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13. SUPPLEMENTARY NOTES

14. ABSTRACT: The Breast Cancer Epidemiology in Puerto Rico project had two major goals: training researchers from a minority academic institution and developing the infrastructure to design and conduct a population based pilot study of breast cancer in Puerto Rico. All investigators from the University of Puerto Rico have acquired new expertise or have strengthened their skills thru weekly conference calls, formal academic training and direct involvement in study design, instruments, quality control processes, data analysis, presentations and manuscripts preparation. A population based case control study was designed to evaluate risk factors for breast cancer among Hispanic women living in the San Juan Metropolitan of Puerto Rico. Breast cancer cases were identified from the Puerto Rico Central Cancer Registry and patient lists from hospitals and physician offices in the Metropolitan San Juan Area. Of 1809 referrals of breast cancer cases, 442 met the eligibility criteria and 317 (72%) agreed to participate and complete the interview and clinical evaluation. Controls were selected from a probabilistic sample of women in the same age groups that lived in the same municipalities as the cases. During the recruitment 1,136 households were visited, 538 women were eligible and 348(65%) agreed to participate.

15. SUBJECT TERMS
Breast cancer, population-based study, epidemiology, Hispanics

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1. INTRODUCTION:

Understanding breast cancer epidemiology in Puerto Rico in particular is important for two different reasons: to allow for better prevention and control among Puerto Rican women if modifiable risk factors are and also to provide insight into breast cancer epidemiology generally because of the unique characteristics of exposures for Puerto Rican women. In Puerto Rico, age-adjusted rates of breast cancer are less than those in the continental United States\(^1\). On the other hand, the age-adjusted (US 2000 Standard Population) incidence rate of breast cancer has been increasing among Puerto Ricans at an average of +1.3\%, (p<0.05) per year from 1987 to 2010\(^2\). In contrast, the overall breast cancer incidence rates did not change significantly among Non-Hispanic White in US from 2003 to 2007\(^3\). The reasons for these differences are not known but could be due to changing lifestyles. Historically low rates in Puerto Rico are interesting in that a number of adverse risk factors are more common for women in Puerto Rico than in the US. Among the 52 US states and territories, Puerto Rico is among the worst for overweight and obesity, physical inactivity and low fruit and vegetable intake. Because of this combination of low overall rates, rapid increase in rates and high rate of exposure to some breast cancer risk factors, Puerto Rico is an ideal location to study breast cancer epidemiology. The paradoxical finding of high rates of exposure and lower disease rates likely means that there is wider variation in genetic and exogenous exposures in Puerto Rico than in other, more studied populations. The Puerto Rican population then provides an excellent opportunity to investigate both early and adult risk factors because of these changes in exposures over time.

The Breast Cancer Epidemiology in Puerto Rico project funded by BC060131 BCRP HBCU/MI Partnership Training Award had two mayor goals:

- To train and develop researchers in breast cancer at the minority institution
- To design and conduct a pilot case-control breast cancer study among Puerto Rican women.

The first mayor overall goal was to develop a team of independent investigators with the necessary skills to build up a program of breast cancer research in Puerto Rico. To accomplish this goal, researchers from the University of Puerto Rico obtained formal
training in cancer epidemiology. They have presented preliminary results in conferences and scientific meetings. Investigators from the minority institution have networked with other scientist and continue to meet to analyze the collected data with emphasis on publication of study results.

For the second goal, we designed a population based case control study for which 665 women 30-79 years of age, residents of San Juan, Bayamón, Guaynabo and Carolina, were enrolled. Cases were women with incident, primary, and pathologically confirmed breast cancer with no history of previous cancer other than non-melanoma skin cancer. Controls were randomly selected from females living in the same geographical area as of the breast cancer cases, of the same age range and with no history of previous cancer other than non-melanoma skin cancer. The data collected from cases and controls has been used and will continue to be analyzed to examine adult and childhood factors in relation to risk of breast cancer in this understudied population of Puerto Rican women.

2. **Keywords:** Breast cancer, Hispanics, population-based research, case-control, epidemiology

3. **Overall Project Summary**

3.1 **Training researchers from the University of Puerto Rico**

The training of investigators was an important goal in this project. Five investigators from the University of Puerto Rico, a minority institution, have been closely involved in the training project. The investigators from the University of Puerto Rico were: (1) Cruz Maria Nazario, professor of epidemiology who has been the PI for the minority institution; (2) Michelle Schelske-Santos, professor of nutrition, who has led the development of the dietary questionnaires as well as the skin color measurements with the colorimeter; (3) Farah Ramirez Marrero, professor of exercise science, who was involved in the development of the physical activity questionnaires; (4) Imar Mansilla Rivera, professor of environmental health involved in the assessment of environmental exposures based on residential location; (5) Rosa Rosario, associate professor of epidemiology involved in the methodological aspects of sample selection of the controls as well as sun exposure and occupational factors; and (6) Johan Hernández, project manager, that has been involved in development of quality control and quality assurance
protocols (clinical and survey) to maintain high scientific standard as well as in the project’s recruitment strategies. She has supervised research assistants and graduate students.

Investigators have participated in activities focused in achieving the following aims:

- To develop expertise in breast cancer epidemiology, especially in the areas of interest of this study.
- To understand cutting edge developments in breast cancer in order to design future studies to test new hypothesis.
- To develop needed capability and infrastructure particularly for the implementation and conduct of a breast cancer study as well as for future studies.

In order to meet the training goals during the award, the investigators from the University of Puerto Rico participated in a number of academic courses, workshops, conferences and scientific activities. Details of these activities have been previously reported in the annual and biannual reports submitted to the US Army Medical Research and Materiel Command (USAMRMC). A list with the training activities is included in Appendix A.

3.2. Communication strategies

Investigators met weekly by phone with Dr. Freudenheim, to discuss methodological issues, study designs, new ideas for research on breast cancer, preliminary findings and observations, and to deliberate the implementation and day-to-day operations of the case-control study. Notes from the telephone meetings were prepared by Dr. Jo Freudenheim and sent to each member of the team via email after each meeting.

