REI R03

PI:	Title: A Prospective Study of Diet and Fibroids in Black Women	
Received: 05/22/2006	FOA: PA06-180	Council: 01/2007
	FOA Title: NIH SMALL RESEARCH GRANT PROGRAM (PARENT R03)	
R03 R03	Dual: AA	Accession Number: 2930174
IPF: 894901	Organization:	
Former Number:	Department:	
IRG/SRG: CHHD-R	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 50,000 Year 2: 50,000	Animals: N Humans: Y Clinical Trial: N Exemption: 20 HESC: N	New Investigator: Y

Senior/Key Personnel:	*Organization:*	*Role Category:*

424 R&R and PHS-398 Specific
Table Of Contents

	Page Numbers
SF 424 R&R Face Page	1
Table of Contents	3
Research & Related Project/Performance Site Location(s)	4
Research & Related Other Project Information	5
Project Summary/Abstract (Description)	6
Public Health Relevance Statement (Narrative attachment)	7
Bibliography & References Cited	8
Facilities & Other Resources	16
Equipment	18
Research & Related Senior/Key Person	19
Biographical Sketches for each listed Senior/Key Person	21
PHS 398 Specific Cover Page Supplement	35
PHS 398 Specific Modular Budget	37
Personnel Justification	41
PHS 398 Specific Research Plan	42
Specific Aims	44
Significance and Related R&D	45
Preliminary Studies/Phase I Final Report	48
Experimental/Research Design and Methods	51
Human Subjects Sections	56
Protection of Human Subjects	56
Inclusion of Women and Minorities	57
Targeted/Planned Enrollment Table	58
Inclusion of Children	59
Vertebrate Animals	60
Consortium/Contractual Arrangements	61
Resource Sharing Plan (Data Sharing and Model Organism Sharing)	62
PHS 398 Checklist	63

Appendix

Number of Attachments in Appendix: 2

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

2. DATE SUBMITTED	Applicant Identifier
3. DATE RECEIVED BY STATE	State Application Identifier
4. Federal Identifier	

1. * TYPE OF SUBMISSION

○ Pre-application ● Application
○ Changed/Corrected Application

5. APPLICANT INFORMATION

* Legal Name:
* Organizational DUNS:
Department:
Division:
* Street1:
Street2:
* City:
County:
* State:
* ZIP Code:
* Country:

Person to be contacted on matters involving this application
Prefix: * First Name: Middle Name: * Last Name: Suffix:
* Phone Number: Fax Number: Email:

6. * EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)*:

7. * TYPE OF APPLICANT
L: I
Other (Specify):

8. * TYPE OF APPLICATION: ● New
○ Resubmission ○ Renewal ○ Continuation ○ Revision

Small Business Organization Type
○ Women Owned ○ Socially and Economically Disadvantaged

If Revision, mark appropriate box(es).
○ A. Increase Award ○ B. Decrease Award ○ C. Increase Duration
○ D. Decrease Duration ○ E. Other *(specify)*:

9. * NAME OF FEDERAL AGENCY:
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:
TITLE:

* Is this application being submitted to other agencies? ○ Yes ● No
What other Agencies?

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:
A Prospective Study of Diet and Fibroids in Black Women

12. * AREAS AFFECTED BY PROJECT *(cities, counties, states, etc.)*
United States

13. PROPOSED PROJECT:
* Start Date: 04/01/2007
* Ending Date: 03/31/2009

14. CONGRESSIONAL DISTRICTS OF:
a. * Applicant: 08
b. * Project: 8th

15. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr.
* First Name: Lauren
Middle Name: A
* Last Name: Wise
Suffix:
Position/Title: Assistant Professor
* Organization Name: Trustees of Boston University, Boston University Medical Campus
Department: Slone Epidemiology Center
Division:
* Street1: 1010 Commonwealth Avenue
Street2:
* City: Boston
County:
* State: MA
* ZIP Code: 02215
* Country: USA
* Phone Number: (617) 734-6006
Fax Number: (617) 738-5119
* Email: lwise@slone.bu.edu

16. ESTIMATED PROJECT FUNDING

a. * Total Estimated Project Funding	$123,901.89
b. * Total Federal & Non-Federal Funds	$123,901.89
c. * Estimated Program Income	$0.00

17. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

18. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● * I agree

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

19. Authorized Representative

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

* Position/Title: * Organization Name:

Department: Division:

* Street1: Street2:

* City: County: * State: MA * ZIP Code:

* Country:

* Phone Number: Fax Number: * Email:

*** Signature of Authorized Representative** *** Date Signed**

20. Pre-application File Name: Mime Type:

RESEARCH & RELATED Project/Performance Site Location(s)

Project/Performance Site Primary Location

Organization Name:

* Street1:

Street2:

* City:

County:

* State:

* Zip Code:

* Country:

File Name	Mime Type

Additional Location(s)

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? ● Yes ○ No

1.a. If YES to Human Subjects

Is the IRB review Pending? ● Yes ○ No

IRB Approval Date:

Exemption Number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

Human Subject Assurance Number 00000301

2. * Are Vertebrate Animals Used? ○ Yes ● No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

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

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

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5.a. * Does this project involve activities outside the U.S. or partnership with International Collaborators? ○ Yes ● No

5.b. If yes, identify countries:

5.c. Optional Explanation:

6. * Project Summary/Abstract	7237-Abstract.pdf	Mime Type: application/pdf
7. * Project Narrative	1810-Project_Narrative.pdf	Mime Type: application/pdf
8. Bibliography & References Cited	7052-Bibliography_Literature_Cited.pdf	Mime Type: application/pdf
9. Facilities & Other Resources	2762-Facilities.pdf	Mime Type: application/pdf
10. Equipment	8242-Equipment.pdf	Mime Type: application/pdf

DESCRIPTION: See instructions. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the **mission of the agency**). Describe concisely the research design and methods for achieving these goals. Describe the rationale and techniques you will use to pursue these goals.

In addition, in two or three sentences, describe in plain, lay language the relevance of this research to **public** health. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

Uterine leiomyomata (UL), or fibroids, are a major source of gynecologic morbidity among reproductive-aged women and account for 1.2 billion dollars in health care costs each year in the United States. Black women are 2-3 times more likely than white women to be diagnosed with UL and have more severe disease at the time of clinical presentation. Both estrogen and progesterone have been implicated in the development and growth of UL. Using data from the Black Women's Health Study (BWHS), a nationwide prospective follow-up study of 59,000 African-American women, we propose to study dietary risk factors (e.g., fiber and fat intake) that might contribute to the high incidence of clinically relevant UL in black women. We will focus on dietary factors that plausibly have an effect on sex hormone synthesis, metabolism, or bioavailability. We will prospectively investigate the influence of these dietary factors on the incidence of self-reported UL confirmed by ultrasound or surgery. Since the inception of the BWHS in 1995, women have been followed biennially by questionnaire. Food frequency questionnaires were completed by participants in 1995 and 2001. Validation studies in the BWHS have demonstrated high accuracy of self-reported UL (>96%) and satisfactory correlation of the food frequency data with dietary recalls and diaries. During follow-up from 1997-2007, we anticipate that over 6000 incident cases of fibroids confirmed by ultrasound or hysterectomy will be reported. The large number of incident cases will provide high statistical power and allow for informative subgroup analyses, e.g. among women under age 35 (N=2400 cases) among whom misclassification should be minimized. The high incidence of symptomatic UL in black women is a problem of public health importance. Dietary patterns hypothesized to increase risk (e.g., high fat and low fiber intake) are more prevalent in black women than white women. Thus, the proposed study will permit the evaluation of risk factors for clinically relevant UL that may contribute to the excess incidence among black women. The findings have the potential to be useful for primary prevention efforts. The proposed study, by a new investigator who has extensive experience in studying risk factors for UL, can be carried out at low cost because data collection in the BWHS is supported by other grants.

Principal Investigator/Program Director (Last, first, middle):_____

Project Narrative

Uterine leiomyomata (UL), or fibroids, are a major source of gynecologic morbidity among black women and account for 1.2 billion dollars in health care costs each year in the United States. Using data from the Black Women's Health Study (BWHS), a large prospective follow-up study of African-American women, we propose to study dietary risk factors that might contribute to the high incidence of clinically relevant UL in black women. Dietary patterns hypothesized to increase risk (e.g., high fat and low fiber intake) are more prevalent in black women than white women. Thus, the proposed study will permit the evaluation of risk factors for clinically relevant UL that may contribute to the excess incidence among black women.

G. LITERATURE CITED

1.

2.

3.

4.

5.

6.

7.

8.

9.

10.

11.

12.

13.

14.

15.

16.

17.

18.

19.

20.

21.

22.

23.

24.

25.

Principal Investigator/Program Director (Last, first, middle):_____

26.

27.

28.

29.

30.

31.

32.

33.

34.

35.

36.

37.

38.

39.

40.
41.

42.

43.

44.

45.

46.

47.

48.

49.

50.

51.

52.

53.

54.

55.

56.

57.

58.

59.

60.

61.

62.

63.

64.

65.

66.

