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PRINCIPAL INVESTIGATOR: Robert R. Clarke, Ph.D., D.Sc.

CONTRACTING ORGANIZATION: Georgetown University
Washington, D.C. 20057-1411

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Abstract

This is a Pilot Award to design a Breast Cancer of Excellence Pilot on the single, unifying question, "*What are the roles of obesity in affecting breast cancer risk and mortality?*" This question is the cornerstone of our proposed Center and is relevant to the prevention, detection, diagnosis and treatment of breast cancer. More specifically, we will study the interactions among timing of obesity, hormones, and breast cancer risk in minority and Caucasian populations and in appropriate animal models. Consistent with the goals of this award mechanism, we will use this pilot to build teams of consumers and leading investigators, in multiple research areas across several institutions in the U.S. and abroad, who will design innovative and imaginative approaches to addressing our overarching goal. We have commitments from consumers, computer scientists, engineers, biostatisticians, epidemiologists, endocrinologists, radiologists, medical oncologists, pathologists, behavioral scientists, and nutritionists. We will apply state-of-the-art technologies including high throughput genotyping, molecular profiling and tumor tissue arrays, digital mammography, magnetic resonance imaging, nanotechnology, bioinformatics, and biostatistics. This represents a unique mix of expertise and institutions, and includes both leading scientists and young investigators poised to address this critical problem in breast cancer research, treatment, and prevention.

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INTRODUCTION

This is the final report for a Pilot Award to design and submit an application to establish a DOD Breast Cancer Center of Excellence. Funding was specifically to prepare a Center on Obesity and Breast Cancer, in which we initially proposed to develop a translational approach with animal models and studies in human populations. The full application has been successfully submitted to the Breast Cancer Research Program and now awaits peer review.

Overview: In the U.S., obesity prevalence doubled between 1980 and 2000; 34% of U.S. women are now obese (body mass index; $BMI \geq 30$). While obesity significantly increases the risk of dying from breast cancer, independent of menopausal status and race/ethnicity, outcomes are worse for African-American compared with White and Hispanic women. A woman's risk of developing breast cancer also is affected by obesity but this relationship is complex and modified by race and the time in her life when she is obese. For example, obesity reduces premenopausal breast cancer risk in non-Hispanic White women but may increase this risk among African-American and Hispanic women. High and very low birth weight increase premenopausal breast cancer risk but high body mass during childhood is associated with reduced pre- and postmenopausal breast cancer risk. These effects of obesity are most closely associated with the pattern of central obesity seen in metabolic syndrome. However, the precise contribution of timing effects, and particularly how this is modified by race, is poorly understood - most studies have been done in largely non-Hispanic White populations.

Lack of a full understanding of how obesity affects both breast cancer risk and survival is a major obstacle to the eradication of breast cancer. We proposed to design a Center of Excellence application focused on the overarching question, "*What are the roles of obesity in affecting breast cancer risk and survival?*" In this Center, we will propose to address the modifying effects of obesity on breast cancer risk and survival by tightly integrating data from laboratory, clinical, behavioral, bioethical, and epidemiologic studies. Successful completion of our studies will enable us to rapidly deploy interventions that reduce the effects of obesity/metabolic syndrome on breast cancer risk and improve breast health care for obese breast cancer patients.

BODY

Background: Obesity is defined as a body mass index (BMI ; weight in kg divided by height in m^2) ≥ 30 (~30 lbs overweight for a 5'4" women). Data from the National Health Examination Study (NHES) and National Health and Nutrition Examination Studies (NHANES) report that the prevalence of obesity among U.S. women was 17% in 1976-80; by 1999-2000 this had doubled [1]. By 1998, over 30% of pregnant women were obese, compared with <15% prior to 1989 [2,3]. Obesity is now one of the most common causes of complications during pregnancy [4]. In the U.S., 65% of the population is overweight (BMI 25.0-29.9) or obese [1].

Adult diet/obesity accounts for 30% of cancer deaths attributable to known causes; overweight and obesity account for 1 in 7 cancer deaths in women [5]. Only tobacco use generates a similar proportion of all cancer deaths; the next nearest contributors account for only 5%, e.g., family history, occupational factors [6]. **Obesity is associated with five of the top ten fatal cancer sites in women: breast (15%; $RR=2.12$; $p<0.001$), ovary (6%; $RR=1.51$; $p=0.001$), uterine corpus (3%; $RR=6.25$; $p<0.001$), pancreas (6%; $RR=2.76$; $p<0.001$), non-Hodgkin lymphoma (3%; $RR=1.95$; $p<0.001$); percentages are of all cancer deaths in women [7]; RRs are risk of death associated with being obese; probabilities are for trend (from Calle *et al.* [8]).**

A pooled analysis of seven prospective cohort studies published prior to 2000 [9] clearly shows the *direct* association of obesity with risk of postmenopausal breast cancer ($RR=1.26$; $CI=1.09-1.46$) and the *inverse* association of obesity with risk of premenopausal breast cancer risk ($RR=0.54$; $CI=0.34-0.85$). Other large studies have since generated similar data, e.g., the inverse association between obesity and premenopausal

breast cancer risk in a cohort of 99,717 women (RR=0.58; CI=0.36-0.95) [10] and a cohort of 21,884 twins (RR=0.51; CI=0.33-0.78) [11]. Subsequent data on the direct association between obesity and **postmenopausal** breast cancer risk also are consistent. A prospective study of 12,159 postmenopausal women reported increased risk in women with a BMI >28.5 (RR=1.54; CI=1.01-2.35) [12]. **Postmenopausal** breast cancer risk is increased in women who were obese during *either* their pre- and/or postmenopausal years. *These studies were done, almost exclusively, in White populations in western countries.* The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence to support weight gain avoidance to reduce **postmenopausal** breast cancer risk [13].