To develop the research infrastructure for an epidemiological study, researchers from the University of Puerto Rico received specific training in the development of protocols for case and control ascertainment, blood collection, and for the storage and processing of biological specimens. In addition to weekly conference calls, Dr. Jo Freudenheim visited the University of Puerto Rico in October 2007 to discuss the development of the protocols and the questionnaire. She also met with University of Puerto Rico researches
during scientific meetings and conferences abroad. In April 2008, Michelle Shelske-Santos, Cruz María Nazario, and Johan Hernández visited University of New York at Buffalo to discuss issues regarding the nutrition questionnaire and met with Dr. Freudenheim and other experts in nutrition epidemiology at the mentoring institution.

One milestone was the capability of the research team to maintain close and frequent communication during the award period to discuss relevant issues regarding the study protocol such as development of the study protocol, develop the study questionnaire, recruitment, interview process, analysis, publication and other.

The clinical research infrastructure developed through weekly conferences between key personnel in the two institutions was complemented with the real time visit to Roswell Park Cancer Institute to agree and coordinate biological specimen collection, processing, storage, and shipping from the University of Puerto Rico Medical Sciences Campus to the University at Buffalo. Lisa Carter from Roswell Park Cancer Institute visited the University of Puerto Rico and evaluated the clinical protocol in June 2007. Nilda González, medical technologist from the Puerto Rico Clinical and Translational Research Consortium (PRCTRC), University of Puerto Rico, visited Roswell Park Cancer Institute in April 2008.

3.3 Specific trainings
Researchers from the University of Puerto Rico, acquired specific training in the epidemiology of breast cancer through participation in congress and scientific meetings such as IARC 2007 in Washington, DC (Cruz María Nazario and Farah A. Ramírez); AACR 2008 in San Diego, CA (Cruz María Nazario, Michelle Santos, Farah A. Ramírez and Jo Freudenheim; John Hopkins Graduate Summer Institute 2007 at the Bloomberg School of Public Health (Michelle Shelske-Santos: 2 courses in epidemiology); Imar Mansilla took an Introduction to Epidemiology course at the UPR-MSC Graduate School of Public Health, and course in Environmental Epidemiology at the Ohio State University (2007) (Appendix B)
The training of minority institution researchers also included the process to develop interview procedures for cases and controls and to complete the comprehensive epidemiological questionnaire for the population-based case-control study of breast cancer including measurement of reliability and relative validity. A pilot study in 100 breast cancer cases and 100 population controls was designed to test case and control ascertainment procedures, to pilot the interviews and develop new procedures when needed, to estimate response rates for participation and blood donation among cases and control, to determine availability of tumor tissue for cases and to test procedures for questionnaire processing and for handling and storage of biological specimens

As a result of these training activities, researchers from the University of Puerto Rico, have assumed leading roles in the development of various manuscripts. For instance, Dr. Shelske-Santos is currently working on a paper that describes the macronutrient intake in the Puerto Rican diet using the information of food items from this study. Dr. Ramírez-Marrero is working on a manuscript on body mass index and its relation to breast cancer in Puerto Rico, as well as the association of breast cancer and lifetime history of physical activity. Dr. Rosario has the leading role on an article on sun exposure and breast cancer. Johan Hernández is working with Dr. Nazario and Dr. Rosario on a paper describing the recruitment methods of the study. Dr. Nazario and Dr. Freudenheim are working on the preliminary analysis of ancestry data and markers of breast cancer in this Hispanic population.

In addition, there have been a number of students who have benefitted from the breast cancer study. They have been trained in recruitment strategies, and also have collaborated in certain aspects of data collection and data cleaning. Several students have used the breast cancer study database for their Master in Science dissertation. For example, Dr. Mansilla and Dr. Rosario are mentors of a graduate student interested in residential proximity during adolescence to energy generating industries. Dr. Rosario mentored a theses on sun exposure and breast cancer risk and is also mentoring a graduate student interested in exploring secondary smoke exposure in this data base. A student in the Master in Science in Epidemiology analyzed the use of metformin and breast cancer risk
using the database from the case-control study. One student evaluated BMI, biological markers and breast cancer risk for her MS degree and is actually completing a PhD in Epidemiology in the US. Dr. Nazario is mentoring a MS student evaluating alcohol consumption and breast cancer risk. Two students received their master degree after completing secondary analysis evaluating physical activity and breast cancer under the mentoring of Dr. Farah Ramírez-Marrero. Dr. Freudenheim mentored a dissertation were differences between the Puerto Rican diet, Hispanic American diet, and the diet of Puerto Ricans living in the United States were evaluated. Dr. Freudenheim has been the fundamental mentor to all the scientific works mentioned above. Students have presented posters with their research outcome in different scientific conferences.

All project investigators have acquired new expertise or have strengthened their skills as a direct outcome of participating in the BCRP HBCU/MI Partnership Training Award, thru the weekly conference calls, the formal academic training and the direct and practical involvement in study design, the development of measuring instruments, their participation in quality control processes, preliminary data analysis and publications. Development of expertise is an ongoing process that will continue during the course of their scientific career and they advance their knowledge of breast cancer epidemiology. Investigators of the project “The epidemiology of breast cancer in Puerto Rico” have presented posters and attended conferences to disseminate preliminary results. All researchers attended the “Building Network Symposium” and the Era of Hope Meetings.

3.4 The second mayor goal was to design, and implement a case control study.
The specific aims of the case-control study of breast cancer in Puerto Rico were: to examine dietary risk factors in relation to breast cancer; to examine other established risk factors such as lifetime weight gain, physical activity, alcohol consumption, and reproductive history among Puerto Ricans in relation to breast cancer risk; and to examine factors related to early life exposure including birth weight, adult height, childhood diet, physical activity, environmental factors, and residential history as a proxy for environmental exposure.
One important challenge was to obtain and maintain approval of the study from all study academic institutions (University of Puerto Rico and University at Buffalo) and from the Human Subjects Protection Scientist of the CDMRP IRB during all years of the award. Also the IRB continuation reports were submitted as required (USAMRMC Human Research Protection Office). The subject protocol for the Breast Cancer Study was initially approved by the Institutional Review Board (IRB) of the Medical Sciences Campus, University of Puerto Rico on May 8, 2009. The protocol was reviewed and approved by the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) on June 2009. The details of the protocol and approval information were reported in the second annual report. Hospitals and private physician that collaborated with the project also required the approval of the study protocol by their Board of Directors. The principal source of breast cancer cases, the Puerto Rico Central Cancer Registry, also required approval of the study protocol. Working with different institutional formats and requisites presented a challenge. These challenges were unraveled by the strong collaboration developed with all the institutions.