67.

68.

69.

70.

71.

72.

73.

74.

75.

Principal Investigator/Program Director (Last, first, middle):

76.

77.

78.

79.

80.

81.

82.

83.

84.

85.

86.

87.

88.

89.

90.

91.

92.

93.

94.

95.

96.

97.

98.

99.

100.

101.

102.

103.

104.

105.

106.

107.

108.

109.

110.

111.

112.

113.
114.

115.

116.

117.

118.
119.

120.

121.

122.

123.

124.
125.

126.

Principal Investigator/Program Director (Last, first, middle):

127.

128.

129.

130.

131.

132.

133.

134.

135.

136.

137.

138.

139.

140.

141.

142.

143.

144.

145.

146.
147.

148.

149.

150.

151.

152.

153.

154.

155.

156.

157.

158.

159.

160.

161.

162.

163.

164.
165.

166.

167.

168.

169.

170.
171.

172.
173.

Principal Investigator/Program Director (Last, first, middle):

174.
175.
176.
177.
178.
179.
180.
181.
182.
183.
184.
185.
186.

RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory:

Clinical:

Animal:

Computer:

). The maintains on site its own dedicated Computer Center. (Neither maintains a central computing facility appropriate for our needs.) Staffing includes a Director and nine full-time analysts, each of whom has extensive experience with epidemiological studies, and database applications.

In addition, there are three Systems Administration specialists who provide hardware and software support to the central server facility as well as to all internal and external users. Our Computing System consists of an 100 Base T Ethernet Local Area Network with over 100 PCs and twelve Servers using client-server technology. The servers include a NetWare File Server, nine Windows NT Servers, a SUN Enterprise 250 server, and a SUN SPARC server 10. This configuration provides more than 1 terabyte of data storage. Peripherals include a number of shared printers and slave printers, and 4 high-speed scanners for data input. In addition we have over 30 laptop computers in the field for interviewing, data entry and coding.

Available software includes Microsoft Office with Access as our prime database development tool, Microsoft SQL server, Clipper database software, SIR (Scientific Information Retrieval), as well as SAS and SPSS Statistical Software. Most users work in a Windows 2000 environment and have access to Outlook email. In addition to the capabilities of SPSS and SAS, we have custom statistical software written by our Computer Center staff. The staff creates and maintains on-line custom dictionaries for coding standard variables like drugs, foods, diagnoses, occupation, etc. Our Computer staff has also developed custom programs for data entry, coding, quality control, and downloading the data from the databases.

All patient data, uploaded and downloaded from our network, is encrypted through our virtual private network (VPN), thus ensuring absolute confidentiality. Our backup system is an automated tape library system capable of backing up 12 terabytes of data. All data are backed up 7 days/week automatically. Offsite storage of all data is done weekly. In addition, we have a Cisco Systems Pix firewall, which prevents any unauthorized access, provides for a virtual private network, and provides for encrypted traffic.

Our telephone and internet access is through a series of 4 T1 connections. Approximately 60% of these lines will provide internet access (including Internet 2 - Gigapop), email, data transfers, program transfers to field staff, etc. The remainders are utilized for voice systems.

Since its founding in 1975, the has collected and maintained over 1 million patient interviews comprising demographic information, medical and disease histories, and pharmaceutical usage data in our databases. Information taken directly from hospital records is also included.

Office:

is located off campus and rents 21,250 sq. ft. of office space at , thus allowing access to medical library, etc.).

Principal Investigator/Program Director (Last, first, middle):

Other:

RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

3 Personal computers
4 High speed laser printers
3 Canon copiers
Grant Manager software (for tracking grant-related expenses and generating financial reports)

RESEARCH & RELATED Senior/Key Person Profile

PROFILE - Project Director/Principal Investigator

Prefix | * First Name | Middle Name | * Last Name | Suffix

Position/Title:

Department:

Organization Name:

Division:

* Street1:

Street2:

* City: | County: | * State: | * Zip Code: | * Country:

*Phone Number | Fax Number | * E-Mail

Credential, e.g., agency login:

*** Project Role:** PD/PI

Other Project Role Category:

	File Name	Mime Type
***Attach Biographical Sketch**		application/pdf
Attach Current & Pending Support		

PROFILE - Senior/Key Person 1

Prefix | * First Name | Middle Name | * Last Name | Suffix

Position/Title:

Department:

Organization Name:

Division:

* Street1:

Street2:

* City: | County: | * State: | * Zip Code: | * Country:

*Phone Number | Fax Number | * E-Mail

Credential, e.g., agency login:

*** Project Role:** Co-PD/PI

Other Project Role Category:

	File Name	Mime Type
***Attach Biographical Sketch**		application/pdf
Attach Current & Pending Support		

PROFILE - Senior/Key Person 2

Prefix | * First Name | Middle Name | * Last Name | Suffix

Position/Title: | Department:

Organization Name: | Division:

* Street1: | Street2:

* City: | County: | * State: | * Zip Code: | * Country:

*Phone Number | Fax Number | * E-Mail

Credential, e.g., agency login:

*** Project Role:** Other (Specify) | **Other Project Role Category:** Other significant contributor

	File Name	Mime Type
***Attach Biographical Sketch**		application/pdf
Attach Current & Pending Support		

PROFILE - Senior/Key Person 3

Prefix | * First Name | Middle Name | * Last Name | Suffix

Position/Title: | Department:

Organization Name: | Division:

* Street1: | Street2:

* City: | County: | * State: MA | * Zip Code: | * Country:

*Phone Number | Fax Number | * E-Mail

Credential, e.g., agency login:

*** Project Role:** Other (Specify) | **Other Project Role Category:** Other significant contributor

	File Name	Mime Type
***Attach Biographical Sketch**		application/pdf
Attach Current & Pending Support		

	File Name	Mime Type
ADDITIONAL SENIOR/KEY PERSON PROFILE(S)		
Additional Biographical Sketch(es) (Senior/Key Person)		
Additional Current and Pending Support(s)		

Principal Investigator/Program Director (Last, first, middle):_____ _____

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
eRA COMMONS USER NAME	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY

A. Positions and Honors.

7.

8.

9.

10.

11.

12.

13.

14.

15.

16.

17.

18.

19.

20.

21.

22.

23.

24.

25.

26.

27.

Principal Investigator/Program Director (Last, first, middle):_____ _____

C. Research Support.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
eRA COMMONS USER NAME	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY

A. Positions and Honors.

B. Selected peer-reviewed publications (in chronological order).

8.

9.

10.

11.

12.

13.

14.

15.

16.

17.

18.

19.

20.

21.

22.

23.

24.

25.

26.

27.

28.

29.

30.

C. Research Support.

Ongoing Research Support

Principal Investigator/Program Director (Last, first, middle):

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
eRA COMMONS USER NAME	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY

A. Positions and Honors

Positions

Honors

4.

5.

6.

7.

8.

9.

10.

11.

12.

13.

14.

15.

16.

17.

18.

19.

20.

21.

22.

23.

24.

25.

26.

Principal Investigator/Program Director (Last, first, middle):_____ __

C. Research Support

Ongoing Research Projects

Principal Investigator/Program Director (Last, first, middle):____

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
eRA COMMONS USER NAME	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY

A. Professional Experience:

Positions and Employment

Other Experience and Professional Memberships

Honors

B. Selected Peer-Reviewed Publications

Original Reports (Selected from 38)

1.

2.

3.

4.

5.

6.

7.

8.

9.

10.

11.

12.

13.

14.

15.

16.

17.

18.

19.

20.

21.

22.

Principal Investigator/Program Director (Last, first, middle):_____

23.

24.

25.

26.

27.

28.

29.
30.

31.

32.

33.

34.
35.

Reviews/Chapters (Selected)
36.

37.

Abstracts (Selected)
1.

2.

3.

4.

5.

6.

7.

8.

9.