Body weight at other life stages also affects breast cancer risk. Childbearing is key in determining adult weight/weight gain [14] and excessive weight gain during pregnancy increases a woman's risk for postmenopausal breast cancer [15]. Both high and very low body weight at birth increases the risk of developing premenopausal breast cancer in adulthood [16-19]; the effect on postmenopausal breast cancer risk is controversial [16,19]. Early growth rate may be most important for affecting later risk [18]. High body mass during childhood is consistently associated with a *reduction* in both pre- and postmenopausal breast cancer risk [15,20-24]. Nonetheless, overweight/obese girls reach puberty earlier than normal weight girls - early puberty is associated with *increased* breast cancer risk [25]. It is unclear whether puberty onset directly affects breast cancer risk or is a marker of another exposure. Animal studies show that *in utero* estrogenic exposures accelerate puberty onset, increase mammary gland density, and increase susceptibility to carcinogenesis [26].

Studies in non-Hispanic White women convincingly show that increasing body size is positively associated with risk of postmenopausal breast cancer and inversely associated with risk of premenopausal breast cancer [9-11,13,27,28]. Studies in non-Hispanic Whites also suggest that breast cancer risk is increased in association with high birth weight [16-19], and high weight gain during pregnancy [15], while risk is reduced in association with high body size (and greater fatness) during childhood and adolescence [24,29]. While there have been relatively few studies in U.S. minority populations, evidence suggests that **the consequences of body composition and obesity-related changes in metabolism and serum estrogens are less harmful in Hispanics, and more deleterious in African-Americans [30,31] - the reasons are unknown.** African-Americans are taller and heavier as adults but smaller at birth; the prevalence of low birth weight (<1,500 g) in African-Americans is twice that of non-Hispanic Whites and Hispanics [32-34]. The higher body size may reflect excessive postnatal catch-up growth typical of low birth weight infants [35]. Low birth weight is associated with increased breast cancer risk [36]. These data imply that African-Americans and Hispanics (and non-Hispanic Whites) differ in their *in utero* nutrition and that the course of childhood/weight gain differs with race/ethnicity. *The extent to which differing birth weight (a proxy for in utero growth and nutrition) and subsequent weight gain patterns contribute to the higher breast cancer incidence and more 'aggressive' tumors seen in African-American women is unknown.*

Summary: It is essential to understand why breast cancer survival is lower in some obese patients and why the *timing* of excessive weight (birth, childhood, premenopause, pregnancy, postmenopause) determines if obesity increases or reduces breast cancer risk (particularly in African-American and Hispanic women). Broad associations implicate estrogens, leptin, insulin (INS) and INS-like growth factors (IGFs), but these do not explain fully the effects of obesity. **In our full Center application, we hypothesize** that, rather than obesity alone, a *combination* of key components of *metabolic syndrome* (e.g., INS-resistance, obesity) and associated factors (e.g., hormones, growth factors, adipocytokines) and timing (age at obesity) are most important in mediating obesity-breast cancer interactions. We will study the role of molecular, cellular, and hormonal changes linked to obesity and metabolic syndrome in mediating the effects of timing of obesity on breast cancer risk and of obesity on recurrence risk. We will study interventions to reduce the effects of obesity on breast cancer. **Prior studies have not tried to link metabolic syndrome and timing of obesity with cellular and molecular changes in normal and neoplastic breast tissues and adipose tissues.** Our bioethicists and behavioral scientists will study the ethical and societal implications of obesity in breast cancer and develop educational tools for health care providers to improve their understanding of the unique problems experienced

by obese women with or at risk for breast cancer. We will *continue* to involve our consumers, who participated fully in Center development. We are now poised to address obesity-breast cancer interactions in new and challenging paradigms, and to generate new insights into this important area.

KEY RESEARCH ACCOMPLISHMENTS

The Pilot Award did not provide funds, or permit the use of resources, to perform research tasks. Thus, our key research accomplishments are related to the goals set towards the establishment of our Center application. These accomplishments are evident in our Statement of Work and the completion of the various tasks defined therein.

Statement of work and its completion (based on the Pilot Award Statement of work)

1. *Aim Leaders will produce a 5-page summary of their activities (e.g., publications, relevant preliminary data, updated literature survey): Months 1-3*

This was completed but in a somewhat different manner – we used email and verbal reporting, rather than more formal documents, since this proved more effective and efficient

2. *Aim Leaders will produce a 2-page outline of the proposed study*

All aim leaders provided a 2-page overview (with citations – some ran to a little over 3-pages) of their proposed aim. These were used to guide our discussions and to help our consumers understand the work as initially proposed. These documents were updated as our discussions progressed and in response to our scientist and consumer colleague suggestions. The 2-page summaries ultimately provided the basis for preparing the section “F. Proposed Methods and Research” in our full application document.

3. *Establish External Advisory Committee (EAC) membership: completed by month 3*

This was completed later than 3-months, since we changed some of the proposed studies and needed to include experts in the most relevant fields. We successfully recruited an outstanding international panel of external advisors, who read and commented in detail upon our center application prior to its submission.