### 3.5 Recruitment and data collection.

The recruitment of study participants and data collection for the study protocol started in November 2009, after full approval of IRB. We began interviewing cases and controls at that time. Participant recruitment ended in May 2014. During June 2014, we worked on quality control of collected data, and completed the final interviews. Data cleaning and data analysis are ongoing.

The estimation of sample size and power was based on the Minimum Detectable Risks (MDR) for a sample of 500 cases and 500 controls, with a two-sided p-value set at 0.05 and power of 0.80, assuming that one third of women will be premenopausal at interview. Odds ratios on the order of 1.5 to 2.0 are detectable. The challenge to reach the sample size was enormous. During the pilot trial we had estimated a refusal rate of 13%, but this estimate was far from the observed refusal rate during the implementation of the case-control study. A refusal rate of 35% from potential and eligible breast cancer patients and
28% refusal rate were observed among potential and eligible population controls. The observed refusal rates implied an increased amount of time and effort to reach the proposed sample size, which we could not comply with. For each completed participant, 6 to 8 telephone calls were made to schedule and remind them of their appointment, to reschedule appointments, and motivate potential cases and controls to participate.

**Case ascertainment and recruitment**

Breast cancer cases were identified from the Puerto Rico Central Cancer Registry and patient lists from hospitals and physician offices in the Metropolitan San Juan Area. In order to meet the case ascertainment and recruitment goals, from November 2009 to May 2014, the project staff established links of collaboration with hospitals and physicians to identify breast cancer cases. Twenty eight primary physicians (or referring physicians) and five hospitals (hospitals with oncology departments) were contacted and agreed to identify and coordinate the recruitment of breast cancer cases. The process of identifying cases is detailed in Appendix C. The sample size estimation and the recruitment strategy to reach the goal,

During the recruitment process we received 1,809 referrals of potential breast cancer cases; but in 140 cases the provided contact information was either incomplete, missing or incorrect (i.e., disconnected phone number). The project staff contacted 1,669 breast cancer cases and evaluated their eligibility to participate in the study. Of these, the vast majority were not eligible. Of the 1227 breast cancer cases contacted that were not eligible, 871 had a different residential area (not within the target study areas) than the one stated in the Cancer Registry data bank or in the physician record. In 282 breast cancer cases, further evaluation of the date of diagnosis, or the tumor status (not been a primary breast cancer) made them ineligible for the study. The age and other miscellaneous reasons excluded 74 breast cancer cases. Only 442 breast cancer cases (27%) met the eligibility requirements: incident, primary, and pathologically confirmed breast cancer with no history of previous cancer, aged 30 to 79, and living in San Juan, Bayamón, Guaynabo or Carolina municipalities in the San Juan metropolitan area. Of those, 317 (72%) agreed to participate and completed the interview and clinical evaluation. (Appendix D).
Control ascertainment and recruitment

Controls were selected from a probabilistic sample of women aged 30-79, who were residents of San Juan, Bayamón, Guaynabo and Carolina at moment of recruitment. Controls were identified from participants in the Estudio Continuo de Salud (ECS), a National Health Survey in Puerto Rico, which was a random sample of Puerto Ricans. The process used to identify the controls is detailed in Appendix E.

During the recruitment of controls 1,136 households were visited. In these households, 720 women were contacted. Of these 720 contacted women, 538 were eligible to participate in the study and 348 (65%) agreed to participate and complete the interview and clinical evaluation (Appendix F).

For both cases and controls, we monitored ascertainment and recruitment procedures to optimize response rates and to maintain the population-based format of the study.

The recruitment process was somewhat slow during some time periods due to several situations beyond the control of the researchers. There were three situations that affected the most the recruitment process. First, the Puerto Rico Cancer Registry, which was the primary source of breast cancer case ascertainment, underwent an administrative restructuring process, interrupting project collaboration during some months. This process delayed the evaluation of pathology reports that allowed us to identify eligible breast cancer cases for the study, slowing the recruitment process and the scheduling of interviews. Trying to avoid interviewers’ bias on the status of the study participant (case or control) the recruitment of controls was also halted. Second, the Clinical Research Center, where we conducted the interviews, does not operate for 3 weeks every December: there were also, workers’ union lockouts as well as administrative shutdown of operation. Lastly, during the past years heavy rains from August to November delayed and interrupted the recruitment process as well as the scheduling of the interviews.

We were fortunate to request and obtain no-costs extensions that made it possible to continue with recruitment. These situations and other were reported in past reports. In spite of the difficulties inherent in the development of a new research infrastructure, we
were able to contact and evaluate the eligibility of more than 1000 cases and 1000 controls.

3.6 Preliminary analysis

We are in the process of data verification and quality control of the data base. Of the total study sample we have a preliminary analysis of 617 study participants. The preliminary analysis is presented a table included as Appendix G.

In the preliminary analysis, controls made up 53% of the sample and the average age of the total study group was 56 years of age (±12.6 years). Almost half of the study population had a technical or bachelor’s degree, the same proportion of the group stated they were married or living with a partner at interview. A very large percentage (71%), was already menopausal at interview, as expected by the age criteria for inclusion. Eighty eight percent (88%) of the participants had their first pregnancy before age 31, with 55% of then having 3 or more children. A considerable proportion (80%) of the participants had a measured BMI classified as overweight or obese.