C. Research Support:

Ongoing Research Support

Completed Research Support

PHS 398 Cover Page Supplement

OMB Number: 0925-0001
Expiration Date: 9/30/2007

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

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

* New Investigator? ○No ●Yes

Degrees:

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:

* Street1:
Street2:
* City:
County:
* State:
* Zip Code
* Country

PHS 398 Cover Page Supplement

OMB Number: 0925-0001
Expiration Date: 9/30/2007

4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells? ●No ○Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/registry/index.asp . Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

PHS 398 Modular Budget, Periods 1 and 2

OMB Number: 0925-0001
Expiration Date: 9/30/2007

Budget Period: 1

Start Date: 04/01/2007 End Date: 03/31/2008

A. Direct Costs

	Funds Requested ($)
* Direct Cost less Consortium F&A	50,000.00
Consortium F&A	
* Total Direct Costs	50,000.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	Facilities and Administration Off-site indirect cost rate	26.00	46,024.80	11,966.45
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date 02/01/2006

Total Indirect Costs 11,966.45

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($) 61,966.45

Budget Period: 2

Start Date: 04/01/2008 End Date: 03/31/2009

A. Direct Costs

	Funds Requested ($)
* Direct Cost less Consortium F&A	50,000.00
Consortium F&A	
* Total Direct Costs	50,000.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	Facilities and Administration Off-site indirect cost rate	26.00	45,905.55	11,935.44
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date 02/01/2006

Total Indirect Costs 11,935.44

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($) 61,935.44

PHS 398 Modular Budget, Periods 3 and 4

OMB Number: 0925-0001
Expiration Date: 9/30/2007

Budget Period: 3

Start Date: ____ End Date: ____

A. Direct Costs

	Funds Requested ($)
* Direct Cost less Consortium F&A	
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date

Total Indirect Costs

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($)

Budget Period: 4

Start Date: ____ End Date: ____

A. Direct Costs

	Funds Requested ($)
* Direct Cost less Consortium F&A	
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date

Total Indirect Costs

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($)

PHS 398 Modular Budget, Period 5 and Cumulative

OMB Number: 0925-0001
Expiration Date: 9/30/2007

Budget Period: 5 Start Date: End Date:

A. Direct Costs

	Funds Requested ($)
* Direct Cost less Consortium F&A	
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date

Total Indirect Costs

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($)

Cumulative Budget Information

1. Total Costs, Entire Project Period

* Section A, Total Direct Cost less Consortium F&A for Entire Project Period	$ 100,000.00
Section A, Total Consortium F&A for Entire Project Period	$
* Section A, Total Direct Costs for Entire Project Period	$ 100,000.00
* Section B, Total Indirect Costs for Entire Project Period	$ 23,901.89
* Section C, Total Direct and Indirect Costs (A+B) for Entire Project Period	$ 123,901.89

2. Budget Justifications

Personnel Justification	5991-Personnel_Justification.pdf
Consortium Justification	
Additional Narrative Justification	

Attachments

PersonnelJustification_attDataGroup0

File Name	Mime Type
5991-Personnel_Justification.pdf	application/pdf

ConsortiumJustification_attDataGroup0

File Name	Mime Type

AdditionalNarrativeJustification_attDataGroup0

File Name	Mime Type

Principal Investigator/Program Director (Last, first, middle):_____

PERSONNEL

CONSULTANTS

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page and PHS398 Checklist. The responses provided on these pages, regarding the type of application being submitted, are repeated for your reference, as you attach the appropriate sections of the research plan.

*Type of Application:

● New ○ Resubmission ○ Renewal ○ Continuation ○ Revision

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application (for RESUBMISSION or REVISION only)	
2. Specific Aims	9747-Specific_Aims.pdf
3. Background and Significance	4813-Background_Significance.pdf
4. Preliminary Studies / Progress Report	9505-Preliminary_Studies.pdf
5. Research Design and Methods	9417-Research_Design_and_Methods.pdf

Human Subjects Sections

Attachments 6-10 apply only when you have answered "yes" to the question "are human subjects involved" on the R&R Other Project Information Form. In this case, attachments 6-10 may be required, and you are encouraged to consult the Application guide instructions and/or the specific Funding Opportunity Announcement to determine which sections must be submitted with this application.

6. Protection of Human Subjects	6906-Protection_of_Human_Subjects.pdf
7. Inclusion of Women and Minorities	t4355-Inclusion_of_Women_and_Minorities.pdf
8. Targeted/Planned Enrollment Table	5588-Targeted_Planned_Enrollment_Table.pdf
9. Inclusion of Children	2117-Inclusion_of_Children.pdf
10. Data and Safety Monitoring Plan	

Other Research Plan Sections

11. Vertebrate Animals	1932-Vertebrate_Animals.pdf
12. Consortium/Contractual Arrangements	1702-Consortium_Contractual_Arrangements.pdf
13. Letters of Support	
14. Resource Sharing Plan(s)	5958-Resource_Sharing_Plan.pdf

15. Appendix

Attachments

IntroductionToApplication_attDataGroup0

File Name	Mime Type

SpecificAims_attDataGroup0

File Name	Mime Type
9747-Specific_Aims.pdf	application/pdf

BackgroundSignificance_attDataGroup0

File Name	Mime Type
4813-Background_Significance.pdf	application/pdf

ProgressReport_attDataGroup0

File Name	Mime Type
9505-Preliminary_Studies.pdf	application/pdf

ResearchDesignMethods_attDataGroup0

File Name	Mime Type
9417-Research_Design_and_Methods.pdf	application/pdf

ProtectionOfHumanSubjects_attDataGroup0

File Name	Mime Type
6906-Protection_of_Human_Subjects.pdf	application/pdf

InclusionOfWomenAndMinorities_attDataGroup0

File Name	Mime Type
4355-Inclusion_of_Women_and_Minorities.pdf	application/pdf

TargetedPlannedEnrollmentTable_attDataGroup0

File Name	Mime Type
5588-Targeted_Planned_Enrollment_Table.pdf	application/pdf

InclusionOfChildren_attDataGroup0

File Name	Mime Type
2117-Inclusion_of_Children.pdf	application/pdf

DataAndSafetyMonitoringPlan_attDataGroup0

File Name	Mime Type

VertebrateAnimals_attDataGroup0

File Name	Mime Type
1932-Vertebrate_Animals.pdf	application/pdf

ConsortiumContractualArrangements_attDataGroup0

File Name	Mime Type
1702-Consortium_Contractual_Arrangements.pdf	application/pdf

LettersOfSupport_attDataGroup0

File Name	Mime Type

ResourceSharingPlans_attDataGroup0

File Name	Mime Type
5958-Resource_Sharing_Plan.pdf	application/pdf

Appendix

File Name	Mime Type
6046-Appendix_2.pdf	application/pdf
3808-Appendix_1.pdf	application/pdf

A. SPECIFIC AIMS

The aim of this proposal is to investigate the effect of hormone-related dietary factors on the risk of clinically relevant uterine leiomyomata (UL), or fibroids, in U.S. black women. UL are 2-3 times more common in black women than white women. UL are associated with considerable gynecologic morbidity. Evidence suggests that the development of UL is influenced by sex hormones. We propose to assess select dietary factors plausibly related to sex hormone synthesis, metabolism, or bioavailability in relation to UL in black women, using data from the Black Women's Health Study (BWHS). We have already assessed several risk factors for UL in this cohort.[1-4] The follow-up of participants and the collection of data are supported by other grants. The present proposal is for the support of analyses of questionnaire data that will test the following hypotheses:

1. High dietary fat intake increases the risk of UL.
2. High dietary fiber intake decreases the risk of UL.
3. A high ratio of fat to fiber intake increases the risk of UL.
4. High intake of fruits and vegetables decreases the risk of UL.
5. High intake of red meat and pork increases the risk of UL.
6. High intake of vitamin C, vitamin A, and carotenoids decreases the risk of UL.
7. Alcohol, body mass index, and hormonal contraception modify the effect of carotenoids on UL risk.

Principal Investigator/Program Director (Last, first, middle):____

B. BACKGROUND AND SIGNIFICANCE

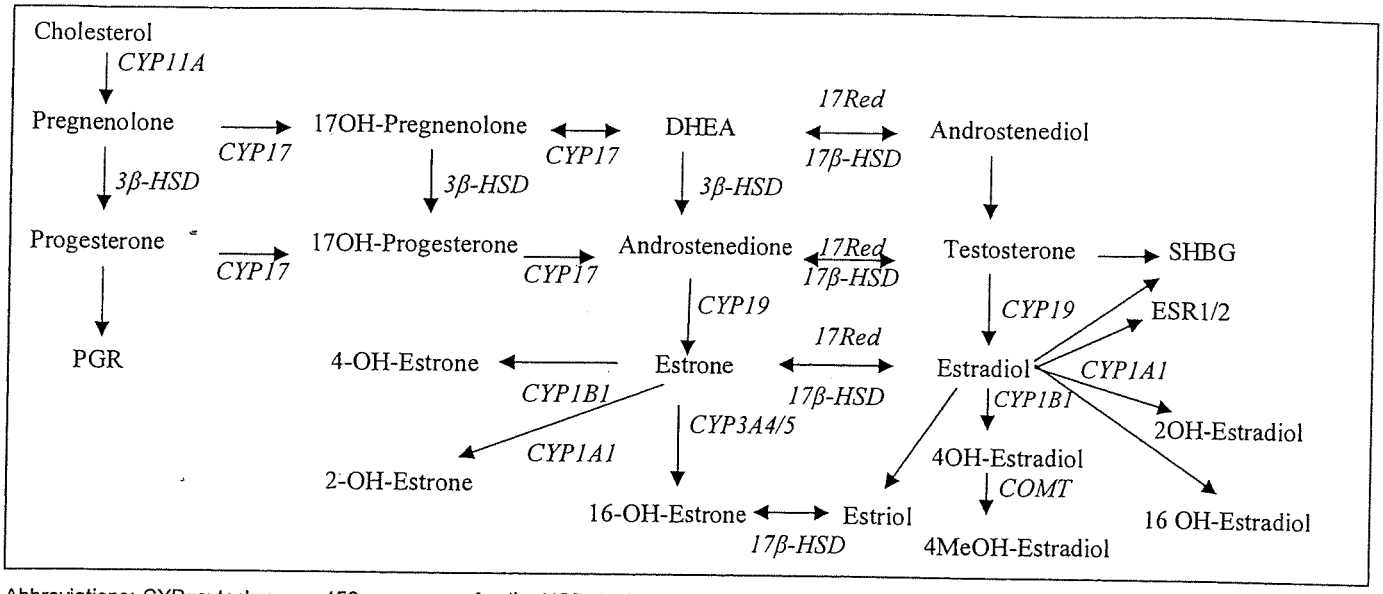
B.1. Epidemiology of uterine leiomyomata. Uterine leiomyomata (UL), or fibroids, are benign neoplasms arising from smooth muscle cells of the myometrium and are clinically recognized in about 25-30% of reproductive-aged women.[5-7] UL are associated with menorrhagia, pelvic pain, and infertility,[6-8] and are the primary indication for hysterectomy.[9, 10] UL account for over 200,000 hysterectomies and more than 1.2 billion dollars in health care costs each year in the United States.[11, 12] Black women are 2 to 3 times more likely to be diagnosed with UL than white women,[9, 13-15] develop the tumors at earlier ages,[15] and have more numerous and symptomatic tumors at the time of diagnosis.[8] Population differences in the prevalence of known risk factors or screening patterns do not satisfactorily explain the black-white difference in rates.[8, 13, 16, 17] Risk factors for UL include premenopausal age,[1, 13-15, 18-24] reproductive history (early age at menarche, decreased parity, infertility, early age at first birth, increased years since last birth),[2, 20, 25-28] hormonal contraception,[18, 20, 23, 26, 27, 29] elevated BMI,[3, 20, 22, 30] hypertension,[31, 32] prenatal exposure to DES (a synthetic estrogen),[33, 34] alcohol,[2, 30, 35] and not smoking.[4, 22, 30] Most of these risk factors are markers of increased endogenous exposure to sex hormones.