4. *Team Leaders will produce a 2-page summary of research activities related to the organization of their research: Months 1-3*

We did this by email and using verbal reports to our regular meetings of scientists and consumers, since this proved to be a more efficient and effective approach than written documents.

5. *Internal Advisory Committee (IAC) will select all aims for inclusion in the final application: Month 4*

This took longer than four months and involved all our consumers, not simply those associated with the IAC. However, the inclusion of a broader range of scientists and consumers proved highly effective and (we contend) led to a much more effective center application. The PI was the final arbiter of the decision on which projects were to be included.

6. *Consumer Advisory Committee and behavioral scientists will generate an initial assessment of the best methods for consumers and advocates to coordinate the Center's community educational activities, assess the impact and reach of these activities, and develop measures of participation, awareness, and knowledge in the community including the development of methods to disseminate project results to consumers: Months 1-6*

This was particularly productive and proved to be the mechanism that encouraged our consumers to challenge us to incorporate studies with more immediate potential impact on breast cancer (see Conclusions - below).

7. Proposed full Center will be evaluated by the External Advisory Committee: Month 5

This was completed but later than initially proposed due to the need to reorganize one aim and two develop two new aims. We also waited until our Center design was sufficiently developed to allow for meaningful comment. We were greatly impressed by the detailed and constructive feedback we received from our external advisors. This was received in sufficient time such that we were able to respond to their concerns and recommendations in full during the writing of our full application. We believe that these comments substantially improved the quality of our proposed research studies and the design of several key aspects of our Center structure.

8. Recommended modifications to the aims or teams (from the EAC/IOC evaluation in month 5) will be implemented: Month 6

We found a continual, ongoing approach to aim/team modification was the most effective for our investigators, consumers and internal advisors. The ongoing process was punctuated by responses to specific requests for feedback from our external and internal advisors, as well as our own Center members (scientists and consumers). Thus, this process continued to within a few weeks of the final submission (though relatively minor corrections and modifications were received at the later stages – major changes were recommended and implemented until ~3 months prior to submission).

9. Initial drafting of the Center grant will begin, with continual evaluation of drafts proceeding until submission at the required DOD deadline: Month 7

This was done using iterations of the 2-page documents from Task #2 (above).

10. Submission of the full Center award: Months 10-12

Submission of the full application was completed as proposed and our full Center application is now awaiting peer review.

REPORTABLE OUTCOMES

There are no specific reportable scientific outcomes from this Pilot Award as might be generated through a research project, e.g., abstracts, book chapters, white papers, or manuscripts. The primary reportable outcome is the submission of an application for a full Center of Excellence Award. We do not append the entire application to this report, since it is over 500 pages. However, we do append the Public and Technical Abstracts and the Proposal Relevance Statement. These documents, in addition to the text in the body of this final report, should provide reviewers with sufficient information to assess the extent to which we completed the work proposed in the initial application for a Pilot Award. We also have created (as we proposed) an initial website that will be further developed as a portal to our proposed *in silico* research environment if our full Center application is funded (currently these unpublished pages – which are still under development – should be accessible at http://lombardi.georgetown.edu/research/bc_obesity).

CONCLUSIONS

The support provided by this Pilot Award was critical to the development of a full and detailed Center of

Excellence application to the BCRP. The importance of the time and resources provided is evident from several observations.

1. We had the time and opportunity to recruit a larger and very enthusiastic group of consumer advocates. The importance of this cannot be overemphasized. While we did involve consumers in the preparation of our Pilot Award application, the time available for consumers to be fully integrated into the proposal, and for our scientists to adapt and adjust our research plan in response to their ideas and comments, was somewhat limited. We were able to make minor modifications to the research plan but felt that we were not in a position to propose fundamentally different or additional research areas with sufficient preparation (see #2 below). This was apparent in the Pilot Award application and was noted in the Summary Statement we received from the BCRP. Thus, when we received notification of funding, we rapidly recruited additional consumers and set about working very closely with them in the design of our Center.

2. The time and input from our consumers dramatically changed key components of our Center design. While our consumers were interested and engaged throughout the design of our Center application (including the core of women who participated in the planning of our Pilot Award application) early in the process they indicated their concern that our studies were somewhat "academic", in the sense that they would generate important new insights and knowledge but the implications and impact of these observations (for women with breast cancer or at risk of developing breast cancer) would not necessarily be short term. Our consumers were quite clear that they did not want us to design a center solely around cell culture or animal model based studies because, in their view, the relevance is not always clear and the impact is often many years in the future. Our consumer colleagues clearly understood the importance of such studies and the ability to use experimental models to understand mechanism in a way that cannot be done in women. However, they strongly encouraged us to limit our use of experimental models to address questions or issues directly related to our proposed concurrent studies in women. In this regard, the consumers remained very enthusiastic about the population-based study of cancer risk in minority populations and the molecular profiling study of breast cancers in obese and non-obese women. Their comments and encouragement enabled us to focus the proposed animal model studies to more directly complement mechanistic aspects of the two studies in women.

However, these three studies (each of which was alluded to in the Pilot Award application), while relevant and tightly integrated, did not convince our consumers that we had sufficient effort directed towards research that could have an immediate or short term impact on the primary goal of the BCRP to eradicate breast cancer. It became clear in our ongoing discussions that what our consumers were really looking for was that the Center also should include research that could directly affect women within the timeframe of the application or very shortly thereafter (within 5-6 years). Thus, our consumers challenged us directly to integrate at least one research aim that would have such a direct and immediate impact. As one consumer put it (this is a paraphrasing of her comment), "I would really like to see you also do something that will benefit women now, not in 10 or 20 years." This was one (of several) notable moments when the consumers changed the direction of our discussions and of our Center design.