Another interesting finding is the relationship between sun exposure and breast cancer. High sun exposure was associated with a protective benefit against breast cancer after controlling for age, education, and sun screen use at some point in the lifetime. A higher percentage of breast cancer cases were in the lowest sun exposure category. Low sun exposure, estimated by skin pigmentation difference, was associated with increased risk of breast cancer (OR adjusted=2.27; 95% CI: 1.50, 3.44). The adjusted OR for premenopausal women was 1.62 (95% CI = 0.86 to 3.03) and for postmenopausal women was 2.60 (95% CI =1.48 to 4.56). This preliminary analysis supports the hypothesis that sun exposure may contribute to a reduction in the risk of breast cancer.

3.7 Manuscripts: No manuscripts have been yet submitted for publication.

Several manuscripts are in preparation. They include an examination of the foods which contribute to the intake of nutrients of interest in the Puerto Rican diet. Another paper in progress is examining body mass index, body fat distribution and other factors related to
body fatness. There is new understanding that the impact of BMI on health differs by race/ethnicity. Understanding BMI and possible differences in BMI distribution between breast cancer cases and controls among Puerto Rican women has considerable potential for public health interventions. Finally, preparation is also underway of a manuscript to describe the findings related to sun exposure and breast cancer risk.

Because the data collection has just been completed, we are still in the process of writing research reports. We expect to explore this data set for a long time to come. At this time, the following papers are in progress:


The following abstracts have been presented at regional, national and international conferences:


4. Key research accomplishment
   • Training investigators from the University of Puerto Rico
   • Participation of investigators from the University of Puerto Rico in formal academic summer courses
   • University of Puerto Rico’s IRB approval of study protocol in coordination with various institutions that required independent informed consent documents
   • Development of a complex questionnaire that was electronically administered and data saved
   • Recruitment of breast cancer cases using different patient data sources
   • Developing and implementing a recruitment strategy for population controls
   • Preliminary results and findings have been presented in scientific meetings and conferences, locally and abroad.

5. Conclusion
The Breast Cancer Epidemiology in Puerto Rico project had two major goals: training researchers from a minority academic institution and developing the infrastructure to design and conduct a population based pilot study of breast cancer in Puerto Rico. All
investigators from the University of Puerto Rico have acquired new expertise or have strengthened their skills as a direct outcome of participating in the BCRP HBCU/MI Partnership Training Award, thru weekly conference calls, formal academic training, practical involvement in study design, developing measuring instruments, participating in quality control processes, preliminary data analysis and manuscripts preparations.

For the second major goal, a population based case control study was designed to evaluate risk factors for breast cancer among Hispanic women living in the San Juan Metropolitan of Puerto Rico. Breast cancer cases were identified from the Puerto Rico Central Cancer Registry and patient lists from hospitals and physician offices in the Metropolitan San Juan Area. Of the 1809 referrals of potential breast cancer cases, 1,669 had contact information and of those 442 met the eligibility requirements: incident, primary, and pathologically confirmed breast cancer with no history of previous cancer, aged 30 to 79, and living in San Juan, Bayamón, Guaynabo or Carolina municipalities in the San Juan metropolitan area. Of those, 317 (72%) agreed to participate and complete the interview and clinical evaluation. Controls were selected from a probabilistic sample of women aged 30-79, who were residents of San Juan, Bayamón, Guaynabo and Carolina at moment of recruitment. During the recruitment of controls 1,136 households were visited and 720 women were contacted. Of these women, 538 were eligible to participate in the study and 348 (65%) agreed to participate and complete the interview and clinical evaluation.

6. Publications. Nothing to report

7. Inventions, patents and licenses: Nothing to report

8. Reportable outcomes: Nothing to report

9. Other achievements:
Serum depository: A biological sample was collected from all study participants that agreed to donate blood or saliva for future studies. We collected a fasting blood sample
that was aliquoted to tubes of 0.5 ml for serum plasma, red blood cells and buffy coat at the UPR Clinical Research Center and then sent to Roswell Park Cancer Institute and University of Buffalo for long term storage. Samples were ID coded with scannable bar codes.

Sun exposure index, measured using a colorimeter (chroma-meter -Minolta CR-400) provided two different skin pigmentation values: the facultative pigmentation (sun-exposed dorsal area of the left hand between the thumb and index finger) and the constitutive pigmentation (relatively unexposed interior area of the upper left arm). The standardized difference in the average of three measurements of the facultative and constitutive skin pigmentation was used to calculate a sun exposure index (SEI).

Application for funding: Project investigators have written and submitted letters of intent, pre-proposals and a full proposal to different funding agencies. Planning and proposal writing continues.

Submitted proposals:


Approved proposal:

- “Preparándonos para vencer: Programa para identificar las necesidades de información y apoyo para las mujeres sobrevivientes de cáncer de mama menores de 50 años y su pareja-cuidadora en Puerto Rico. Proposal, submitted by Johan Hernández, was approved and supported by Susan G. Komen-Puerto Rico (2012-2013 cycle).
10. References


11. Appendices

- Training study investigators (Appendix A).
- Summer courses (Appendix B)
- Process for identifying cases (Appendix C)
- Flowchart describing case recruitment data (Appendix D)
- Process for identifying control (Appendix E)
- Flowchart describing control recruitment data (Appendix F)
- Table with preliminary data analysis (Appendix G)
Appendix A
Training study investigators

Breast Cancer Epidemiology in Puerto Rico
Annual Report (1)
June 2007 to June 2008

Imar Mansilla Rivera
1. Training and meeting
   a. Registered at the 19th Conference of the International Society for Environmental Epidemiology (ISEE), held in Mexico City, September 5 – 9, 2007.
      • Attended a pre-conference workshop on “Children’s Vulnerability to Pollution”
      • Attended a training session on “Cancer susceptibility and environmental interactions”
      • Attended several oral and poster presentations on topics such as environmental exposures at different stages of development, health effects of various groups of contaminants (e.g. air pollutants, trace metals, persistent chlorinated and brominated compounds)
      • Presented a poster on “Arsenic exposure from fish consumption in Vieques, Puerto Rico”, sponsored by the University of Puerto Rico-Roswell Park Cancer Institute Partnership (NIH/NCI P20 CA096257).
   b. Audited conferences on design and analysis of descriptive, cohort, case-control, and experimental studies, as well as confounding factors of epidemiologic studies in the course EPID 6523, Epidemiologic Methodology, September 12 – October 15, 2007.
   c. Registered at the Building Network Symposium and at the Era of Hope Meeting, held in Baltimore, Maryland, from June 24 – 28, 2008.

