term health, and that African American women are most likely to have gynecologic surgery at younger ages, we will further investigate whether age at surgery influences the relation of oophorectomy or hysterectomy to cancer incidence and mortality. In addition, we will also assess whether use of menopausal hormones influences the relation of oophorectomy and hysterectomy to cancer incidence and mortality. This will be the first study to examine the relation of bilateral oophorectomy and hysterectomy to cancer incidence and mortality among African American women. It is particularly important to elucidate the long-term health effects of bilateral oophorectomy and hysterectomy in this population of women because of the high prevalence of these surgeries.

PROJECT NARRATIVE

Bilateral oophorectomy has been linked to increased cancer mortality. African American women are much more likely than white women to have these gynecologic surgeries, particularly at younger ages. The proposed study will provide much needed information on the relation of bilateral oophorectomy and hysterectomy to cancer incidence and mortality among African American women, allowing clinicians and patients to make more informed decisions regarding the long-term health risks and benefits of bilateral oophorectomy and hysterectomy.

FACILITIES AND OTHER RESOURCES

Slone Epidemiology Center

The Slone Epidemiology Center (Slone) has all facilities and resources necessary for the successful execution and completion of the proposed research project. The facilities and resources available at Slone to support the proposed project include office resources, computer resources, and the scientific environment.

Office Resources

Slone is located off campus and rents 21,250 sq. ft. of office space at 1010 Commonwealth Avenue in Boston. This location, which is less than 5 miles from Boston University Medical Campus, allows access to all Medical Campus facilities (i.e., School of Public Health, seminars and conferences, medical library, etc.). Slone maintains ongoing collaborations with departments in all relevant disciplines providing ready access to expertise in many fields including all interest areas of epidemiology, biostatistics, genetics, informatics, and various other medical and public health disciplines. An office with a PC has been supplied to Dr. Boggs.

In addition to the central research administration, Slone has a full administrative staff that supports investigators in the areas of proposal development, budget management, compliance requirements, financial administration, and all related research administration functions. The administrative staff is also available to assist with project specific tasks as necessary.

Computer Resources

Physical resources. Slone maintains an on-site computer center that houses servers and network infrastructure in three data closets attached to a central data center. Boston University provides Slone high-speed access to the Internet, electronic mail, and the Web. Internet resources are provided via a primary and backup link to Boston University campus network. Internet resources include electronic mail, file protocol transfers, database replication, and secure virtual private network connections as well as remote maintenance and remote management.

About 100 data ports—supporting communication rates up to 100 Mbps/full-duplex—make up the Slone local area network. These ports are interconnected via Ethernet wires and optical fiber to managed Cisco Systems switches. Slone network connects eighty (80) workstations and ten (10) servers. The ports connecting these workstations are located in staff offices and department common areas. These ports link back to a local data closet which in turns links to the central data center. The Slone servers connect to the local area network using optical fiber or gigabit Ethernet connections in the central data center.

Slone supports an array of computer peripherals, network printers and photocopiers, and high-speed optical scanners. In addition, Slone maintains its own telephone exchange, voicemail software and management, and telephone cost accounting systems.

Data security. A security team at Boston University actively monitors the traffic into and out of the managed Cisco System switches. Data ports are disabled if unused. Access to workstations is limited to specific individuals and groups. These security principals are set using Boston University Active Directory objects. Users must log into the workstation using a Boston University login name and Kerberos password. Each user is assigned to specific security groups based on project/research association and employment. Setup and management of these Active Directory objects is limited to authorized network administrators at Slone and Boston University. In addition, each workstation is protected by a software firewall that is managed using Active Directory group policies and an enterprise-class centrally managed software security solution.

Access to Slone servers is determined by a combination of security measures. All Slone workstations and servers are part of a specific Internet Protocol (IP) address pool. Access control lists block non-authorized IP address connections as well as attempts using unauthorized TCP/IP ports. Active Directory security principals lock out entry to servers, shares, folders, and files based on membership. Each server is part of the enterprise-class centrally managed software security solution.

Software. Data management, analysis, and survey processing are done in the Microsoft Windows environment. Workstations are installed with Microsoft Windows XP Professional. Microsoft Windows 2003 Server or Microsoft Windows 2008 Datacenter Server are the operating system of choice for Slone servers. Research work will be conducted using R 2.10.1, SAS 9.2, and SUDAAN where needed. The primary database tools used are Microsoft SQL and Microsoft Access. The network file-serving architecture provides

over six (6) terabytes of data storage. File access is restricted to authorized groups and users using Active Directory security principals.

Backup capabilities. Slone employs a backup system using LTO tape technology. The tape library device is capable of holding up to 40 tapes at one time and an unlimited tape media pool and catalog. Network data is scheduled for daily backup and kept onsite. A weekly offsite backup storage offers disaster protection. Biannual backups are sent offsite for archiving. The daily onsite backups are retained for three months. After three months, the daily backups are overwritten. After 12 weeks in offsite storage, the weekly offsite tapes are reintroduced into the tape library media pool from the offsite storage location. Biannual backups are recalled after three years and placed back into the tape media pool.