We took this challenge to heart and quickly came to understand their concern that studies in experimental models can take decades to realize, *e.g.*, if the results were proposed to identify a drug target that would eventually lead to a therapeutic intervention in the clinic. Moreover, our consumers wanted an intervention-based strategy that was non-toxic but could have a demonstrable effect on either breast cancer risk or risk of recurrence in obese women. As a direct result of these discussions, we designed an exercise-based intervention to reduce the risk of postmenopausal breast cancer. This involved recruiting a group of international experts in the design of such studies. We were able to identify colleagues in Finland, where such research is particularly active and has led to changes in national health policy. **Thus, because of the specific encouragement and direction provided by our consumers, we incorporated a specific aim into our Center that was not envisioned in the original Pilot Award. Of particular importance, the aim we designed with them was easily integrated into the other aims of the Center and so maintained the interdependent nature of the**

research as required in the BCRP RFA.

Our consumers were not content to stop here. While they continued to advise and guide the research directions of the animal, population and profiling studies alluded to in the Pilot application, they read the RFA when it was released with considerable insight and enthusiasm. These remarkable women became particularly excited by the encouragement to incorporate behavioral and bioethical components into the Center. They again challenged us, asking now that we also address this issue in our Center. Several of our consumers had specific expertise and experiences directly relevant to this goal and they played a central role in identifying the specific question to be addressed and directly guided the development of the research strategy. At their insistence, we incorporated a study to allow us to better understand the obese woman's interaction with the health care system (in the context of mammographic screening) and to design education interventions to improve the continuing education of existing health care providers and to better train the next generation of physicians and nurses. Furthermore, we were able to design a study that directly involves consumers as co-leaders of research focus groups, such that our consumers can directly participate in the collection and interpretation of research data. Indeed, this is one of the very few areas of research where participation of the target population is *essential* to the design, performance and interpretation of the studies [37-41]. **Thus, as a direct result of our ability to spend sufficient time working closely with our consumers, we incorporated two specific aims in our final Center application that were not proposed in the Pilot Award application - aims that were instigated specifically as a consequence of the encouragement and guidance of our consumers.**

3. Time and resources to build a stronger and more truly integrated and interdependent, multidisciplinary Center. During our many meetings and interactions, we identified new investigators and other institutions that greatly strengthened our Center. For example, we initially proposed a population based study of African-American and Caucasian women. However, our consumers were very keen to incorporate Hispanic women, and as our discussions progressed, we determined that we needed a larger and more diverse population and a more focused, underexplored research question. This led us to propose a collaborative study with the leaders in population-based studies at the University of Southern California. The modified study provided access to a large, well-define population in which we could now study the timing of weight gain and incorporate both African-American and Hispanic women with sufficient statistical power. We believe that this will be a more cutting edge and more powerful study than that initially alluded to in our Pilot Award application. Again, we believe that the input of our consumers and the time and resources made available by the Pilot Award allowed us to design a much stronger, more integrated, more relevant study with a much greater probability of success.

The time and resources provided by this Pilot Award allowed us to fully integrate consumers into every aspect of our proposed Center in unique and powerful ways. The design of a Center of Excellence, at least as we interpret the BCRP RFP, clearly requires the time needed to build solid relationships between scientists and consumers. These two communities have different perspectives and expertise, differences that can complement one another and fundamentally affect how science is directed (as evidenced above). For our consumers and investigators, the ability to develop an understanding of each other and to enable us to communicate freely and openly, would not have been as effective had we designed our Center in the time available only between issuance of the RFP and the grant submission deadline. Based on our experience, we strongly encourage the BCRP to continue to offer the Pilot Award at least for as long as the program anticipates also funding full Centers.