Michele Schelske-Santos
1. Training and meeting
2. Conferences  
a. April 23, 2008, Dr. Michelle Schelske Santos was invited to give a conference from 9:30 a.m. – 11:00 a.m. titled, *Diet, Nutrition and Cancer Prevention*, to the employees of the Procurement Office, University of Puerto Rico, Rio Piedras, as part of the special activities scheduled for Administrative Assistant’s Week (Secretary’s Day).

3. Course curriculum and incorporation of technology  
a. As part of the Biochemistry course (ECDO 4158) for undergraduate nutrition and dietetics students at the University of Puerto Rico, Rio Piedras Campus, Dr. Michelle Schelske Santos integrated an electronic discussion board (in Blackboard) on the subject of Diet, Nutrition and Cancer Prevention, in order for students to explore and dialog the biochemical and nutritional implications of traditional food and alternative nutrition therapies on cancer prevention.

4. Student Mentoring  
a. Under the mentorship of Dr. Michelle Schelske Santos, two undergraduate students of the Nutrition and Dietetics Program, UPR-Rio Piedras, Jacqueline Martínez-Chaluisant and Dariana Soto-Reyes were accepted for and attended the 2008 Nutrition and Cancer Prevention Research Practicum sponsored by the Nutritional Science Research Group, National Cancer Institute, National Institutes of Health, and the Department of Nutrition at the Clinical Center, National Institutes of Health in Bethesda, Rockville, and Beltsville, MD, held March 17 – 21, 2008. These students competed at the national (USA) level with graduate students and interns, professionals in the health sciences, such as physicians and licensed dietitians; they were the only two undergraduates chosen for the cohort of 40 selected participants.

**Breast Cancer Epidemiology in Puerto Rico**  
**Annual Report (2)**  
**June 2008 to June 2009**

**Dr. Cruz M. Nazario**

1. Weekly conference call with investigators from Puerto Rico and Dr. Jo Freudenheim from the University at Buffalo.
2. Weekly meeting with project coordinator.
3. Training and meetings  
   a. Attendance to Annual Meetings:  
      i. The Joint Annual Conference of the International Society for Environmental Epidemiology (ISEE) and International Society of Exposure Analysis (ISEA), held in Pasadena, California, from October 12-16, 2008.

      1. I met with epidemiologists participating in the meeting to discuss ideas for future studies on environmental contamination and breast cancer risk.

1. I was invited to present about *Breast Cancer Research in Puerto Rico* at the pre-meeting workshop Latino Breast Cancer Consortium.

**Dr. Farah A. Ramírez-Marrero**

1. Weekly conference call with investigators from Puerto Rico and Dr. Jo Freudenheim from the University at Buffalo.
2. Training and meetings
   a. Attendance to Annual Meetings:
      i. **Experimental Biology 2009** in New Orleans, Louisiana (April 18-22)
         1. Monday, April 19:
            a. Session: Obesity, Aging and Cancer
         2. Tuesday, April 20:
      3. Wednesday, April 21:
         a. Poster: Molecular mechanism effect of taxotere and ukrain in cell cycle regulating genes in positive and negative breast cancer cell lines. Alokail, Al-Mansouri, Bin Amer. King Saud University, Saudi Arabia.
      4. Thursday, May 28:
         a. Session: Exercise interventions in Cancer Survivors: A diverse Perspective
         i. Effect of physical activity on weight and body composition in breast cancer survivors. Cadmus, Yu, Wiley, Chung, Irwin. Yale University, CT.
         ii. One-year randomized, controlled trial of strength training in older breast cancer survivors: preliminary findings. Winters-Stone, Reiner, Dobek, Nail, Bennet, and Naik. Oregon Health and Science University, Portland, OR.
         b. Session: Physical activity, fatigue and pain
         i. The effects of 12-weeks cross training on fatigue and mood in recent breast cancer survivors. Pouvevigne, Wojcik, Lane, Polovich and Simonishvili. Emory University, Atlanta.
      5. Friday, May 29:
         a. Session: Exercise with Cancer Patients
i. The relationship of physical activity across the lifespan and breast health. Sprod, Hsieh, Carter, Hayward, Schneider. Univ. Northern Colorado, CO.

6. Saturday, May 30:
   a. Session: Clinical Medicine II – Medical


iii. 2009 International Conference on Diet and Activity Methods in Washington, DC (June 5-7)
   1. Friday, June 5:
      a. Conference: Climate change: interrelationships with diet and physical activity.
      c. Symposium: Measures of the physical activity built environment
      d. Symposium: Measuring change in diet and physical activity in intervention studies
   2. Saturday, June 6:
      a. Conference: The magnitude of the energy gap and its determinants
      b. Conference: The energy gap for obesity
      c. Symposium: Physical activity measurement of individuals
      d. Symposium: Energy balance: synchronized measures of energy intake and output, and data complexity in physical activity measures
      e. Dinner meeting with Dr. Jo Freudenheim.
   3. Sunday, June 7:
      a. Symposium: Lessons learned from national surveillance studies on physical activity.