B.2. Sex hormones and uterine leiomyomata. The development and growth of UL is thought to depend on the biological activity of endogenous sex steroid hormones—estrogens (estradiol, estrone, estriol) and progesterone[36-38]—and locally derived growth factors.[5, 39-44] The hormone-dependent nature of UL is supported by the following observations: UL do not occur before menarche, UL increase in size during pregnancy when levels of estradiol and progesterone are high, and UL shrink in volume after menopause or with suppression of ovarian function via GnRH agonist therapy or oophorectomy.[45] UL also have an increased concentration of estrogen and progesterone receptors compared with normal myometrium.[46] In a recent study, urinary concentrations of many sex hormones, including 17β-estradiol, were significantly higher among UL cases than controls, and the ratio of 17β-estradiol to estrone was also higher among UL cases.[47] The significant increase in 17β-estradiol may be due to a decrease in steroid metabolism in women with UL,[47] because 17β-estradiol is converted to estrone through oxidation by 17β-hydroxysteroid dehydrogenase (see Figure 1). This mechanism is consistent with findings from a previous study showing *in vitro* conversion of 17β-estradiol to estrone in normal myometrium and leiomyoma.[48] In a study of premenopausal women, blacks had significantly higher plasma levels of estradiol, free estradiol, IGF-1, and significantly lower SHBG levels than whites.[49] Racial differences in hormone and growth factor levels may contribute to the 2- to 3-fold difference in UL rates.

B.3. Sex steroid hormone biosynthesis. Estrogens and progesterone are produced primarily by the ovaries in premenopausal women. Figure 1 illustrates the major steps in the synthesis of estrogens and androgens.[50, 51] Steroid synthesis consists of two general pathways, a pregnenolone pathway and a progesterone pathway. The initial stage is the conversion of cholesterol to pregnenolone. 17β-hydroxysteroid dehydrogenase activity converts androstenedione to testosterone, which is rapidly demethylated and aromatized to estradiol, the most potent of all estrogens. Estradiol also arises from androstenedione via estrogen, and estrone itself is secreted in significant daily amounts. Estriol is the peripheral metabolite of estrone and estradiol, and not a secretory product of the ovary. The formation of estriol is typical of metabolic "detoxification," conversion of biologically active estrogens to less active forms. Free androgens are peripherally converted to free estrogens (e.g., in adipose cells). Thus, circulating estrogens in women are the sum of direct ovarian secretion of estradiol and estrone plus peripheral conversion of C-19 precursors. Progesterone synthesis involves secretion from both the ovaries and adrenal gland. As discussed below, diet can produce variations in sex hormone levels.[52-70]

B.4. Overview of diet in relation to sex hormones. Diet can play an important role in the metabolism, synthesis, and bioavailability of endogenous sex hormones.[52-67] Dietary intervention studies suggest that low-fat diets (10-25% of total calories) significantly reduce plasma estradiol concentrations.[72, 73] Estrone is metabolized through two main pathways: the C-2 hydroxylation pathway and the 16α-hydroxylation pathway (see Figure 1). A shift in estrogen metabolism towards C-2 hydroxylation might protect against UL because C-2 hydroxylation yields less potent catechol estrogens than does 16α-hydroxylation.[74] High fiber intake is associated with an increase in C-2 hydroxylation and a decrease in 16α-hydroxylation.[74] Other studies show that dietary fiber independently decreases sex hormone levels but did not examine the specific metabolic pathways affected.[60, 75, 76] Antioxidants in fruits and vegetables have been shown to influence the hydroxylation of estrogens.[68-70] Links have been found between diet and hormone-dependent diseases, such as breast, prostate, and endometrial cancer,[61, 77, 78] conferring biologic plausibility for an effect of diet on risk of UL.

Figure 1. Biosynthesis of estrogens and progesterone.[50, 51, 71]



Abbreviations: CYP=cytochrome p450 supergene family, HSD=hydroxysteroid dehydrogenase; Red=reductase; PGR=progesterone receptor gene; ESR=estrogen receptor gene; OH=hydroxy; MeOH=methoxy. SHBG=sex hormone binding globulin. Other abbreviations are described in section C.

B.5. Diet in African-Americans. Data from the Third National Health and Nutrition Examination Survey (NHANES III)[79] and the 1994-1996 Continuing Surveys of Food Intakes by Individuals (CSFII)[80] show important differences in dietary intake between U.S. black and white women. Blacks have a lower intake of fruits, vegetables, whole grains, fiber, dairy products,[81] carotenoids,[81] vitamins A and C,[79] folate,[81] iron,[82] and calcium,[81] and a higher intake of meat products and discretionary fats than whites.[79, 81, 82] Moreover, blacks are less likely than whites to take vitamin and mineral supplements.[83] Black women of higher socio-economic status (SES) have a greater intake of whole grains, fruits, vegetables, and dairy products, and a lower intake of meat products, and saturated fat than black women of lower SES.[81] There are also regional differences in diet;[83] e.g., individuals who live in the Northeast consume more fruits and vegetables, and fewer meat products, than those who live in the South.[83] Heterogeneity in intake among U.S. black women makes a study of diet among BWHS participants—a geographically dispersed group with varying levels of SES—worthwhile.[81]

B.6. Previous studies of diet and uterine leiomyomata. In the sole study to examine the role of diet, a case-control study of Italian women,[84] UL risk was positively associated with high intake of beef, other red meat, and ham, and inversely associated with high intake of green vegetables, fruits, and fish. No associations were found for milk, liver, carrots, eggs, cheese, whole-grain foods, butter, margarine, oil, coffee, tea, or alcohol consumption. In this study, dietary data were collected after the diagnosis of UL, thereby introducing potential for recall bias. The study did not obtain quantitative estimates of portion size and could not control for energy intake, an important confounder in nutritional studies.[62] The dietary instrument was not validated. Our proposed study of diet and risk of UL will overcome these limitations.[85]

B.7. Selected dietary factors

B.7.1. Dietary fat. Dietary fat may increase risk of UL by elevating levels of circulating estrogens.[86, 87] In premenopausal women, total fat and saturated fat were positively correlated with plasma estradiol,[87] estrone,[87] and IGF-1[88] levels, and reduced fat intake was associated with a decrease in serum estradiol levels among both premenopausal and postmenopausal women.[65] Diets high in fat have been linked to an increased risk of hormone-dependent cancers, including cancers of the endometrium,[89-95] prostate,[96] and ovary.[97] In our dietary validation study, correlations between the FFQ and 24-hour recall were 0.51 for total fat and 0.63 for saturated fat following energy-adjustment and correction for within-person standard deviation (SD) of recall.[8]

B.7.2. Dietary fiber. Dietary fiber consists of nondigestible polysaccharides, naturally occurring resistant starch and oligosaccharides, and lignins in plants.[98] Fiber may reduce UL risk through increased fecal excretion of estrogens, competition for estrogen-binding sites by phytoestrogens, direction of estrogen

metabolism toward less active forms (e.g., increased C-2 hydroxylation; decreased 16α-hydroxylation),[74] and changes in levels of SHBG, which binds free estrogen (see Figure 1).[99] Three studies found that fiber independently decreased endogenous hormone levels.[60, 75, 76] Fiber intake can be categorized according to fiber fractions (total, soluble, insoluble, cereal, fruit, and vegetable fiber, as well as lignin and cellulose). Both the 1995 and 2001 BWHS FFQs provide data on total fiber intake and fiber fractions. In our validation study, correlations of the FFQ with diet recalls and diaries for fiber were 0.67 and 0.57, respectively. Because the Italian study found an inverse association for intake of fruits and vegetables, but not whole-grain foods,[84] we hypothesize that greater intake of fruit and vegetable fiber, but not cereal fiber, will reduce UL risk.