REFERENCES

1. Centers for Disease Control. Overweight and obesity.
<http://www.cdc.gov/nccdphp/dnpa/obesity/index.htm>. 2005.
2. Schieve, L. A., Cogswell, M. E., and Scanlon, K. S. Trends in pregnancy weight gain within and outside ranges recommended by the Institute of Medicine in a WIC population. *Matern. Child Health J*, 2: 111-116, 1998.
3. Centers for Disease Control. Pediatric and Pregnancy Nutritional Surveillance Program.
<http://www.cdc.gov/pednss/>. 2005.
4. Galtier-Dereure, F., Boegner, C., and Bringer, J. Obesity and pregnancy: complications and cost. *Am J Clin Nutr*, 71: 1242S-1248, 2000.
5. Calle, E. E. and Thun, M. J. Obesity and cancer. *Oncogene*, 23: 6365-6378, 2004.
6. Harvard Center for Cancer Prevention. Harvard report on cancer prevention.
http://www.hsph.harvard.edu/cancer/publications/reports/vol1_summary.html. 1996.
7. Jemal, A., Tiwari, R. C., Murray, T., Ghafoor, A., Samuels, A., Ward, E., Feuer, E. J., and Thun, M. J. Cancer statistics, 2004. *CA Cancer J Clin*, 54: 8-29, 2004.
8. Calle, E. E., Rodriguez, C., Walker-Thurmond, K., and Thun, M. J. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*, 348: 1625-1638, 2003.
9. van den Brandt, P. A., Spiegelman, D., Yaun, S. S., Adami, H. O., Beeson, L., Folsom, A. R., Fraser, G., Goldbohm, R. A., Graham, S., Kushi, L., Marshall, J. R., Miller, A. B., Rohan, T., Smith-Warner, S. A., Speizer, F. E., Willett, W. C., Wolk, A., and Hunter, D. J. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol*, 152: 514-527, 2000.
10. Weiderpass, E., Braaten, T., Magnusson, C., Kumle, M., Vainio, H., Lund, E., and Adami, H. O. A prospective study of body size in different periods of life and risk of premenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev*, 13: 1121-1127, 2004.
11. Jonsson, F., Wolk, A., Pedersen, N. L., Lichtenstein, P., Terry, P., Ahlbom, A., and Feychting, M. Obesity and hormone-dependent tumors: cohort and co-twin control studies based on the Swedish Twin Registry. *Int J Cancer*, 106: 594-599, 2003.
12. Lahmann, P. H., Lissner, L., Gullberg, B., Olsson, H., and Berglund, G. A prospective study of adiposity and postmenopausal breast cancer risk: the Malmo Diet and Cancer Study. *Int J Cancer*, 103: 246-252, 2003.
13. International Agency for Research on Cancer. IARC Handbooks of Cancer Prevention. Weight Control and Physical Activity. Lyons: International Agency for Research on Cancer, 2002.
14. Rosenberg, L., Palmer, J. R., Wise, L. A., Horton, N. J., Kumanyika, S. K., and Adams-Campbell, L. L. A prospective study of the effect of childbearing on weight gain in African-American women. *Obes Res*, 11: 1526-1535, 2003.
15. Kinnunen, T., Luoto, R., Hemminki, E., Gissler, M., and Hilakivi-Clarke, L. Pregnancy weight gain and breast cancer risk. *BMC Womens Health*, 4: 7: 1-10, 2004.

16. Michels, K. B., Trichopoulos, D., Robins, J. M., Rosner, B. A., Manson, J. E., Hunter, D. J., Colditz, G. A., Hankinson, S. E., Speizer, F. E., and Willett, W. C. Birthweight as a risk factor for breast cancer. *Lancet*, 348: 1542-1546, 1996.
17. Ahlgren, M., Sorensen, T., Wohlfahrt, J., Haflidadottir, A., Holst, C., and Melbye, M. Birth weight and risk of breast cancer in a cohort of 106,504 women. *Int J Cancer*, 107: 997-1000, 2003.
18. McCormack, V. A., dos, S. S., I, De Stavola, B. L., Mohsen, R., Leon, D. A., and Lithell, H. O. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. *Br Med J*, 326: 248, 2003.
19. Sanderson, M., Williams, M. A., Malone, K. E., Stanford, J. L., Emanuel, I., White, E., and Daling, J. R. Perinatal factors and risk of breast cancer. *Epidemiology*, 7: 34-37, 1996.
20. Le Marchand, L., Kolonel, L. N., Earle, M. E., and Mi, M. P. Body size at different periods of life and breast cancer risk. *Am J Epidemiol*, 128: 137-152, 1988.
21. Magnusson, C., Baron, J., Persson, I., Wolk, A., Bergstrom, R., Trichopoulos, D., and Adami, H. O. Body size in different periods of life and breast cancer risk in post-menopausal women. *Int J Cancer*, 76: 29-34, 1998.
22. Berkey, C. S., Frazier, A. L., Gardner, J. D., and Colditz, G. Adolescence and breast carcinoma risk. *Cancer*, 85: 2400-2409, 1999.
23. Swerdlow, A. J., De Stavola, B. L., Floderus, B., Holm, N. V., Kaprio, J., Verkasalo, P. K., and Mack, T. Risk factors for breast cancer at young ages in twins: an international population-based study. *J Natl Cancer Inst*, 94: 1238-1246, 2002.
24. Baer, H., Colditz, G., Rosner, B., Michels, K., Rich-Edwards, J., Hunter, D., and Willett, W. Body fatness during childhood and adolescence and incidence of breast cancer in premenopausal women: a prospective cohort study. *Breast Cancer Research*, 7: R314-R325, 2005.
25. Hulka, B. S. and Stark, A. T. Breast cancer: cause and prevention. *Lancet*, 346: 883-887, 1995.
26. Hilakivi-Clarke, L. A., Clarke, R., Onojafe, I., Raygada, M., Cho, E., and Lippman, M. E. A maternal diet high in n - 6 polyunsaturated fats alters mammary gland development, puberty onset, and breast cancer risk among female rat offspring. *Proc Natl Acad Sci USA*, 94: 9372-9377, 1997.
27. Ahlgren, M., Melbye, M., Wohlfahrt, J., and Sorensen, T. I. Growth patterns and the risk of breast cancer in women. *N Engl J Med*, 351: 1619-1626, 2004.
28. Lahmann, P. H., Hoffmann, K., Allen, N., van Gils, C. H., Khaw, K. T., Tehard, B., Berrino, F., Tjonneland, A., Bigaard, J., Olsen, A., Overvad, K., Clavel-Chapelon, F., Nagel, G., Boeing, H., Trichopoulos, D., Economou, G., Bellos, G., Palli, D., Tumino, R., Panico, S., Sacerdote, C., Krogh, V., Peeters, P. H., Bueno-de-Mesquita, H. B., Lund, E., Ardanaz, E., Amiano, P., Pera, G., Quiros, J. R., Martinez, C., Tormo, M. J., Wirfalt, E., Berglund, G., Hallmans, G., Key, T. J., Reeves, G., Bingham, S., Norat, T., Biessy, C., Kaaks, R., and Riboli, E. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). *Int J Cancer*, 111: 762-771, 2004.
29. Hilakivi-Clarke, L., Wang, C., Kalil, M., Riggins, R., and Pestell, R. G. Nutritional modulation of the cell cycle and breast cancer. *Endocr Relat Cancer*, 11: 603-622, 2004.