Dr. Michelle Schelske-Santos
1. Weekly conference call with Dr. Jo Freudenheim (University at Buffalo) and Puerto Rico investigators team.
2. Training and Meetings:
   i. Seventh International Conference on Diet and Activity Methods Hyatt Regency Capitol Hill Washington DC June 4 – 7, 2009
      1. Pre-Conference Workshop: Understanding Measurement Error in Diet and Activity Assessment (This conference was very useful in presenting systematic and random measurement errors common to food frequency questionnaires, 24h dietary recalls, physical activity questionnaires and accelerometer measures, in addition to how a variety of statistical models can be applied to collected data to help correct for these errors during data analyses.)
      2. Conferences: Climate Change: Interrelationships with Diet and Physical Activity
      3. Conferences: Technological Advances in Measuring Diets of Individuals, Dietary Biomarkers: Novel Techniques
4. Conferences: Advances in Coping with Measurement Error in Diet and Physical Activity Measures
5. Conferences: Diet Measurement of Individual Intake: Development of Instruments
6. Conferences: technology demonstration of on line 24h dietary recalls
7. Conferences: Dietary Patterns: Research Challenges and New Methodologic Directions, Energy Gap that Causes Obesity;

This three-day conference was very informative and useful in helping with the concepts of instrument development, validation, and analysis in order to obtain the data necessary to link dietary and physical activity patterns and lifestyles to disease outcomes and prevention. These techniques and potential applications are directly related to the development and validation of our food frequency questionnaire to assess potential exposures related to breast cancer incidence and prevention in our Puerto Rican population.

Dr. Imar Mansilla-Rivera
1. Weekly conference call.
2. Training and meeting
   a. Attendance to Annual Meetings:
      i. The Joint Annual Conference of the International Society for Environmental Epidemiology (ISEE) and International Society of Exposure Analysis (ISEA), held in Pasadena, California, from October 12-16, 2008.
         1. Attended a pre-conference workshop on “Ultrafine and fine particulate matter monitoring in exposure and epidemiological studies”.
         2. Attended several oral and poster presentations on topics such as environmental exposures at different stages of development, health effects of various groups of contaminants (e.g. air pollutants, trace metals, persistent chlorinated and brominated compounds).
         3. Also, I met with other researchers working in the area of endocrine disruptor exposures and their health effects (e.g. breast cancer) to exchange ideas for future collaborations and potential studies.

Johan Hernandez, MPH
1. Weekly meeting with principal investigator and other staff project.
2. Training and meeting:
   a. Attendance to Annual Meetings:
         1. Attended several conferences and workshop on cancer and epidemiology (Cancer and its Impact on Women's Lives and Health, Cancer Epidemiology I and II and Social Epidemiology: Effects of Race/Ethnicity and Socioeconomic Disparities on Health).
   1. Attended a pre-meeting workshop Latino Breast Cancer Consortium.
   2. Attended several conferences on cancer epidemiology.

Breast Cancer Epidemiology in Puerto Rico
Annual Report (3)
June 2009 to June 2010

Dr. Cruz M. Nazario
1. Weekly conference call with investigators from Puerto Rico and Dr. Jo Freudenheim from the University at Buffalo.
2. Weekly meeting with project coordinator.
3. Training and meetings:
      i. I attended sessions on breast cancer prevention, screening and histopathology.
   b. AACR Special Conference in Cancer Epigenetic, held in San Juan PR, January 2010
      i. I attended sessions on cancer epigenetic and participated in workshop was held to discuss the bioinformatics challenges of whole genome epigenetic analyses.
      ii. I met with Dr. Jo Freudenheim (Co-investigator and mentor) to discuss relevant issues regarding the study protocol development (recruitment, interview process, biological sample and other).
      i. I participated in several sections related to cancer science from basic through clinical and epidemiological research.
      ii. I met with researchers participating in the meeting to discuss ideas for future studies on breast cancer risk.
      iii. I met with Dr. Jo Freudenheim (Co-investigator and mentor) and Dr. Theresa J. Miller (Task Manager, Congressionally Directed Medical Research Programs) to discuss relevant issues regarding the study protocol (interview process, biological sample and other).

Dr. Michelle Schelske-Santos
1. Weekly conference call with Dr. Jo Freudenheim (University at Buffalo) and Puerto Rico investigators team.
2. Training and meetings:
      i. I participated in several sections directly related to dietary, physical activity patterns, lifestyles and Breast Cancer.
Dr. Imar Mansilla-Rivera
1. Weekly conference call.
2. Training and meetings:
   a. The Joint Annual Conference of the International Society for Environmental
      Epidemiology (ISEE), held in Dublin, Ireland, from August 25 – 29, 2009.
      i. I participated in a pre-conference workshop on “DAGviromental Health:
         Introduction to Causal Diagrams and Their Application in Environmental
         Epidemiology Research

Johan Hernandez, MPH
1. Weekly meeting with principal investigator and other staff project.
2. Training and meetings:
   a. The American Public Health Association’s 137th Annual Meeting & Exposition:
      i. I attended several conferences and workshop on cancer epidemiology:
         1. Epidemiology Education – The many faces of epidemiology training in
            today dynamic and global public health.
         2. Health Disparities and Epidemiology
         3. Cancer Epidemiology Section I
         4. Genetic and Molecular Epidemiology and Breast Cancer Awareness
         5. Screening and Control Innovative Strategies for Reducing Disparities.

Breast Cancer Epidemiology in Puerto Rico
Annual Report (4)
June 2010 to June 2011

Dr. Cruz M. Nazario
1. Weekly conference call with investigators from Puerto Rico and Dr. Jo Freudenheim from
   the University at Buffalo.
2. Weekly meeting with project coordinator.

Dr. Farah Ramirez
1. Weekly conference call with investigators from Puerto Rico and Dr. Jo Freudenheim from
   the University at Buffalo.
2. Training
   a. AICR Annual Research Conference on Food, Nutrition, Physical Activity and
      Cancer, held in Washington, DC from October 21 & 22, 2010
      i. I attended the following sessions and conferences:
         1. Aging: issues related to diet, physical activity and cancer.
         2. Diet, Physical Activity and Cancer Survivorship.
         3. Diet and Cancer: what cohort studies are telling us
         4. Obesity and cancer: implications for public health
         5. New and Emerging Science: the Microbiome-implications for diet and
cancer.