Information Systems (IS) staff. The Slone computer center employs an experienced, highly skilled IS staff with backgrounds in medicine, engineering, and computer science. There are five full-time employees—one desktop, server, and network coordinator and four database application and software programmers. The desktop, server, and network coordinator provides management, coordination, and support of hardware, software, and networking services used by Slone. The four database application and software programmers' extensive experience with database management, structure, and implementation affords them the ability to supply functional applications and modules for research and epidemiological studies.

Scientific Environment

Intellectual Environment. Slone employs 12 doctoral-level epidemiologists who have faculty appointments at the Boston University Schools of Public Health and Medicine. Epidemiologists have regular monthly meetings to discuss current projects and advise each other on specific project-related issues or problems. In addition, Slone is less than 5 miles from the Boston University Medical Center, thus allowing access to all Medical Center facilities (e.g., School of Public Health, seminars and conferences, medical library). Slone epidemiologists frequently collaborate with epidemiologists, biostatisticians, and clinicians at the Boston University School of Public Health and Boston University School of Medicine. Thus, a high level of intellectual rapport and support are available to the PI (Dr. Boggs) and will contribute to the successful conduct of the proposed study.

The Black Women's Health Study (BWHS). The BWHS was initiated in 1995 by Dr. Lynn Rosenberg, PI of BWHS and a co-investigator on the proposed study. Dr. Rosenberg will serve as a mentor to Dr. Boggs and advise her on all aspects of the study. The availability of data from this unique cohort makes it possible to accomplish the study aims in a timely and cost-effective manner. The population of African American women that comprises BWHS is large and 16 years of follow-up will be available to the study. The prevalence of bilateral oophorectomy and hysterectomy is high in BWHS. The large numbers of incident breast cancer cases, cancer deaths, and total deaths provide for a statistically powerful evaluation of the proposed hypotheses. The numbers of incident cases of colorectal cancer and lung cancer will allow for sufficient power to detect relative risks that might be expected based on limited epidemiologic data for oophorectomy and hysterectomy that occurred under age 45 years. Thus, the present study is well suited to facilitate the successful accomplishment of the study aims.

1. Project Director / Principal Investigator (PD/PI)

Prefix: * First Name:
 Middle Name:
 * Last Name:
 Suffix:

2. Human Subjects

Clinical Trial? No Yes
 * Agency-Defined Phase III Clinical Trial? No Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix: * First Name:
 Middle Name:
 * Last Name:
 Suffix:
 * Phone Number: Fax Number:
 Email:

* Title:
 * Street 1:
 * City:
 County/Parish:
 * State:
 * Country: *Zip/Postal Code:

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells?

No Yes

PHS 398 Research Plan**1. Application Type:**

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:

New Resubmission Renewal Continuation Revision

SPECIFIC AIMS

(Please note: the bibliography with the references listed throughout this section in the original grant application was omitted in order to decrease the file size.)

Hysterectomy is one of the most common surgical procedures in the U.S., and half of women also undergo prophylactic bilateral oophorectomy at the time of hysterectomy. African American women are much more likely than white women to undergo gynecologic surgery, particularly at younger ages. Bilateral oophorectomy results in abrupt loss of ovarian function, and evidence suggests that hysterectomy may lead to impaired ovarian function. The effect of premature loss of ovarian hormones on long-term health is not well understood. Based on limited epidemiologic data, bilateral oophorectomy has been associated with a reduced risk of breast cancer but an increased risk of colorectal cancer, lung cancer, cancer mortality, and all-cause mortality. The effect of hysterectomy with retention of one or both ovaries on long-term health outcomes is less clear. None of the few studies to date on the relation of oophorectomy and hysterectomy to cancer outcomes has reported separately on African American women. In view of the high occurrence of hysterectomy and oophorectomy among African American women, it is important to study the long-term health effects of these exposures in this population of women.

With data from the Black Women's Health Study, an ongoing cohort study of 59,000 African American women from all regions of the U.S. aged 21-69 years at enrollment in 1995, we propose to assess the relation of bilateral oophorectomy and hysterectomy to incidence of the most common cancers in women (breast, colorectal, and lung) and to cancer mortality and all-cause mortality in African American women. This will be the first study to examine these hypotheses among African American women. We propose the following specific aims:

- 1A** Investigate the relation of hysterectomy with removal of both ovaries to incidence of common cancers (breast, colorectal, and lung), cancer mortality, and all-cause mortality. We hypothesize that:
 - 1A.1. Bilateral oophorectomy is associated with *reduced* risk of breast cancer.
 - 1A.2. Bilateral oophorectomy is associated with *increased* risk of colorectal cancer.
 - 1A.3. Bilateral oophorectomy is associated with *increased* risk of lung cancer.
 - 1A.4. Bilateral oophorectomy is associated with *increased* risk of cancer mortality.
 - 1A.5. Bilateral oophorectomy is associated with *increased* risk of all-cause mortality.
- 1B** We hypothesize that associations are more pronounced for women who underwent bilateral oophorectomy earlier in life (age < 40 years).
- 1C** We hypothesize that associations are stronger for women with a history of bilateral oophorectomy who had never used menopausal hormones.