B.7.3. Dietary fat and fiber. A change from a high-fat/low-fiber diet to a low-fat/high-fiber diet in premenopausal black women resulted in statistically significant decreases in serum levels of estrone sulfate and estradiol.[100] Other investigations in non-black populations have shown similar reductions in estradiol and estrone levels in response to a low-fat, high-fiber diet.[60, 76, 101-107] Dietary fat and fiber alter the activity of glucuronidase, which in turn affects the degree of reabsorption of estrogen from the intestines. The decrease in estrogens may also be due to down-regulation of aromatase (CYP19), which converts andronestendione into estrone (see Figure 1). Among blacks, average intakes exceed the current USDA guidelines for fat (<30% kcal as fat and <10% saturated fat) and are below requirements for fiber (20-25g per day).[83]

B.7.4. Fruits and vegetables. Fruits and vegetables contain various antioxidants and phytochemicals (e.g., vitamins C, A, carotenoids, selenium, flavonoids, and indoles)[108] that may decrease risk of UL via hormone-dependent pathways.[108-113] For example, phytoestrogens can compete with estradiol for estrogen receptors in a manner that would reduce risk of UL.[52-56, 110, 111] Studies in cell culture, animals, and humans show that indole-3-carbinol (found in cruciferous vegetables) exhibits antiestrogenic activity via induction of C-2 but not 16α-hydroxylation.[57, 58, 66, 67] As shown in Figure 1, C-2 hydroxylation is associated with the production of non-potent catechol estrogens that have reduced uterotrophic activity.[58, 114] Vegetarians have lower urinary and plasma levels of estriol and total estrogens, and higher levels of SHBG,[62] compared with omnivores of the same age.[59, 63] We would expect such changes in endogenous hormone levels to decrease the risk of UL.[3] The Italian case-control study found an inverse association between intake of fruits and vegetables and the risk of UL.[84] The multivariate OR in the upper versus lower tertiles was 0.5 (95%CI=0.4-0.6) for green vegetables and 0.8 (95%CI=0.6-1.0) for fruit.

B.7.5. Red meat and pork products. Intake of red meat and ham was positively associated with risk of UL in the Italian case-control study.[84] The OR in the upper versus lower tertiles was 1.7 (95%CI=1.4-2.2) for beef and other red meat, and 1.3 (95%CI=1.0-1.6) for ham.[84] Intake of red meat has also been associated with colon cancer risk in many case-control and cohort studies,[115] including the BWHS. Endogenous levels of sex steroids may be influenced by meat consumption. Greater amounts of estrogen residues have been found in the edible tissues of animals treated with estrogen compared with untreated animals.[116]

B.7.6. Micronutrients. The Italian case-control study found an inverse association between fruit and vegetable intake and risk of UL.[84] We propose to limit our analysis of micronutrients to vitamins A, C, and the carotenoids (e.g., lycopene, lutein, β-cryptoxanthin, α-carotene, and β-carotene) because these are most likely to have an impact on endogenous sex hormones. Animal and human studies suggest a protective effect of vitamin C,[117, 118] preformed vitamin A,[119] and carotenoids[111, 120-130] against hormone-dependent cancers. Lycopene is a carotenoid of interest because it is inversely associated with prostate[121] and ovarian cancers,[131] inhibits endometrial and breast cell proliferation *in vitro*,[130] and has been associated with a reduced incidence of leiomyomas of the oviduct in the Japanese quail.[132]

Metabolic studies in premenopausal women suggest that alcohol may interfere with the conversion of β-carotene to vitamin A.[133, 134] In addition, plasma levels of α-carotene and β-carotene following dietary supplementation were significantly higher in normal weight women than in obese African-American women (BMI >=30).[135] Higher plasma levels of carotenoids were also found in women taking exogenous estrogens compared with women not taking exogenous estrogens.[136] Therefore, we plan to assess whether alcohol, BMI, and hormonal contraception modify the association between carotenoids and UL risk.

C. PRELIMINARY STUDIES

C.1. Establishment and follow-up of the cohort. The BWHS is an ongoing prospective follow-up study of health and illness among U.S. black women led by investigators at and The National Cancer Institute supports data collection and study infrastructure. The study began in 1995 when 64,500 U.S. black women 21-69 years of age completed a 14-page postal health questionnaire (see APPENDIX I). Biennial mail questionnaires are used to follow participants. After excluding initial respondents who could not be located one year after entry due to faulty name or address, 59,000 women comprise the cohort being followed. Over 80% of the cohort has completed a questionnaire in each follow-up cycle through 2003. Data collection for the 2005 follow-up questionnaire is currently in process. BWHS participants represent various regions of the U.S., with the majority residing in New York, California, Illinois, Michigan, Georgia, and New Jersey.[137] At baseline, over 80% of women were under 50 years of age and most women reported having had a recent Pap smear (>91%). Median educational attainment was 15 years.

C.2. Questionnaire data. The baseline (1995) questionnaire elicited data on a wide range of variables (see APPENDIX I), including demographic factors, use of medical care, reproductive and medical history, current and past cigarette and alcohol use, current weight and weight at age 18, height, waist and hip circumference, use of vitamin supplements and medications including oral contraceptives (OCs). Diet was recorded using the short version (68 item) NCI-Block FFQ[138] to which we had added several food items after testing among several hundred African-American women. Biennial follow-up questionnaires are mailed to ascertain new cases of UL and other illnesses, and to update information on exposures (see APPENDIX I). The 2001 survey included a FFQ that was a revision of the modified NCI-Block questionnaire used in 1995.

C.3. Tracking of the cohort. We make intensive efforts to locate women whose addresses become unknown to us. We use the National Change of Address File, commercial search firms, and contacts named on previous questionnaires. We send a Newsletter every 6 months to learn about address changes and to supply participants with information on study methods, progress, and results. The deceased are identified through the National Death Index, postal service, and relatives/friends, and we obtain death certificates for these women. To assess the possibility of bias due to selective losses, we compared 47,913 women who completed a questionnaire in the 2001 cycle with nonrespondents with respect to demographic and lifestyle characteristics (data not shown). The respondents were older than nonrespondents (mean age: 39.2 vs. 37.2) and had higher educational attainment (14.9 vs. 14.5 years), but were similar in every other factor assessed. For example, the proportions of respondents and nonrespondents with the following factors are as follows: saturated fat intake (g), 16.7 vs. 16.6; % calories from fat, 33.4 vs. 33.3; body mass index 30+, 30% vs. 31%; current alcohol intake, 28% vs. 29%; OC use 5+ years, 31% vs. 28%; parity 3+, 20% vs. 20%. These comparisons suggest that major bias from selective losses is not likely.

C.4. Definition and validation of uterine leiomyomata. The diagnosis of UL is often suspected when an enlarged irregular uterine contour is palpable on pelvic examination. Ultrasound is the clinical standard used to confirm diagnoses.[7] Although histologic evidence is the gold standard,[7] histologically-confirmed cases represent only 10-30% of cases for whom ultrasound evidence is available.[13, 139] Studies limited to histologic cases may spuriously identify risk factors associated with large tumor size, symptoms, or treatment preference.[139] The outcome definition used in our analyses includes confirmation by either ultrasound or surgery. Ultrasound has high sensitivity (99%) and specificity (91%) relative to histologic evidence.[140, 141]

The 1995 baseline and 1997 follow-up questionnaires asked if the woman had been diagnosed with "uterine fibroids," but did not ask about the method of confirmation used for diagnosis. As a result, our analyses do not include incident cases from 1995-1997. Rather, we start our follow-up in 1997 because we first asked about method of confirmation on the 1999 survey. We restrict our analyses to premenopausal women because UL are rare after menopause.[7] Starting with 53,322 women who completed the 1997 survey, we exclude women who are postmenopausal or have unknown menopausal status, women who report having a previous diagnosis of UL (i.e., prevalent cases), women who report UL without a year of diagnosis or method of confirmation, and women with incomplete data on relevant covariates. After these exclusions, about 22,500 premenopausal women remain and are followed for the incidence of UL.

On the 1999, 2001, and 2003 follow-up questionnaires, women were asked if they had been diagnosed with "uterine fibroids" in the previous two-year interval and, if yes, the calendar year in which they were first

Principal Investigator/Program Director (Last, first, middle):_____

diagnosed and whether their diagnosis was confirmed by pelvic exam and/or by ultrasound/hysterectomy. A diagnosis is considered hysterectomy-confirmed if the participant reported hysterectomy on the same questionnaire. On subsequent surveys, the latter confirmation type was changed to ultrasound/surgery, as uterus-preserving surgeries (e.g., myomectomy) are becoming more common. On the 1999, 2001, and 2003 surveys, 3,631 incident cases of UL confirmed by ultrasound (N=2,926) or surgery (N=705) were reported. We expect more than 6,000 new cases of UL from the 1999, 2001, 2003, 2005, and 2007 surveys combined.