Johan Hernandez, MPH
1. Weekly meeting with principal investigator and other staff project.
2. Training:
      i. I attended several conferences and workshop on cancer epidemiology:
         2. Epidemiology of Breast Cancer
         3. Health Disparities
         4. Poster presentations

Breast Cancer Epidemiology in Puerto Rico
Annual Report (5)
July 2011 to June 2012

Dr. Cruz M. Nazario
1. Weekly conference call with investigators from Puerto Rico and Dr. Jo Freudenheim from the University at Buffalo.
2. Weekly meeting with project coordinator.
3. Training:
   a. “Role of Obesity in Cancer Survival and Recurrence” in Washington, DC from October 31-November 1, 2011. This workshop was hosted by the National Cancer Policy Forum to examine issues related to diet, physical activity, obesity and cancer survival.

Johan Hernandez, MPH (Project Coordinator)
1. Weekly meeting with principal investigator and other staff project.
2. Training: Attendance to Annual Meetings

Breast Cancer Epidemiology in Puerto Rico
Annual Report (6)
July 2012 to June 2013

Dr. Cruz M. Nazario
1. Weekly conference call with investigators from Puerto Rico and Dr. Jo Freudenheim from the University at Buffalo.
2. Weekly meeting with project coordinator.
3. Workshop and meeting
i. Participate in panel and roundtable of discussions relating to public health issue such cancer, environmental pollution and other.

**Dr. Michelle Schelske-Santos**
1. Weekly conference call with investigators from Puerto Rico and Dr. Jo Freudenheim from the University at Buffalo.
2. Workshop and meeting
      i. Presenter a poster with preliminary data of the Breast Cancer Epidemiology Study (ATABEY).

**Dr. Imar Mansilla-Rivera**
1. Weekly conference call with investigators from Puerto Rico and Dr. Jo Freudenheim from the University at Buffalo.
2. Workshop and meeting
      i. Participate in roundtable of discussions relating to public health issue such cancer and environmental pollution.
      ii. Co-Presenter a poster with preliminary data of the Breast Cancer Epidemiology Study (ATABEY).

**Dr. Farah Ramirez**
1. Weekly conference call with investigators from Puerto Rico and Dr. Jo Freudenheim from the University at Buffalo.
2. Workshop and meeting
      i. Co-presenter a poster with preliminary data of the Breast Cancer Epidemiology Study (ATABEY).

**Dr. Rosa Rosario**
1. Weekly conference call with Dr. Jo Freudenheim (University at Buffalo) and Puerto Rico investigators team.
2. Workshop and meeting
      i. Presenter a poster with preliminary data of the Breast Cancer Epidemiology Study (ATABEY).

**Johan Hernandez, MPH**
1. Weekly meeting with principal investigator and other staff project.
2. Workshop and meeting
   i. Attended several conferences and workshop on cancer:
      a. Cancer Epidemiology
      b. Latino Cancer Research jointly (presented by the Cancer Forum and the Latino Caucus)
      c. Impact of Social Determinants on Cancer Morbidity and Mortality
      e. Poster presentations
   i. Attended conferences and workshop on Public Health
   ii. Presenter a poster with preliminary data of the Breast Cancer Epidemiology Study (ATABEY) Recruitment Process.
Appendix B
Courses of study investigators

Breast Cancer Epidemiology in Puerto Rico
Annual Report (1)
June 2007 to June 2008

Imar Mansilla Rivera

Registered in a course on “Environmental Epidemiology”, sponsored by the 2007 Summer Program in Applied Biostatistics & Epidemiological Methods, The Ohio State University, Columbus, Ohio. July 16-20, 2007.

Course description

**Environmental Epidemiology**

*Harvey Checkoway, Ph.D., University of Washington*

This course will provide a summary of the epidemiologic study designs and methods for investigating health hazards associated with environmental exposures. Related topics that will be covered include: case cluster investigation methods; approaches to characterizing environmental exposures; sources of and methods to minimize study bias; and applications of epidemiologic data, such as for environmental risk assessment. Methodological concepts will be illustrated with examples of research on environmental risk factors for cancer, neurological diseases, respiratory diseases, and adverse reproductive outcomes. Lectures will be supplemented by discussions of selected journal articles and by in-class exercises that emphasize the roles public health practitioners play in the conduct of environmental epidemiology.

Registered in a short course titled Logistic Regression Modeling, held in San Juan, Puerto Rico, May 12 – 14, 2008.


Michelle Schelske-Santos
i. Courses Epidemiological Methodology at Graduate School of Public Health, University of Puerto Rico. The course presents epidemiological principles and methods as an approach to the study of the phenomena of health and disease. The scientific method, the epidemiological method, the concept of causality, descriptive epidemiology, and hypothesis formulation, case studies, cohort studies, intervention studies, screening, outbreaks, and research design are among the topics covered.
ii. Summer course Nutritional epidemiology at Johns Hopkins summer institute, 2008. The course presents an introduction to the methodological issues involved in the design, conduct, analysis and interpretation of studies investigating the relationship between nutritional status, diet and disease.
iii. Summer course Diabetes and Obesity Epidemiology at Johns Hopkins summer institute, 2008. This course describes the epidemiology and prevention of diabetes, obesity, and associated complications.

Breast Cancer Epidemiology in Puerto Rico
Annual Report (2)
June 2008 to June 2009

Imar Mansilla Rivera

Breast Cancer Epidemiology in Puerto Rico
Annual Report (3)
June 2009 to June 2010

Imar Mansilla-Rivera
i. Attended a course on “Molecular Epidemiology of Cancer”, offered by the 44th Graduate Summer Session on Epidemiology, The University of Michigan, School of Public Health, Ann Arbor, Michigan. July 13-17, 2009. The course explored concepts and issues found at the interface of the basic sciences and cancer epidemiology, including discovery of new biomarkers, whole genome association studies, expression profiling and proteomics, and development of new technologies for cancer screening. Students were asked to apply the knowledge gained to a particular problem in cancer epidemiology.