30. Wenten, M., Gilliland, F. D., Baumgartner, K., and Samet, J. M. Associations of weight, weight change, and body mass with breast cancer risk in Hispanic and non-Hispanic white women. *Ann Epidemiol*, 12: 435-4, 2002.
31. Zhu, K., Caulfield, J., Hunter, S., Roland, C. L., Payne-Wilks, K., and Texter, L. Body mass index and breast cancer risk in African American women. *Ann Epidemiol*, 15: 123-128, 2005.
32. Kleinman, J. C. and Kessel, S. S. Racial differences in low birth weight. Trends and risk factors. *N Engl J Med*, 317: 749-753, 1987.
33. Shiono, P. H., Klebanoff, M. A., Graubard, B. I., Berendes, H. W., and Rhoads, G. G. Birth weight among women of different ethnic groups. *J Am Med Assoc*, 255: 48-52, 1986.
34. Dawson-Hughes, B. and Harris, S. Regional changes in body composition by time of year in healthy postmenopausal women. *Am J Clin Nutr.*, 56: 307-313, 1992.
35. Bhargava, S. K., Sachdev, H. S., Fall, C. H., Osmond, C., Lakshmy, R., Barker, D. J., Biswas, S. K., Ramji, S., Prabhakaran, D., and Reddy, K. S. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. *N.Engl.J.Med.*, 350: 865-875, 2004.
36. Møller, L., Olsen, M. L., Sørensen, H. T., Thulstrup, A. M., Olsen, J., and Olsen, J. H. Birth weight and risk of early-onset breast cancer. *Cancer Causes Control*, 14: 61-64, 2003.
37. Lythcott, N. Changing the research paradigm: community involvement in population-based research. *Cancer*, 88: 1214-1216, 2000.
38. Ramirez, A. G., Gallion, K. J., Suarez, L., Giachello, A. L., Marti, J. R., Medrano, M. A., Perez-Stable, E. J., Talavera, G. A., and Trapido, E. J. A national agenda for Latino cancer prevention and control. *Cancer*, 103: 2209-2215, 2005.
39. Taylor, J. Y. Womanism: a methodologic framework for African American women. *ANS Adv Nurs Sci*, 21: 53-64, 1998.
40. Constan, M. A. Qualitative analysis as a public event: the documentation of category development procedures. *Am Education Res J* 8, 209-228. 1992.
41. Strauss, E. S. and Corbin, J. *Basics of Qualitative Research: Grounded Theory Procedures and Techniques*. Newbury Park, CA: Sage, 1990.

APPENDICES

1. Public Abstract (from the submitted full center application)
2. Technical Abstract (from the submitted full center application)
3. Relevance Statement (from the submitted full center application)

PUBLIC ABSTRACT

PROJECT DESCRIPTION: The prevalence of obesity, which is associated with 5 of the top 10 cancers in women, doubled in the U.S. between 1980 and 2000. Over 30% of American women are now obese (about 30 lbs overweight for a 5'4" women); a similar proportion are overweight. These proportions are still increasing. Being obese (and to a lesser extent being overweight) has profound implications for a woman's risk of developing breast cancer and for her ability to survive a breast cancer diagnosis. However, the effects of obesity on **breast cancer risk** are complex and modified by timing (age at which a woman is obese) and race. The reduced **breast cancer survival** experienced by obese women also is poorly understood, e.g., how does obesity affect breast cancer and why do only some obese breast cancer patients die from this disease? These issues are further compounded by the well-documented pervasive social stigma experienced by obese women, even from health care providers. Some studies show that obese women are often undertreated with chemotherapy and may delay health care services to avoid negative interactions with providers. Less aggressive therapy or delayed screening/diagnosis could have additional detrimental outcomes in obese women. ***Lack of a full understanding of how obesity affects breast cancer risk and survival is a major obstacle to the eradication of breast cancer.***

We will study the role of molecular, cellular, and hormonal changes linked to obesity in mediating the effects of timing of obesity on breast cancer risk and of obesity on risk of recurrence. We will use animal models and human populations, and study interventions to reduce the effects of obesity on breast cancer. Our bioethicists and behavioral scientists will study the ethical and societal implications of obesity in breast health and develop educational tools for health care professionals to improve their understanding of the unique problems experienced by obese women with or at risk for breast cancer. We will *continue* to involve our consumers, who participated fully in Center development, e.g., **Aims 4 and 5 were developed at their request.**

APPLICABILITY OF THE RESEARCH: We will focus on the overarching question, ***"What are the roles of obesity in affecting breast cancer risk and survival?"*** Rather than work mostly in cell lines or animal models, we have chosen to address this question primarily in human studies. We propose only one aim in experimental models, a key mechanistic study of timing of obesity and hormones in rodents that cannot be done easily in humans (**Aim 1**). Reflecting specific input from our consumers, several of our studies are designed to have both immediate and long term impact on breast cancer. **Obesity is among the very few potentially modifiable factors that could reduce breast cancer risk and improve survival.** Thus, we will assess an exercise and counseling intervention to reduce breast cancer risk in obese and overweight perimenopausal and postmenopausal women (**Aim 4**). To better understand the unique problems faced by obese women seeking breast health services, **Aim 5** will study the social and ethical issues faced by these women and their providers. We will then develop educational tools to improve their experiences with existing providers and improve the training of the next generation of physicians and nurses. In **Aim 2**, we will study how age at excessive weight affects breast cancer risk in African-American and Hispanic women, e.g., weight at birth, puberty, and pregnancy. The limited data currently available suggest that obesity may have different effects on breast cancer risk in these women, although the majority of studies have been done in predominately non-Hispanic White populations. The timing effects are those to be studied mechanistically in the animal models (**Aim 1**).