A validation study was conducted in a random sample of 248 self-reported UL cases from the BWHS. Cases were mailed supplemental surveys regarding their date of initial diagnosis, method of confirmation, symptoms, and treatment, and were asked for permission to review their medical records. 178 completed the supplemental survey and 128 gave permission to review their medical records. (The most common reason for unwillingness to sign a medical release was concern about privacy and confidentiality). Among the 127 cases whose medical records we obtained, self-report of UL was confirmed in 122 (96%). There were no material differences in demographic, lifestyle, and reproductive factors between cases who did and did not release their medical records—in terms of age, education, BMI, parity—suggesting that cases who provided records are representative of the larger case group. Among cases who completed the supplemental survey, 87% came to clinical attention because they sought treatment for symptoms, or a tumor was palpable at the time of a routine pelvic exam, and only 13% reported that their UL were detected incidentally (e.g., during work-up for another condition). The most commonly reported symptoms were heavy bleeding, pelvic pain, infertility, frequent urination, and anemia/fatigue. BWHS results will apply to women with symptomatic or clinically relevant UL, which ultimately represents the disease burden in reproductive-aged women and the bulk of health care costs attributed to UL in the United States.

C.5. Validation of dietary data. A validation study of the 1995 FFQ was carried out by a dietary consultant to the BWHS.[85] Between 1996 and 1998, 400 BWHS subjects provided up to three 24-hour telephone recall interviews and one three-day food record over a one-year period. Nutrient estimates were compared with estimates from the baseline FFQ. Pearson correlations, adjusted for energy and corrected for intrapersonal variation, were computed to compare estimates for total fat, saturated fat, protein, carbohydrate, dietary fiber, calcium, vitamin C, folate, β-carotene, and vitamin E. Coefficients were similar to those found in studies of other populations,[142-145] ranging from 0.5 to. 0.8.[12] However, the correlation coefficient for vitamin E was low (0.25), as consistent with other studies.[146] In addition, food group servings based on the 1995 FFQ were similar to those from the average of 3 days of DRs. The mean ± SD intakes as estimated by FFQ vs. DR were: vegetables (1.6±1.0 vs. 2.3±1.3), fruit (1.2±0.9 vs. 1.2±1.2), dairy (1.0±1.3 vs.1.1±1.0), and meat (1.8±1.0 vs.1.9±0.9).

Other studies show correlations ranging from 0.4 to 0.7 for nutrient comparisons between FFQ and dietary recalls.[147] Results from the OPEN study[148, 149] show lower correlations of biomarkers for energy (doubly-labeled water method) and protein (urinary nitrogen) intake with FFQ data. However, biomarkers such as plasma triglycerides,[150] carotenoids,[122, 136, 151-153] and vitamin C,[152] have considerably higher correlations with FFQ estimates of macro-[150] and micro-nutrients.[151, 152] Energy-adjustment in the OPEN study improved correlations,[1, 2] supporting the rationale for energy-adjustment in the BWHS.

C.6. Other risk factors for uterine leiomyomata. The BWHS has prospectively collected data on a variety of established and suspected risk factors for UL, including reproductive factors (age at menarche, parity, age at first and last birth, and hormonal contraception), lifestyle factors (tobacco, alcohol, and caffeine consumption; physical activity), anthropometric factors, SES (education, marital status, income, occupation, working a second job), and health care utilization (health insurance, Pap smear screening). Data on infertility, a potential confounder of the association between parity and UL, were obtained on the 1995, 2003, and 2005 surveys.

C.7. Previous studies of uterine leiomyomata in the BWHS. BWHS analyses of UL risk in relation to age[1]; reproductive history and hormonal contraception;[2] body size;[3] and tobacco, alcohol, and caffeine consumption[4] provide the first prospective results for U.S. black women. Published results are consistent with other studies (largely of white women).[20, 22, 27, 28]

C.8. Strengths of the research team. principal investigator of the proposed study, is a new investigator. is a recent graduate of the and wrote doctoral dissertation on risk factors for UL in the BWHS. e has published 4 manuscripts on risk factors for UL in the

BWHS,[1-4] and has published 3 additional manuscripts on UL in other study populations.[34, 154, 155] is principal investigator of the BWHS. , an expert on the molecular biology[44, 156-162] and clinical management of UL,[7, 154, 163, 164] has served as clinical consultant to the BWHS on all previous UL publications.[1-4] has been a dietary consultant to the BWHS since its inception.[85, 165]

C.9. Publications. A list of manuscripts and abstracts based on BWHS data is included in APPENDIX II.

D. RESEARCH DESIGN AND METHODS

D.1. Overview of proposal. We will use BWHS data from 1997 through 2007 to investigate the relation of selected dietary factors to risk of self-reported UL confirmed by ultrasound or surgery. The analysis will be confined to approximately 22,500 women with intact uteri who were premenopausal in 1997 and did not report a previous diagnosis of UL. We expect a total of 6,000 incident cases of UL identified on the 1999 through 2007 follow-up questionnaires, of which 2,400 will be reported among women less than 35 years of age.

D.2. The usefulness of the BWHS for the proposed analyses. The BWHS is in its 11th year of follow-up and cohort retention has remained high (>80%). Data have been collected through biennial questionnaires on self-reported UL and potential risk factors. Dietary data were collected in 1995 and again in 2001, and these data have been validated. Data on self-reported UL have also been validated. The large number of incident UL will provide excellent statistical power for the proposed study, which will be by far the largest study of risk factors for UL ever conducted.

D.3. Dietary data. Diet has been assessed in two questionnaire cycles (1995 and 2001) with a modified version of the NCI-Block short form FFQ.[85, 138] The 1995 NCI-Block 68 item FFQ collected data on the consumption of specified foods during the previous year, with frequencies ranging from "never or <1 per month" to "2 or more per day" and portion sizes of "small," "medium," or "large."[85] Frequencies for beverages range from "never or <1 per month" to "6 or more per day." Fortified foods (e.g., fortified cereals, fortified juice drinks) were specifically asked about on the FFQ. Widespread food fortification with folate in the U.S. food supply did not occur until 1998 and is accounted for in the revised nutrient database used for the 2001 FFQ. The 2001 FFQ added several items and an extra portion size option ("super size"). The FFQs will provide data on specific foods, types and amounts of dietary fat and other macronutrients (protein, carbohydrate), micronutrients (vitamins, minerals, phytochemicals), fiber, and total caloric intake. Special focus will be given to dietary fat and fiber; fruits and vegetables, beef and other red meat, pork; and vitamins A, C, and carotenoids (e.g., β-carotene, α-carotene, β-cryptoxanthin, lutein, lycopene). Nutrient intake will be computed by multiplying the frequency of consumption of each food by the nutrient content of the specified portion. For the 1995 FFQ, values for the amounts of dietary fats, fiber, and other nutrients have been calculated from the DIETSYS Foods Database (version 3.7c).[138] The DIETSYS software (version 4.01) for the 1995 FFQ provides estimates on total fat and saturated fat. Software for the 2001 FFQ (DIETCALC version 1.4.1) will provide direct estimates for all types of fat, including trans, mono-, and poly-unsaturated fats.

In 1995, participants were also asked to report their use of multivitamins as well as individual supplements of vitamins A and C in the past year. Current use of multivitamins was updated on all follow-up questionnaires. Data on vitamin A and C supplementation were updated on the 1997 questionnaire. On each follow-up questionnaire, participants were asked to report all medications or supplements currently used 3 or more times a week. We will examine micronutrients according to whether they were derived from: 1) food only, or 2) food *and* supplements. We will also classify women according to their use of multivitamins and supplements of vitamins A and C, by dose and duration among current users.

In our examination of specific food groups, frequencies will be summed over all fruits and vegetables to obtain estimates of overall fruit and vegetable intake. For the analysis of red meat consumption, frequencies will be summed over: hamburgers, cheeseburgers, meatloaf, beef burritos, and tacos; beef (steaks, roasts, including on sandwiches); beef stew; liver; hot dogs; pork (chops, roasts); bacon; sausage; and ham, bologna, salami and other lunch meats. For the analysis of pork consumption, frequencies will be summed over: pork (chops, roasts); bacon; sausage; ham, bologna, salami and other lunchmeats. We will create a subcategory for "cured or processed meats" that includes hot dogs; sausage; and ham, bologna, salami and other lunchmeats because these are common choices among black women.[81, 83] Since nutritional epidemiologists often employ different food groupings,[166, 167] (dietary consultant) will periodically review the proposed groupings for appropriateness and timeliness before we proceed with the final analysis.