- 2A** Investigate the relation of hysterectomy with retention of one or both ovaries to incidence of common cancers (breast, colorectal, and lung), cancer mortality, and all-cause mortality. We hypothesize that:
 - 2A.1. Hysterectomy is associated with *reduced* risk of breast cancer.
 - 2A.2. Hysterectomy is associated with *increased* risk of colorectal cancer.
 - 2A.3. Hysterectomy is associated with *increased* risk of lung cancer.
 - 2A.4. Hysterectomy is associated with *increased* risk of cancer mortality.
 - 2A.5. Hysterectomy is associated with *increased* risk of all-cause mortality.
- 2B** We hypothesize that associations are more pronounced for women who underwent hysterectomy earlier in life (age < 40 years).
- 2C** We hypothesize that associations are stronger for women with a history of hysterectomy who had never used menopausal hormones.

Impact

The proposed study will provide much needed information on the long-term effects of bilateral oophorectomy and hysterectomy on risk of common cancers, cancer mortality, and all-cause mortality in African American women. Especially given the concern about the overuse of hysterectomy and oophorectomy, the results from the proposed study will help to inform clinical practice and potentially lower the rates of inappropriate use of these elective surgeries.

RESEARCH STRATEGY

SIGNIFICANCE

Hysterectomy is one of the most common surgical procedures in the U.S., with an estimated one-third of women having had a hysterectomy by age 60 years.¹ About 600,000 U.S. women undergo hysterectomy each year, and about half of these women also undergo bilateral oophorectomy.² Bilateral oophorectomy is commonly offered to women who are having a hysterectomy after age 40 years to reduce the risk of ovarian cancer.³ Clinical guidelines now recommend against bilateral oophorectomy for premenopausal women with average risk of ovarian cancer.⁴

There is concern about overuse of hysterectomy, with many hysterectomies not meeting recommendations based on clinical guidelines.⁵ In addition, there are racial differences in the use of these surgeries. The prevalence of hysterectomy for benign disease has been reported to be two to four times higher in African American women relative to white women.^{6,7} One large study observed a 65% higher prevalence of hysterectomy among African American women, even after adjustment for risk factors including fibroids.⁶ The average age at hysterectomy is also lower for African American women than white women for all indications.⁸ Furthermore, the prevalence of elective bilateral oophorectomy at the time of hysterectomy is higher in women with low socioeconomic status among both African American and white women.⁹ Data from the Black Women's Health Study indicate a higher prevalence of hysterectomy and bilateral oophorectomy among African American women than in the overall U.S. population: in 2007, 47% of women in the BWHS had had a hysterectomy by age 60 years; among those women, 52% had had a bilateral oophorectomy, and 49% of those occurred before age 40 years. In addition, as in other studies, the prevalence of hysterectomy was higher among women with lower socioeconomic status.¹⁰

Bilateral oophorectomy results in abrupt loss of ovarian function, and the effect of premature loss of ovarian hormones on long-term health is not well understood.^{11,12} There are questions regarding the risks and benefits of prophylactic bilateral oophorectomy for women at average risk of ovarian cancer, with increasing concern that the decreases in risk of ovarian and breast cancers do not outweigh the potential increases in risk of cardiovascular disease, bone fractures, and cognitive impairment.¹¹⁻¹⁴ There is some evidence that premenopausal hysterectomy may lead to impaired ovarian function,¹⁵ and hysterectomy has been associated with earlier onset of menopause.^{16,17} However, the effect of hysterectomy without bilateral oophorectomy on long-term health outcomes is unclear.

With regard to breast cancer, bilateral oophorectomy has been associated with a 20-30% reduction in risk.¹⁸⁻²⁰ It is unclear whether this is the case for hysterectomy when one or both ovaries are retained. Few studies have separately assessed bilateral oophorectomy and hysterectomy with risk of breast cancer. Two studies observed a reduced risk for bilateral oophorectomy and not for hysterectomy,^{21,22} whereas three studies found a lower risk for both surgeries, with a 13-30% decrease in risk for hysterectomy.^{18,19,23} A 34-50% reduction in breast cancer risk was observed for bilateral oophorectomy at younger ages (under age 40 years¹⁸ or under age 45 years^{20,21,23}). In a study in which there was a 20% reduction in overall risk for bilateral oophorectomy, among women who had never used menopausal hormones the reduction was 40%.¹⁸