CLINICAL APPLICABILITY: We have one study with direct clinical applicability. In **Aim 3**, we will look for ways to identify each *individual* obese patient's risk of recurrence (a surrogate for survival), which could help direct the most aggressive therapy to those in greatest need. This will be done by looking at gene expression and single nucleotide polymorphism (SNP) patterns in tumors, and hormone profiles in women.

OUTCOMES AND IMPACT: Our studies could benefit many obese or overweight women and particularly African-American and Hispanic women. A clearer understanding of the effects of obesity on risk in African-American and Hispanic women could rapidly change risk assessment and screening patterns, leading to better breast health care (**Aim 2**). Outcomes from **Aims 4 and 5** also could begin to have an impact on breast cancer prevention and screening in obese women within the 5 years of this application. Data showing an ability to predict each individual patient's recurrence risk (based on the hormone measures) could be rapidly applied (**Aim 3**). The gene-based predictors of recurrence risk, which may require the use of technologies that are still primarily research tools, may take a little longer before they can be widely adopted. Data from **Aim 1** should lead to new insights into the cellular, molecular, and hormonal basis for the effects of timing of obesity on breast cancer risk and lead to new diagnostic, preventive, or therapeutic strategies in the longer term.

TECHNICAL ABSTRACT

BACKGROUND: In the U.S., obesity prevalence doubled between 1980 and 2000; 34% of U.S. women are now obese (body mass index; BMI $\geq$ 30). While obesity significantly increases the **risk of dying from breast cancer**, independent of menopausal status and race/ethnicity, outcomes are worse for African-American compared with White and Hispanic women. A woman's **risk of developing breast cancer** also is affected by obesity but this relationship is complex and modified by race and the time in her life when she is obese. For example, obesity reduces premenopausal breast cancer risk in White women but may increase this risk among African-American and Hispanic women. High and very low birth weight increase premenopausal breast cancer risk but high body mass during childhood is associated with reduced pre- and postmenopausal breast cancer risk. These effects of obesity are most closely associated with the pattern of central obesity seen in metabolic syndrome. However, the precise contribution of timing effects, and particularly how this is modified by race, is poorly understood - most studies have been done in largely non-Hispanic White populations. ***Lack of a full understanding of how obesity affects both breast cancer risk and survival is a major obstacle to the eradication of breast cancer.***

OBJECTIVE/HYPOTHESIS: It is essential to understand why breast cancer survival is lower in obese patients and why the *timing* of excessive weight (birth, childhood, premenopause, pregnancy, postmenopause) determines if obesity increases or reduces breast cancer risk (particularly in African-American and Hispanic women). Broad associations implicate estrogens, leptin, insulin (INS) and INS-like growth factors (IGFs), but these do not explain fully the effects of obesity. We will establish a Center of Excellence focused on the overarching question, "*What are the roles of obesity in affecting breast cancer risk and survival?*" We **hypothesize** that, rather than obesity alone, a combination of key components of metabolic syndrome (*e.g.*, INS-resistance, obesity) and associated factors (*e.g.*, serum hormones, adipocytokines) and age at obesity are central in mediating obesity-breast cancer interactions.

SPECIFIC AIMS: **Aim 1:** we will study how timing of obesity (and other metabolic syndrome components) *in utero* and during puberty and pregnancy affect mammary cancer risk in animal models. **Aim 2:** we will show how timing of weight gain (body size at birth, puberty, pregnancy) is associated with breast cancer risk in African-American and Hispanic women. **Aim 3:** we will identify endocrine and molecular differences in breast cancers in obese and normal weight women (or who do or do not exhibit metabolic syndrome) to build predictors of recurrence risk in obese women. We will also study differences among central, peripheral, and breast adipocytes. **Aim 4:** we will study a 2-year exercise intervention program to reduce breast cancer risk and metabolic syndrome in obese/overweight perimenopausal and early postmenopausal women. **Aim 5:** we will study the social and ethical impact of obesity on women seeking breast cancer health services and develop/evaluate teaching tools for medical/nursing students and consumers.

STUDY DESIGN: **Aim 1** is an animal model study using Sprague-Dawley rats, nonobese, and genetically obese Zucker rats and peroxisome proliferator-activated receptor- γ (PPAR γ) null mice, focused on the mechanistic roles of leptin and INS signaling (increased risk) and PPAR γ and mammary gland differentiation (reduced risk). **Aim 2** is a case control study of breast cancer risk and timing of weight gain/obesity in African-American and Hispanic women (Los Angeles County, CA). **Aim 3** is a transcriptome, SNP, and hormone profiling study of breast cancer in obese and non-obese women (Washington, DC). **Aim 4** is an exercise and counseling intervention in perimenopausal and early postmenopausal women (Tampere, Finland). **Aim 5** applies focus group and internet survey methods to design, and quantitative methods to then validate, an educational intervention for health care providers and consumers to improve breast health care for obese/overweight women (Washington and Tampere). All human and animal studies are statistically powered. **Aims 1,3,4** will measure the same serum biomarkers, *e.g.*, INS-resistance, serum INS, IGF-I and binding proteins, triglycerides, HDL-cholesterol, total and free steroids, sex hormone binding globulin, adiponectin, leptin, and prolactin.