D.4. UL data. On the 1999, 2001, and 2003 follow-up questionnaires, women were asked if they had been diagnosed with "uterine fibroids" in the previous two-year interval, the calendar year in which they were first diagnosed, and whether their diagnosis was confirmed by pelvic exam and/or by ultrasound/hysterectomy. On subsequent surveys, the latter confirmation type was changed to ultrasound/surgery. A diagnosis will be considered surgically-confirmed if the participant reported hysterectomy or surgery on the same questionnaire.

In large prospective cohort studies such as the BWHS, it is not feasible to systematically screen all participants for the presence of UL. While rates from the BWHS are consistent with other studies,[1] the pool of non-cases will include some women with undetected tumors.[15] The vast majority of BWHS participants have health insurance (96%) and routine gynecologic care, as indicated by the prevalence of Pap smear (91%). High levels of screening minimize the potential for detection bias. Misclassification of UL that is not related to the dietary factors under study will generally result in an underestimation of effect,[168] unless there is perfect specificity of disease classification. With perfect specificity, there will be *no* bias the rate ratio (IRR) [169] if misclassification negligibly alters person-time. Our validation study of UL confirmed over 96% of cases by medical record (4% false positives),[2] which reduces concerns about bias from nondifferential misclassification.

D.5. Validation of the absence of UL among non-cases. Data on recency of pelvic exam will be obtained from all cohort participants on the 2007 follow-up survey. To confirm the absence of disease among non-cases in the BWHS, we will also include a series of questions to validate the absence of UL and to verify the presence of routine gynecologic care (see APPENDIX I). Women will be asked about the presence of UL-related symptoms. To evaluate the extent of bias due to misclassification of UL, we will restrict the non-case group to those who reported a recent pelvic exam on the 2007 follow-up survey. If the restricted analyses reveal evidence of significant bias due to misclassification, we will exclude non-cases who report UL-related symptoms and/or those without a recent pelvic exam from the main analyses and report these results only.

D.6. Statistical analysis. Each participant will contribute person-time at risk from the start of follow-up (March 1997) until the diagnosis of UL, menopause, loss to follow-up, death, or end of follow-up (March 2007), whichever comes first. Incidence rate ratios (IRRs) will be computed as the ratio of the incidence rate in the exposure category of interest to the incidence rate in the referent category. We will conduct multivariable Cox regression analyses,[170] stratified by age at baseline in 1-year intervals and questionnaire cycle (1997-1999, 1999-2001, 2001-2003, 2003-2005, 2005-2007), to estimate IRRs and 95% confidence intervals for different levels of the exposure variables.[171] The basic model for analysis is expressed as:

$$I(t,x,U,i) = I_{0i}(t) * \exp(\alpha * x(t) + \beta * U(t)),$$

where:

α is the $\log_e$ incidence rate ratio describing the change in the baseline incidence rate at time t due to a one-unit increase in exposure x(t) measured at time t;

U(t) is a vector of other determinants of risk for UL at time t;

β is the vector of $\log_e$ incidence rate ratios describing the change in the baseline incidence rate due to a one-unit increase in other determinants of UL risk;

t is the age at UL diagnosis (or censoring due to menopause, death, loss to follow-up, or end of follow-up); and

$I_{0i}(t)$ is the baseline incidence rate at age t in stratum i.

SAS PROC PHREG[172] will be used for all analyses. The Anderson-Gill data structure will be used to update time-varying covariates.[171] This analytic method maintains the prospective nature of data collection. Women will be excluded if their energy intakes are implausibly low or high (<500 or >3500 kcal per day). All food and nutrient items will be categorized into quantiles of intake based on the distribution among all women. We will fit Cox regression models that include main effects for dietary factors, while controlling for potential confounders. Dietary variables will be adjusted for total energy using regression analyses because energy requirements depend on BMI, physical activity, and metabolic efficiency, which collectively may confound diet-disease associations.[173, 174] In addition, errors in measuring individual nutrients are strongly correlated with errors in measuring energy intake because over- or under-reporting of individual foods leads to similar errors in all constituents.[175] In addition to energy, we will adjust for physical activity and BMI, as a recent study found that adjustment for these variables removed more than two thirds of the FFQ error in estimating fat intake.[176] We will assess the 1995 diet data in relation to UL reported through 2001 (1997-2001), and the 2001 dietary data in relation to UL reported through 2007 (2001-2007). Because the average of the two FFQs may provide a better assessment of long-term dietary intake,[177-180] we will carry out separate analyses that use this average for the 2001-2007 follow-up period.

A covariate will be included in multivariable analyses if the literature supports its role as a risk factor for UL and this risk factor is associated with exposure in the cohort at baseline,[181] or if adding the covariate to a model containing all other predictors of UL changes the point estimate by 10% or more.[182] Because dietary

Principal Investigator/Program Director (Last, first, middle):____

patterns are strongly related to SES, we will control for several SES variables (education, occupation, household income, and marital status) and assess whether SES modifies the associations of interest. Tests for trend will be conducted using the median value for each category of the exposure variable as a continuous variable.[183] To examine whether associations between diet and UL are modified by other factors, a cross-product term of the ordinal score for the level of each factor and dietary factor expressed as a continuous variable will be included in the multivariable model. As possible effect modifiers, we will examine factors identified in the literature to interact with diet (e.g., alcohol,[133, 134] hormonal contraception,[136] and BMI[135]). Two-sided p-values for tests of interaction will be obtained from a likelihood ratio test with the degrees of freedom equal to the difference in the number of parameters between the null and alternative models. Departures from the proportional hazards assumption will be tested by the likelihood ratio test comparing models with and without interaction terms for age and time with the main exposure variables; if violated, we will present data separately by age group.

We will conduct several sensitivity analyses to assess the robustness of our findings. With respect to errors in UL classification, one approach will be to study a group in which the illness is rarer, so that the pool of non-cases will include fewer women with undiagnosed UL. We will conduct separate analyses among women aged less than 35 years. This strategy has the added advantage of including cases with "newer" disease which is less likely to be subclinical for many years, so that the time period during which exposures are assessed might have greater etiological relevance. We will also stratify analyses according to method of confirmation (ultrasound vs. hysterectomy), to assess whether risk factors differ according to detection method. We expect about 10% of cases to be hysterectomy-confirmed.[2] To assess the impact of detection bias, we will restrict the sample to women with high levels of gynecologic care, such as women who reported a Pap smear or pelvic exam within the prior 2-year interval. Finally, we will conduct separate analyses after the exclusion of non-cases who report UL-related symptoms (see section D.5). If the results show material bias due to underdiagnosis, we will present the restricted findings as our main results.

D.7. Statistical power. We anticipate that over 6,000 cases will be reported during the 1997-2007 follow-up period, with 2,400 among women in their early reproductive years (age < 35). The prevalence of selected dietary factors is shown in Table 2. Estimates of statistical power are given in Table 3, among all women and women aged < 35 years, for dietary factors with prevalences ranging from 3% to 20%. Overall, for exposure prevalences as low as 3%, power will be over 95% to detect rate ratios of 1.3 or greater. Among women aged < 35 years, for an exposure prevalence of 3%, power will be over 82% to detect rate ratios of 1.4 or greater.

Table 2. Selected exposures relevant to dietary analyses

	Percentile (%)				Percentile (%)		
Exposure	25	50	75	Exposure	25	50	75
% kcal from total fat/day	28	33	38	Vitamin A, IU/day	2581	4143	6664
Total fat, g/day	35	51	73	Pro-A carotenes, mcg/day	1403	2416	4081
Saturated fat, g/day	10	15	22	Retinol, mcg/day	183	300	470
Fiber, g/day	7	9	13	α-carotene, mcg/day	73	206	390
Servings of red meat/week	1.5	3.5	6.4	β-carotene, mcg/day	1535	2650	4400
Servings of pork/week	0.4	1.5	3.3	Cryptoxanthin, mcg/day	25	56	100
Servings of fruits/day	0.4	0.8	1.2	Lutein, mcg/day	1280	2496	4153
Servings of vegetables/day	0.7	1.1	1.7	Lycopene, mcg/day	331	599	1123
Vitamin C, mg/day	54	86	128				

Table 3. Statistical power (%) to detect incidence rate ratios (IRRs) for range of exposure prevalences during follow-up from 1997-2005. Assumes attrition of 2% per year and alpha-level=0.05 (two-tailed).

	All women (N=6,000 cases)				Age < 35 yrs (N=2,400 cases)			
Prevalence of exposure	IRR				IRR			
	1.2	1.3	1.4	1.5	1.2	1.3	1.4	1.5
0.03	69	95	>99	>99	31	58	82	95
0.05	88	>99	>99	>99	46	79	95	>99
0.10	99	>99	>99	>99	72	97	>99	>99
0.15	>99	>99	>99	>99	85	99	>99	>99
0.20	>99	>99	>99	>99	92	>99	>99	>99

Even in the extreme and unlikely case where there is attenuation of the IRRs (as observed for protein in the OPEN study) such that a true IRR of 2.5 will be attenuated to 1.3 (i.e., applying attenuation factor for energy-adjusted protein in the OPEN study, i.e., $2.5^{0.3}=1.3$),[148, 149] we will have >95% power to detect an association for exposures with a prevalence of 3% or higher. If the true IRR is 2.0 and the observed IRR is 1.2 (i.e., $2.0^{0.3}=1.2$), we will have >88% power to detect an association for exposures with a prevalence of 5% or higher.