Little is known regarding the relation of hysterectomy and oophorectomy to the incidence of non-reproductive cancers. Several studies suggest a role for female hormones in the occurrence of colorectal cancer and lung cancer. Specifically, later age at menopause²⁴ and use of exogenous hormones^{25,26} have been associated with decreased colorectal cancer risk, and later age at menopause has also been associated with decreased lung cancer risk.²⁷⁻²⁹ Few studies have specifically investigated the relation of oophorectomy or hysterectomy to risk of these cancers. Three studies reported increases in colorectal cancer risk associated with bilateral oophorectomy^{20,30} or hysterectomy,^{30,31} with increases of 15-40%. Stronger associations were observed for women who had gynecologic surgery before age 45 years, with relative risks ranging from 1.36 to 2.19.^{20,30,31} Three studies found bilateral oophorectomy^{20,29} or hysterectomy³¹ to be associated with lung cancer risk, with increases ranging from 20-77%. In a study that observed a 20% increase in lung cancer risk for hysterectomy, risk was 73% higher for women with a hysterectomy before age 45 years.³¹ In a study that reported a relative risk of 1.26 for overall lung cancer risk associated with bilateral oophorectomy, the relative risk was 2.09 among women who had never used menopausal hormones.²⁰

Bilateral oophorectomy has been associated with increased risk of all-cause mortality in two recent studies.^{20,32} One study reported a significant 67% increase in all-cause mortality for bilateral oophorectomy that occurred before age 45 years,³² and another study observed a significant 12% increase in all-cause mortality among all women.²⁰ Each study also reported increases in both cancer and non-cancer mortality.^{20, 32}

A nonsignificant 45% increase in cancer mortality was observed in the former study for bilateral oophorectomy before age 45 years, with a 127% increased risk for the women who had never used menopausal hormones until age 45 years.³² The latter study reported a significant 17% increase in cancer mortality, with no stronger association for bilateral oophorectomy before age 45 years or for women who had never used menopausal hormones.²⁰ Whether hysterectomy without bilateral oophorectomy influences mortality has not been assessed.

The use of different reference groups in previous studies of bilateral oophorectomy in relation to various health outcomes has made it difficult to compare results. For instance, one of the aforementioned all-cause mortality studies compared women with a bilateral oophorectomy with women who had never had an oophorectomy,³² whereas the other all-cause mortality study restricted the analysis to women with a hysterectomy and assessed bilateral oophorectomy relative to hysterectomy with ovarian conservation.²⁰ In the proposed study, we will carry out separate analyses with each comparison group, as each answers a different question.

The few studies to date on the relation of hysterectomy and oophorectomy to cancer incidence and mortality have been conducted in populations that were predominantly white, and none has reported separately on these associations among African American women. In view of evidence that African American women are more likely than white women to undergo gynecologic surgery, particularly at younger ages, it is important to study the long-term health effects of these exposures in this population of women.

The proposed study will provide much needed information on the long-term effects of bilateral oophorectomy and hysterectomy on risk of common cancers, cancer mortality, and all-cause mortality in African American women. Especially given the concern about the overuse of hysterectomy and oophorectomy, the results from the proposed study will provide information to help guide clinical practice and potentially lower the rates of inappropriate use of these elective surgeries. Findings from our study will help clinicians and patients to make more informed decisions regarding the choice of these procedures.

INNOVATION

This will be the first study to assess the relation of bilateral oophorectomy and hysterectomy to risk of the most common cancers in women (breast, colorectal, and lung) and to cancer mortality and all-cause mortality in African American women, a population with a high prevalence of these surgeries. Of the women in our study population who have had gynecologic surgery, a large proportion had a bilateral oophorectomy or hysterectomy before age 40 years, and therefore we will be able to examine the effects of these surgeries at particularly young ages.

APPROACH

Overview. Using data collected from 1995 through 2011 in the Black Women's Health Study (BWHS), an ongoing cohort study of 59,000 African American women, we propose to prospectively examine the relation of bilateral oophorectomy and hysterectomy with retention of one or both ovaries to risk of common cancers (breast, colorectal, and lung) and to cancer mortality and all-cause mortality.

Preliminary Studies

Cohort establishment of the BWHS. The Black Women's Health Study is an ongoing prospective follow-up study of African American women in the U.S. The study was established in 1995 when women from across the U.S. were enrolled through postal questionnaires.³³ The baseline questionnaire collected information on demographic characteristics, lifestyle factors, and medical history. A total of about 59,000 women aged 21 to 69 years in 1995 (median age, 38 years) whose addresses were judged to be valid have been followed through mailed questionnaires every two years. Biennial follow-up questionnaires update exposure information and identify incident cancers and other illnesses (Appendix). Follow-up of the baseline cohort (i.e., the proportion of the baseline cohort who completed a questionnaire or is known to be deceased) has exceeded 80% in each follow-up cycle and was 81% in 2007. Respondents to the 2007 questionnaire were more educated than nonrespondents but were similar with respect to other baseline characteristics, including important risk factors for breast cancer, colorectal cancer, and lung cancer. Follow-up for the 2009-2010 questionnaire cycle is ongoing.