RELEVANCE: Achieving our research goals will enable us to (i) apply interventions that reduce the impact of obesity/metabolic syndrome on breast cancer risk (*prevention*) and (ii) improve breast health care for obese women seeking screening services (*detection/diagnosis*), (iii) understand how age at obesity affects breast cancer risk in African-American and Hispanic women (*prevention*), (iv) identify those obese women (or women with metabolic syndrome) at greatest risk of disease recurrence (*treatment/prognosis*), and (v) identify endocrine, cellular, and molecular mechanisms that functionally mediate interactions among timing obesity/metabolic syndrome and breast cancer leading to new findings in prevention, detection, diagnosis and treatment.

RELEVANCE STATEMENT

HOW THIS CENTER OF EXCELLENCE MEETS THE INTENT OF THE AWARD MECHANISM: We will integrate a comprehensive array of personnel and resources into a multinational, multi-institutional, and multidisciplinary Center of Excellence focused on the single, unifying question: "*What are the roles of obesity in affecting breast cancer risk and survival?*" This overarching question is relevant to the prevention, detection, diagnosis, and treatment of breast cancer. **We will show** how an individual's age when obese and the patterns of adiposity, functionally linked to underlying hormonal, molecular, and genetic factors associated with metabolic syndrome (e.g., INS-resistance, changes in serum steroids and adipocytokines) and differences in adipose cell function, are key in mediating obesity-breast cancer interactions. Breast cancer and obesity/metabolic syndrome interactions are **notably understudied** at the *individual* patient, tissue, cellular, and molecular levels. Title/abstract searches of the DOD BCRP database returned no matches for "metabolic syndrome" and only 5 for "obesity."

Lack of a full understanding of how obesity affects breast cancer risk and survival is a major limitation to the eradication of breast cancer. We will study the role of molecular, cellular, and hormonal changes linked to obesity and metabolic syndrome in mediating the effects of timing of obesity on breast cancer risk and of obesity or metabolic syndrome on risk of recurrence. Mechanistic studies will be done mostly in animal models (Aim 1). To ensure a more immediate impact on breast cancer, we have fully integrated (with Aim 1) four aims comprising epidemiologic (Aim 2), prognostic (Aim 3), intervention (Aim 4), and **behavioral/ethical** studies (Aim 5) in women. **These studies have a strong emphasis on minority populations.** We have assembled a multidisciplinary and multi-institutional team of bioethicists, biostatisticians, clinicians, computer scientists, consumers, endocrinologists, epidemiologists, molecular biologists, and nutrition scientists at *Georgetown University* and its Lombardi Comprehensive Cancer Center and the *University of Southern California*; informaticians and engineers at *Virginia Tech*; molecular geneticists at *Children's National Medical Center*; consumers, epidemiologists, and lifestyle/health researchers at the *UKK Institute* and the *University of Tampere* (Finland); and molecular pathologists at *Lund University* (Sweden). Our investigators are promising young scientists/clinicians and accomplished experts in traditional and nontraditional scientific disciplines. Our consumers *continue* (since planning for our Pilot Award) to be involved in every aspect of this Center.

HOW THIS CENTER OF EXCELLENCE WILL ACCELERATE THE SOLUTION OF OUR OVERARCHING PROBLEM: Our *in silico* research and communication system maximizes the ability of Center members to exchange ideas and multiple data types in real time and provide a portal for the general public to access our findings. Data stored within this system, and the tools to be developed for data analysis, will represent powerful new resources for the broader breast cancer research community. Since many of our investigators are working together on other funded projects, and regular formal and informal meetings already are ongoing, we can rapidly deploy resources across this Center of Excellence to accelerate our studies. An External Advisory Committee reviewed drafts of this application and will continue to provide scientific advice in collaboration with our active Consumer Advisory (CAC) and Internal Advisory (IAC) Committees. These committees will meet regularly (on various schedules); investigators and consumers working on each aim will meet biweekly to discuss problems and progress. Our consumers played a critical role in Center development. At their specific request we include two aims not included in our Pilot Award. Their continued input will further accelerate our studies by helping to keep much of our work focused on those directions of greatest and most immediate benefit to women.

HOW THIS CENTER OF EXCELLENCE WILL HAVE A MAJOR IMPACT ON BREAST CANCER: We will address the modifying effects of obesity/metabolic syndrome on breast cancer risk and survival by tightly integrating data from laboratory, clinical, behavioral, bioethical, and epidemiologic studies. Successful completion of our studies will enable us to rapidly deploy interventions that reduce the effects of obesity/metabolic syndrome on breast cancer risk and improve breast health care for obese breast cancer patients. By understanding how age at obesity affects breast cancer risk, particularly in African-American and Hispanic women, we can improve risk assessment and screening. The ability to identify those obese women (or women with metabolic syndrome) at greatest risk of recurrence will allow physicians to make better treatment decisions. We will also acquire a greater understanding of the endocrine, cellular, and molecular mechanisms that functionally mediate interactions between timing of obesity/metabolic syndrome and breast cancer. This knowledge will lead to new developments in breast cancer prevention, detection, diagnosis, and treatment and generate fundamentally new insights into the effects of obesity on breast cancer risk and survival.