D.8. Strengths and Limitations

D.8.1. Public health importance. The incidence of symptomatic UL is very high in black women.[1, 13, 15] The identification of modifiable risk factors (e.g., high fat intake) could yield useful information for primary prevention efforts and have a large impact on the public health burden of this disease.

D.8.2. Innovation. To our knowledge this is the first prospective study of dietary risk factors for UL.

D.8.3. Cost and efficiency. Because data collection for the present study is supported by funds from other grants, the present ancillary study can be carried out at low cost.

D.8.4. Disease classification. The high accuracy of self-reported UL (>96%) observed in the BWHS validation study suggests that our case group will be highly specific – that is, women classified as UL cases will be true cases.[184] The series of symptom-related questions to be asked of non-cases (see APPENDIX I) will provide reassurance that the "control" group does not contain a material proportion of women with clinically relevant undetected UL. If there is a marked difference in results comparing analyses that include relative to those that exclude non-cases with UL-related symptoms, we will present the latter results only. To further minimize the potential for bias, we will carry out all analyses within subgroups of women with a recent Pap smear or pelvic exam, and among women under age 35 in whom there will be less undetected disease and a lower likelihood of misclassification. In the validation study, incidental detection of UL was low (13%) and the majority of cases had symptomatic disease at the time of diagnosis. Since symptomatic disease has the greatest impact on a woman's quality of life and health care utilization,[222] results from the BWHS can greatly contribute to efforts aimed at reducing UL-associated morbidity.

D.8.5. Exposure classification. Validation of the NCI-Block FFQ used at baseline in the BWHS showed that the instrument worked well at discriminating levels of intake for most macro and micronutrients.[85] The questionnaire in 2001 was modified to incorporate what was learned from the 1995 questionnaire, and the food composition database was updated to account for changes in U.S. eating patterns and in food fortification over time. Recall bias will be avoided because dietary data were assessed before the diagnosis of disease.

D.8.6. Confounding. We will control for important potential confounders, including age at menarche, parity, age at first birth, years since last birth, BMI, alcohol consumption, smoking, geographic region, SES measures (education, income, marital status, occupation), and Pap smear screening.

D.8.7. Selection bias. In the BWHS, participation has exceeded 80% in each round of follow-up. High cohort retention minimizes the influence of selection bias on the study findings. To address any concerns about selection bias, we will compare women who remained participants in the study with those were lost to follow-up with respect to UL risk factors.

D.8.8. Statistical power. The BWHS will have excellent power to study the main effects of diet. The large sample size will also allow for the assessment of risk factors in subgroups for which misclassification will be reduced (women age < 35; women with a recent pelvic exam; and non-cases without UL-related symptoms). The large size of the BWHS will provide sufficient power to detect IRRs as small as 1.2 or 1.3.[148, 149]

D.8.9. Consistency of our results with previous studies. Our analyses to date have provided results on reproductive and hormonal factors consistent with previous studies.[2] These data were featured as the leading article in the January 15, 2004 issue of the AJE and an invited commentary was included.[185] Results for smoking, alcohol, and caffeine have also been published,[4] as have results for BMI.[3] Age-incidence rates of UL in the BWHS are highly consistent with those from prospective cohort and hospital-based studies.[1]

D.8.10. Generalizability. Because women must be literate to participate in a study that collects data via mailed questionnaires, almost all BWHS participants are high school graduates. About 85% of black women of the same ages nationally have graduated high school.[186] Thus, the BWHS represents the educational levels of most U.S. black women. Generalizability of etiologic results requires, first and foremost, that the study results be internally valid,[222] which depends on the absence of confounding, selection bias, and information bias. The results of the proposed study should have high internal validity. Generalization of our results to other U.S. black women is a matter of scientific judgment taking into account all information about the topic, including whether the mechanism is likely to operate similarly in other black women or vary according to key factors.

E. HUMAN SUBJECTS RESEARCH

Protection of Human Subjects

Risks to the subjects

Human subjects involvement and characteristics. The women in the proposed study are participants in the BWHS, a follow-up study of African-American women who were 21-69 years of age at entry in 1995. These women 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. Follow-up of the women is through mail questionnaires; completion of these questionnaires is voluntary. Premenopausal women with intact uteri who completed the 1997 questionnaire and at least one subsequent follow-up questionnaire (e.g., 1999, 2001, 2003, 2005, or 2007) will be eligible for inclusion in the present study. Women who reported a UL diagnosis before 1997 will be excluded.

Sources of materials. Information from various health questionnaires and medical records obtained after signed informed consent will be used in the analyses.

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. Medical records are stored in locked files. We have obtained a federal Certificate of Confidentiality to further protect the data. All analyses are conducted using anonymous data.

Adequacy of protection against risks

Recruitment and informed consent. The participants indicate their consent to participate in the BWHS by supplying data on questionnaires, by signing informed consents for releases for medical records.

Protection against risks. The data are protected against breach of confidentiality. Subjects who are annoyed by data requests may refuse to answer particular questions, refuse to allow access to their medical records, or withdraw entirely from the study.

Potential benefits of the proposed research to the subjects and others

The participants are informed of study results through newsletters, which are sent twice a year, and through the BWHS website (www.bu.edu/bwhs). In general, benefits to women will be large if knowledge gained from the present study leads to interventions that might lower risk of UL.

Importance of the knowledge to be gained

The potential benefit of the present study is elucidation of the causes of UL that might lead to interventions that reduce risk. The risk of UL in African-American women is higher than in other ethnic groups and there is considerable morbidity associated with the disease. The potential benefit of the proposed study far outweighs any potential risks.

Principal Investigator/Program Director (Last, first, middle):____

E. HUMAN SUBJECTS RESEARCH

Women and Minority Inclusion in Clinical research (see Targeted/Planned Enrollment Table)

Inclusion of women. Because the goal of the BWHS is to find causes of illness in black women, all participants are women.

Inclusion of minorities. Because the goal of the BWHS is to elucidate causes of illness in U.S. black women, all of the participants self-identify as black. About 1.8% report Hispanic heritage.

Targeted/Planned Enrollment Table

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

Study Title: A Prospective Study of Diet and Fibroids in Black Women

Total Planned Enrollment: 22,500

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	416		416
Not Hispanic or Latino	22,084		22,084
Ethnic Category: Total of All Subjects *	22,500		22,500
Racial Categories			
American Indian/Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American	22,500		22,500
White			
Racial Categories: Total of All Subjects *	22,500		22,500

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

Principal Investigator/Program Director (Last, first, middle):

E. HUMAN SUBJECTS RESEARCH

Inclusion of Children. Because the goal of the BWHS is to elucidate causes of illness that occur in adults, all of the participants are adults.

F. VERTEBRATE ANIMALS - Not applicable.

Principal Investigator/Program Director (Last, first, middle):_____

H. Consortium/Contractual Arrangements - None.

I. Resource Sharing – None.

PHS 398 Checklist

OMB Number: 0925-0001
Expiration Date: 9/30/2007

1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

* Type of Application:

● New ○ Resubmission ○ Renewal ○ Continuation ○ Revision

Federal Identifier:

2. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

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

☐ Change of Grantee Institution

* Name of former institution:

3. Inventions and Patents (For renewal applications only)

* Inventions and Patents: Yes ○ No ○

If the answer is "Yes" then please answer the following:

* Previously Reported: Yes ○ No ○

Tracking Number:

4. Program Income

Is program income anticipated during the periods for which the grant support is requested?

○Yes ●No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

5. Assurances/Certifications (see instructions)

In agreeing to the assurances/certification section 18 on the SF424 (R&R) form, the authorized organizational representative agrees to comply with the following policies, assurances and/or certifications when applicable. Descriptions of individual assurances/certifications are provided at: http://grants.nih.gov/grants/funding/phs398/PolAssurDef.doc

*Human Subjects; *Research Using Human Embryonic Stem Cells; *Research on Transplantation of Human Fetal Tissue; *Women and Minority Inclusion Policy; *Inclusion of Children Policy; *Vertebrate Animals; *Debarment and Suspension; *Drug- Free Workplace (applicable to new [Type 1] or revised [Type 1] applications only) ; *Lobbying; *Non-Delinquency on Federal Debt; *Research Misconduct; *Civil Rights (Form HHS 441 or HHS 690); *Handicapped Individuals (Form HHS 641 or HHS 690); *Sex Discrimination (Form HHS 639-A or HHS 690); *Age Discrimination (Form HHS 680 or HHS 690); *Recombinant DNA and Human Gene Transfer Research; *Financial Conflict of Interest (except Phase I SBIR/STTR); *Prohibited Research; *Select Agents; *Smoke-Free Workplace; *STTR ONLY: Certification of Research Institution Participation.

If unable to certify compliance, where applicable, provide an explanation and attach below.

Explanation:

Attachments

CertificationExplanation_attDataGroup0

File Name	Mime Type