Correlates of hysterectomy in the BWHS. In a study of correlates of hysterectomy in the BWHS, the prevalence of hysterectomy at baseline in 1995 increased from 2% among women aged 30-34 years to 39% among women aged 45-49 years.¹⁰ Among women with hysterectomies, about 30% had reported a bilateral oophorectomy and 15% had had only one ovary removed. Hysterectomy rates were highest in the South and lowest in the Northeast, and women with the least education were the most likely to have had a hysterectomy. The differences in the prevalence of hysterectomy were not explained by differences in the prevalence of uterine fibroids and endometriosis.

Correlates of postmenopausal hormone use in the BWHS. In a study of postmenopausal women in the BWHS, the strongest correlate of use of menopausal hormones was type of menopause.³⁴ The prevalence of ever use and current use of menopausal hormones was highest among women with a bilateral oophorectomy, intermediate among women with a hysterectomy alone, and lowest among women with a natural menopause.

Risk factors for breast cancer and mortality in the BWHS. Many risk factors have been examined in relation to breast cancer in the BWHS, including parity,³⁵ menopausal hormone use,³⁶ oral contraceptive use,³⁷ body size and obesity,³⁸ family history of cancer,³⁹ hair relaxer use,⁴⁰ experiences of perceived racism,⁴¹ dietary patterns,⁴² fruit and vegetable intake,⁴³ height,⁴⁴ induced abortion,⁴⁵ and physical activity.⁴⁶ Experiences of perceived racism have also been investigated in relation to all-cause mortality in the BWHS.⁴⁷

Research Design and Methods

Study population. The data to be used in the proposed study will be derived from the Black Women's Health Study. This ongoing follow-up study of 59,000 U.S. black women, in progress for 15 years, has collected the needed information on hysterectomy, oophorectomy, incident cancer, mortality, and covariates, and has published extensively on risk factors for breast cancer.³⁵⁻⁴⁶ The BWHS cohort is currently funded by

Table 1. Baseline demographic characteristics among 57,542 participants in the BWHS, 1995

Age, years	%	Geographic region	%
<30	22	Northeast	27
30-39	34	South	31
40-49	28	Midwest	23
≥50	16	West	19

the NCI through 2014. The analytic cohort will be restricted to 57,542 participants without a history of cancer at baseline and will include follow-up through 2011. Baseline demographic characteristics of the study participants are shown in Table 1. Over half (56%) of participants were under age 40 years at baseline. Participants reside in all regions of the U.S.

Assessment of hysterectomy and oophorectomy. Menopausal status and age at menopause were obtained at baseline and have been updated on each biennial follow-up questionnaire. On each questionnaire, women were asked about the type of menopause, whether natural, due to surgery, or due to medication, chemotherapy, or radiation. Women were also asked if they had both ovaries removed, only one ovary removed, or removal of the uterus without removal of ovaries. There is evidence that hysterectomy and oophorectomy are reported accurately.⁴⁸⁻⁵⁰

We assessed the reliability of self-report of gynecologic surgery on the 1997 questionnaire using data from 1,148 participants who inadvertently completed and returned two questionnaires during the follow-up cycle; the kappa coefficient was 0.91, indicating very high reproducibility in the reporting of whether a woman had had a bilateral oophorectomy, unilateral oophorectomy, or hysterectomy alone.

Table 2 shows the distribution of menopausal status and history of hysterectomy and oophorectomy in 1995, 2001, and 2007. The prevalence of bilateral oophorectomy and hysterectomy with retention of one or both ovaries was 8% and 10%, respectively, in 1995, and increased to 13% and 15%, respectively, in 2007.

Table 2. Distribution of menopausal status and history of hysterectomy and oophorectomy

	1995 (%)	2001 (%)	2007 (%)
Premenopausal	74	59	45
Natural menopause	8	14	23
Bilateral oophorectomy	8	11	13
Unilateral oophorectomy	2	3	4
Hysterectomy alone	8	10	11
Other or unknown status*	<1	3	4

*Includes women with menopause due to chemotherapy/radiation, unknown status due to use of hormones, and missing data.

Age at hysterectomy (N = 5,380)	%	Age at bilateral oophorectomy (N = 4,415)	%
<35	33	<35	26
35-39	34	35-39	23
40-44	23	40-44	25
≥45	10	≥45	26

Among women with a history of gynecologic surgery at baseline, the distribution of age at hysterectomy and bilateral oophorectomy is presented in Table 3. Of women who had had a hysterectomy with retention of one or both ovaries, 67% had undergone the surgery before age 40 years, whereas 49% of women with a bilateral oophorectomy had undergone the procedure before age 40.

Assessment of potential confounders. Information on education, age at menarche, weight at age 18, and height was obtained at baseline in 1995. Data on current weight, vigorous physical activity, smoking status, alcohol intake, parity, age at first birth, oral contraceptive use, and menopausal hormone use were obtained at baseline and have been updated on biennial follow-up questionnaires. Self-reported height and weight were highly correlated with measured values in a validation study.⁵¹ A validation study of self-reported physical activity also found significant correlations of questionnaire responses with 7-day actigraph measures and physical activity diaries.⁵¹ First-degree family history of breast cancer was asked on the 1995 questionnaire, and family history of breast, lung, colorectal, prostate, and ovarian cancer was asked on the 1999 questionnaire. The 1997 questionnaire included questions on exposure to the smoke of others at various ages. The 2003 questionnaire had questions about household income. The 2009 questionnaire asked about the educational attainment of parents of BWHS participants and home ownership across the lifespan.