Rosa Rosario
i. Attended a course on Social Epidemiology at Johns Hopkins Bloomberg School of Public Health Baltimore, MD. June 29 to July 3, 2009. This course offered an overview of conceptual and methodological approaches relevant to the study of the impact of social factors on the population health.
Other course and educational activity

Imar Mansilla
August 2012  24th Annual Conference International Society for Environmental Epidemiology (ISEE), Columbia, South Carolina. Short course on “Epigenetics-Memories of past exposures and predictors of diseases: Methodological considerations”

Michelle Schelske-Santos
The participation in the American Association of Cancer Research Annual Conference contributed to the development of educational modules in Diet, Nutrition and Cancer for two courses: ECDO 5997, Special Topics in Foods and Nutrition, (August, 2010; 6 undergraduate students), and an online distance education course NUTR 5997, Contemporary Issues in Foods and Nutrition (August 2013, 6 undergraduate students). These elective courses will be offered periodically with the intent of increasing interest in diet, nutrition and cancer among undergraduate nutrition students to stimulate graduate studies and investigative projects in related areas.
Appendix C
Process for identifying cases

Step A
Identification of sources

Primary source
Puerto Rico Central Cancer Registry (PRCCCR)
Evaluate the pathology reports to identify a breast cancer cases.

Secondary source
Hospitals with oncology department
Verify cancer registry data to avoid duplication of cases.

Enter patients and primary physician information into cases data base.

Step B
Determine eligibility
Step C
Contact primary physician

Primary breast cancer
(< 1 year of diagnosis, not recurrence or metastasis)

Yes

Women between 30 to 79 years?

Yes

Step C
Contact primary physician

No

No
Primary physician agree to participate and to contact patient?

Yes

Step D
Contact patient and evaluate eligibility

No

Resident of San Juan, Bayamón, Carolina and Guaynabo?
Step E
Invitation to participate

- Coordinate appointment

Women agree to participate?

Yes

No
Cases received from primary and secondary source \( (n=1,809) \)

Step A
Establish contact

Pending to contact \( n=0 \)

Contacted \( n=1,669 \)

Not available \( n=140 \)

Step B
Determine eligibility

Eligible \( n=442 \ (27\%) \)

Not eligible \( n=1,227 \ (73\%) \)

Step C
Invitation to participate

Agreed to participate \( n=317 \ (72\%) \)

Refused to participate \( n=125 \ (28\%) \)

Residence area = 871
Time of diagnosis = 282
Age = 32
Others = 42

Appendix D
Flowchart describing case recruitment data
Step A
Identify Household

An adult present in the household?

Yes

Briefly explain Atabey study

Step B
Identify potential Participant

Women between 30 to 79 years?

No

-Go to the next house to the left

No

-Go to the next house to the left

-Go to the next house to the left

Appendix E
Process for identifying control
Step C
Invitation to participate

Yes

History of cancer?

No
- Provide study information

Step C
Invitation to participate

Yes

Agree to participate?

No

Other Women between 30 to 79 years?

No
- Go to the next house to the left

Step A

Yes
- Coordinate appointment
Potential controls identified (n=720)

Determine eligibility

Women aged 30-79 years?

Yes

n=570

No

n=150

Previous history of cancer?

Yes

n=32

No

n=538

Agreed to participate

n= 348 (65%)

Refused to participate

n=190 (35%)
### Table 1.

<table>
<thead>
<tr>
<th>Demographic characteristics of study participants.</th>
<th>Number</th>
<th>% (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer cases</td>
<td>292</td>
<td>47.3%</td>
</tr>
<tr>
<td>Population controls</td>
<td>325</td>
<td>52.7%</td>
</tr>
<tr>
<td><strong>Age group (yrs.)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>73</td>
<td>11.8%</td>
</tr>
<tr>
<td>40-49</td>
<td>132</td>
<td>21.4%</td>
</tr>
<tr>
<td>50-59</td>
<td>143</td>
<td>23.2%</td>
</tr>
<tr>
<td>60-69</td>
<td>172</td>
<td>27.9%</td>
</tr>
<tr>
<td>70-79</td>
<td>97</td>
<td>15.7%</td>
</tr>
<tr>
<td><strong>Age average (n=617)</strong></td>
<td>617</td>
<td>56.02±12.6</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School or less</td>
<td>244</td>
<td>39.6%</td>
</tr>
<tr>
<td>Bachelor or technical program</td>
<td>308</td>
<td>49.9%</td>
</tr>
<tr>
<td>Graduate credits or degree</td>
<td>65</td>
<td>10.5%</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married or living with partner</td>
<td>309</td>
<td>50.5%</td>
</tr>
<tr>
<td>Single</td>
<td>86</td>
<td>14.0%</td>
</tr>
<tr>
<td>Divorce</td>
<td>140</td>
<td>22.9%</td>
</tr>
<tr>
<td>Widow</td>
<td>77</td>
<td>12.6%</td>
</tr>
<tr>
<td><strong>Menopausal status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause</td>
<td>438</td>
<td>71.1%</td>
</tr>
<tr>
<td><strong>Age at first pregnancy (n=542)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 yrs.</td>
<td>141</td>
<td>26.0%</td>
</tr>
<tr>
<td>20-29 yrs.</td>
<td>336</td>
<td>61.9%</td>
</tr>
<tr>
<td>30-39 yrs.</td>
<td>62</td>
<td>1.4%</td>
</tr>
<tr>
<td>40-49 yrs.</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td><strong>Number of pregnancies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>75</td>
<td>12.2%</td>
</tr>
<tr>
<td>1</td>
<td>66</td>
<td>10.7%</td>
</tr>
<tr>
<td>2</td>
<td>137</td>
<td>22.2%</td>
</tr>
<tr>
<td>≥3</td>
<td>339</td>
<td>54.9%</td>
</tr>
<tr>
<td><strong>Use of HRT</strong></td>
<td>474</td>
<td>77.5%</td>
</tr>
<tr>
<td><strong>Family history of breast cancer</strong></td>
<td>488</td>
<td>79.1%</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under weight</td>
<td>10</td>
<td>1.7%</td>
</tr>
<tr>
<td>Normal</td>
<td>109</td>
<td>18.2%</td>
</tr>
<tr>
<td>Over weight</td>
<td>188</td>
<td>31.4%</td>
</tr>
<tr>
<td>Obese</td>
<td>292</td>
<td>48.8%</td>
</tr>
</tbody>
</table>