Case ascertainment. Incident cases of cancer are ascertained through self-report on biennial follow-up questionnaires. We ask all women who report incident cancer for written permission to review their medical records; we also obtain information on cancer diagnoses from state cancer registries. To date, we have obtained medical record or cancer registry data for 85%, 78%, and 78% of breast, colorectal, and lung cancer cases, respectively. Of these, 99%, 94%, and 96% of breast, colorectal, and lung cancer cases, respectively, have been confirmed. Obtainment of medical records and registry data is ongoing.

During follow-up from 1995-2009, a total of 1,660 incident cases of breast cancer, 320 colorectal cancer cases, and 310 lung cancer cases have been reported. On the 2011 questionnaire, we expect an additional 265 breast, 50 colorectal, and 50 lung cancers to be reported. Therefore, we expect that 1,925 breast cancer cases, 370 colorectal cancer cases, and 360 lung cancer cases will contribute to analyses with follow-up through 2011. We will exclude cases disconfirmed by medical records or cancer registry data.

We learn about deaths from family members, the U.S. Postal Service, and searches of the National Death Index (NDI). We then obtain death certificate data and coded causes of death. Through 2007, we have identified 2,025 deaths with information on coded cause of death, including 715 deaths with cancer as the underlying cause. We are in the process of obtaining 2008 deaths through NDI; 2009 deaths are expected to be available from NDI in Spring 2011. By Year 2 of the proposed study, we expect to identify an additional 400 deaths, including 140 cancer deaths, through the end of 2010. Therefore, we expect that 2,425 total deaths and 855 cancer deaths will contribute to analyses with follow-up through 2010.

Statistical analysis. We will first assess potential confounders by examining the association of cancer risk factors with bilateral oophorectomy and hysterectomy. We will then conduct separate analyses for bilateral oophorectomy and hysterectomy in relation to each outcome: breast cancer, colorectal cancer, lung cancer, cancer mortality, and all-cause mortality. Participants will contribute person-years from the beginning of follow-up in 1995 until diagnosis of cancer (for incident cancer analyses only), death, loss to follow-up, or end of follow-up in 2011, whichever occurs first. Cox proportional hazards models, jointly stratified by age in one-year intervals and by questionnaire cycle, will be used to estimate incidence rate ratios (IRR) and 95% confidence intervals for risk of cancer or mortality in relation to bilateral oophorectomy and hysterectomy status. Multivariable models will be adjusted for covariates that may include age at menarche, body mass index at age 18, family history of the cancer under study, education, geographic region, parity, age at first birth, oral contraceptive use, vigorous activity, cigarette smoking (active and passive), and alcohol intake. Oophorectomy and hysterectomy status and covariate information will be updated throughout follow-up in a time-dependent manner.

Relation of bilateral oophorectomy to cancer incidence and mortality. We will conduct two separate analyses for the relation of bilateral oophorectomy to cancer incidence and mortality, using a different reference group in each analysis: 1) women who have never had gynecologic surgery, and 2) women who have had a hysterectomy with retention of one or both ovaries.

The first analysis will estimate the IRRs for bilateral oophorectomy compared with women who have never had gynecologic surgery (i.e., women who are premenopausal or naturally postmenopausal). Women with a history of hysterectomy with retention of one or both ovaries will be excluded from the analysis. Bilateral oophorectomy and hysterectomy status will be updated as a time-varying exposure. Therefore, women who are premenopausal at baseline and report a bilateral oophorectomy during follow-up will be considered "exposed" at the date of oophorectomy, whereas initially premenopausal women who report a hysterectomy with retention of one or both ovaries will be censored at the date of hysterectomy. Women who are naturally postmenopausal and report a subsequent hysterectomy or oophorectomy during follow-up will be censored at the date of the reported surgery.

In order to estimate IRRs for bilateral oophorectomy that are independent of risk associated with hysterectomy, a separate analysis will be restricted to women with a bilateral oophorectomy or hysterectomy with retention of one or both ovaries (prior to natural menopause). Bilateral oophorectomy and hysterectomy status will be updated as a time-dependent variable. Women who are premenopausal at baseline will enter the analysis at the date of hysterectomy or bilateral oophorectomy. IRRs of cancer incidence and mortality will be estimated for bilateral oophorectomy relative to hysterectomy with retention of one or both ovaries.

We will also assess cancer incidence and mortality associated with age at bilateral oophorectomy. We will estimate IRRs for categories of age at bilateral oophorectomy (<35, 35-39, 40-44, and ≥ 45 years) compared with each reference category in the two separate analyses described above. We will calculate tests for trend by modeling the median of each age category as a continuous variable.

In addition, we will assess whether risk of cancer and mortality differs according to use of menopausal female hormones. To do so, we will stratify analyses by menopausal hormone use and estimate IRRs separately among women who have ever used menopausal hormones and among women who have never used menopausal hormones. In further analyses, we will use interaction terms in the Cox models to assess if the associations of bilateral oophorectomy with cancer risk or mortality differ according to hormone use.

Relation of hysterectomy to cancer incidence and mortality. IRRs will be calculated for cancer incidence and mortality in relation to hysterectomy with retention of one or both ovaries compared with a reference category of women who have never had gynecologic surgery (i.e., women who are premenopausal or naturally postmenopausal). Women with a history of bilateral oophorectomy will be excluded from the analysis. Hysterectomy status will be updated as a time-varying exposure, such that women who are premenopausal at baseline and report a hysterectomy without bilateral oophorectomy during follow-up will be classified as exposed at the date of hysterectomy, whereas initially premenopausal women who report a bilateral oophorectomy will be censored at the date of oophorectomy. Women who are naturally postmenopausal and report a subsequent hysterectomy or oophorectomy during follow-up will be censored at the date of the reported surgery.

Cancer incidence, cancer mortality, and all-cause mortality may differ between women with a unilateral oophorectomy and women with a hysterectomy alone. Therefore, we will also conduct a secondary analysis that excludes women with a unilateral hysterectomy in order to estimate IRRs for hysterectomy with retention of both ovaries relative to no hysterectomy.

Similar to the subgroup analyses of bilateral oophorectomy described above, we will also assess IRRs for age at hysterectomy (<35, 35-39, 40-44, and ≥ 45 years) and IRRs separately among women who have ever used menopausal hormones and those who have never used them.

Statistical power. In Table 4, we show the minimum relative risk detectable with 80% power for exposure frequencies of 10% and 15%. The prevalence of bilateral oophorectomy and hysterectomy with retention of one or both ovaries was 8% and 10%, respectively, in 1995, and increase over follow-up to 13% and 15%, respectively, in 2007. For an exposure prevalence of 10%, power will be 80% or greater to detect IRRs of 0.8 for breast cancer risk, 1.6 for colorectal cancer risk, 1.6 for lung cancer risk, 1.3 for cancer mortality, and 1.2 for all-cause mortality. The study has adequate power to detect relative risks for breast cancer risk, cancer mortality, and all-cause mortality that are similar in magnitude to those of previous studies.

Table 4. Minimum detectable RRs with 80% power, two-sided $\alpha = 0.05$, by exposure prevalence

Exposure prevalence	Breast cancer (n=1,925)	Colorectal cancer (n=370)	Lung cancer (n=360)	Cancer mortality (n=855)	All-cause mortality (n=2,425)
0.10	0.8	1.6	1.6	1.3	1.2
0.15	0.8	1.4	1.4	1.3	1.2

Some previous studies found stronger associations for bilateral oophorectomy and hysterectomy for women who had the surgery under age 45 years. Among women in the BWHS with a history of gynecologic surgery at baseline, 74% and 90% had their bilateral

oophorectomy or hysterectomy, respectively, before age 45 years; therefore, the prevalence of bilateral oophorectomy and hysterectomy that occurred before age 45 years was 6% and 9%, respectively, at baseline. For an exposure prevalence of 6%, power will be 80% or greater to detect an IRR of 1.8 for both colorectal cancer and lung cancer. For bilateral oophorectomy before age 45 years, previous studies reported IRRs ranging from 1.36 to 2.19 for colorectal cancer and from 1.21 to 1.73 for lung cancer. Thus, the study has adequate power to detect relative risks towards the upper end of the range that might be expected based on the few prior studies of colorectal cancer and lung cancer.

Strengths of the proposed study. The proposed study is unique in being the first study of the association of bilateral oophorectomy and hysterectomy with cancer incidence and mortality in African American women. The population of African American women that comprises BWHS is large and 16 years of follow-up will be available to the study. It has a prospective design, with baseline data on prior gynecologic surgery obtained in 1995 and updated every two years. The prevalence of hysterectomy and bilateral oophorectomy, particularly before age 40 years, is high. Extensive data on demographics, reproductive history, lifestyle factors, and other exposures are available to control for confounding. The availability of data from this unique cohort makes it possible to accomplish the study aims in a timely and cost-effective manner.

Potential problems and alternative strategies. We have modest power to detect small associations of oophorectomy or hysterectomy with colorectal and lung cancer risk. However, prior studies reported stronger associations for colorectal cancer and lung cancer risk with bilateral oophorectomy and hysterectomy that occurred before age 45 years. Most of the women in our study who have had a hysterectomy or oophorectomy underwent these surgeries before age 45 years, and therefore we should have sufficient power to detect a relative risk of 1.8, which is in or near the range of relative risks reported in the previous studies.

Our analyses of hysterectomy will include women with retention of both ovaries as well as women with a unilateral oophorectomy. Among women who had a hysterectomy with retention of one or both ovaries, about 20% had had a unilateral oophorectomy. Given that cancer risk, cancer mortality, and all-cause mortality may differ between women with a unilateral oophorectomy and women with a hysterectomy alone, we will conduct a secondary analysis that excludes history of unilateral oophorectomy in order to estimate IRRs for hysterectomy with retention of both ovaries relative to no hysterectomy.

Most (97%) BWHS participants have completed high school or a higher level of education. Among the African American female population from the same birth cohorts, 83% have at least a high school education.⁵² Therefore, women with less than a high school education are underrepresented in the BWHS. However, the results from this study should be applicable to most African American women, and possibly to other women, because it is plausible that the same underlying mechanism for the associations between the proposed exposures of interest and cancer outcomes would be at work in all these groups.

Timeline

Year 1: Perform quality control of exposure variables for history of hysterectomy and oophorectomy. Finalize case files following medical record review for new cases of breast, colorectal, and lung cancer. Begin analyses of hysterectomy and oophorectomy in relation to cancer incidence and mortality.

Year 2: Conduct linkages with National Death Index to ascertain confirmed causes of death for deaths occurring in 2009 and 2010, and finalize case file for total deaths and cancer deaths. Complete analyses of hysterectomy and oophorectomy in relation to cancer incidence and mortality. Manuscript preparation.

PROTECTION OF HUMAN SUBJECTS

Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

No new subjects will be recruited for this prospective study of the relation of hysterectomy and oophorectomy to risks of incident cancer and cancer mortality. The participants in the present study will be drawn from the approximately 59,000 women enrolled in the BWHS, a follow-up study of African American women. These are free-living U.S. black women who were 21-69 years of age at the start of the study in 1995 and who accepted an invitation to participate in a long-term study of the health of African American women. The participants indicated their consent to participate by completing a 14-page baseline health questionnaire at entry in 1995 and by completion of follow-up questionnaires. The analytic cohort for the proposed analysis will include women at risk of incident cancer at baseline in 1995 (n≈57,542).

b. Sources of Materials

Information from the various health questionnaires that the women have completed will be used in the analyses. BWHS data are maintained within a large database on the dedicated BWHS server. Access to BWHS data is limited to BWHS staff, who must log into their workstations using a Boston University login name and Kerberos password. Each workstation is protected by a software firewall. Other data to be used in the study include information from medical records and the National Death Index.

c. Potential Risks

There is a theoretical risk of breach of confidentiality. However, the data supplied by the participants, identified by ID number only, are stored in computer files that are protected by a series of passwords known only to staff working on the BWHS. The data are stored separately from identifiers needed for follow-up. We have obtained a federal Certificate of Confidentiality to further protect the data. All analyses will be of anonymous data.

Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

Subjects for the proposed study will come from the BWHS cohort and no new subjects will be recruited for this study. Participants in BWHS indicate their informed consent by completing the questionnaires. Participants who report a cancer diagnosis are asked to sign written informed consents to allow access to the portions of their medical records concerning these diagnoses.

b. Protections against Risk

As noted above, the data will be protected against breach of confidentiality. The computerized data are protected by a series of passwords. Only anonymous data are analyzed. We have never had a breach of confidentiality.

Potential Benefits of the Proposed Research to Human Subjects and Others

Results of this study will not directly benefit study participants. The study will provide information on the risk of common cancers, cancer mortality, and overall mortality among women who have had bilateral oophorectomy or hysterectomy. The results will also inform decisions made by clinicians and patients regarding the risks and benefits of undergoing these surgeries.

Importance of Knowledge to be Gained

The hypothesis to be addressed in the proposed study is of public health importance, given the high prevalence of hysterectomy and oophorectomy. The proposed study will provide information on the risks with respect to cancer incidence and mortality of bilateral oophorectomy and hysterectomy and will help clinicians and patients make more informed decisions regarding the decision to undergo these surgeries. The potential benefit of the proposed study far outweighs any potential risks.

INCLUSION OF WOMEN AND MINORITES

All participants will be women since they will be drawn from the BWHS, a study confined to women. All the participants will be African American. In 1995, potential participants were invited to enroll in the Black Women's Health Study, the purpose of which was to learn about causes and preventives of disease in African American women. In 1997, participants were asked their race, and 99.6% marked the category "black". The 0.4% who were not black have been excluded. Approximately 1.8% also identified themselves as of Hispanic origin.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Bilateral oophorectomy and cancer risk and mortality in African American women

Total Planned Enrollment: 57,542

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Females	Males	Total
Hispanic or Latino	1,036		1,036
Not Hispanic or Latino	56,506		56,506
Ethnic Category: Total of All Subjects *	57,542		57,542

Racial Categories	Females	Males	Total
American Indian/Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American	57,542		57,542
White			
Racial Categories: Total of All Subjects *	57,542		57,542

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

INCLUSION OF CHILDREN

Because the BWHS enrolled adults (women aged 21-69 years in 1995), all of the participants in the present study will be adults.