HHS Public Access

Author manuscript

Epidemiology. Author manuscript; available in PMC 2017 March 08.

Published in final edited form as:

Epidemiology. 2016 May ; 27(3): 438–448. doi:10.1097/EDE.0000000000000456.

The LEGACY Girls Study: Growth and development in the context of breast cancer family history

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Conflicts of interest: None declared

Abstract

Background—Although the timing of pubertal milestones has been associated with breast cancer risk, few studies of girls' development include girls at increased breast cancer risk due to their family history.

Methods—The LEGACY (Lessons in Epidemiology and Genetics of Adult Cancer from Youth) Girls Study was initiated in 2011 in the USA and Canada to assess the relation between early-life exposures and intermediate markers of breast cancer risk (e.g., pubertal development, breast tissue characteristics) and to investigate psychosocial well-being and health behaviors in the context of family history. We describe the methods used to establish and follow a cohort of 1,040 girls ages 6–13 years at baseline, half with a breast cancer family history, and the collection of questionnaire data (family history, early-life exposures, growth and development, psychosocial and behavioral), anthropometry, biospecimens, and breast tissue characteristics using optical spectroscopy.

Results—During this initial 5-year phase of the study, follow-up visits are conducted every six months for repeated data and biospecimen collection. Participation in baseline components was high (98% for urine, 97.5% for blood or saliva, and 98% for anthropometry). At enrollment, 77% of girls were pre-menarcheal and 49% were at breast Tanner stage T1.

Conclusions—This study design allows thorough examination of events affecting girls' growth and development and how they differ across the spectrum of breast cancer risk. A better understanding of early-life breast cancer risk factors will be essential to enhance prevention across the lifespan for those with and without a family history of the disease.

INTRODUCTION

Evidence is growing that early-life factors, including prenatal, childhood, and adolescent exposures, may play an important role in breast cancer etiology.[1,2] Early menarche is a well established breast cancer risk factor,[3] and a recent prospective study has shown that early breast development is also associated with increased risk.[4] Despite this emerging evidence, the time around puberty, when rapid growth, breast tissue development, and hormonal changes take place, is one of the least understood windows of breast cancer susceptibility. Furthermore, the role of early-life factors, including growth and developmental trajectories, in breast cancer etiology has not been evaluated in the context of a family history of breast cancer or genetic susceptibility. Familial clustering of cancer is likely to be associated with clustering of risk factors influenced by genetics, epigenetics, and environment,[5,6] including health-related behaviors. Therefore, studies of individuals with a family history of breast cancer are critical to identify factors important in familial vs. sporadic breast cancer.

Understanding the role of early-life factors in breast cancer development is important for effective cancer prevention strategies. Our early data suggest that awareness of breast cancer risk during adolescence may be a "teachable moment", enhancing and maximizing adoption of cancer prevention measures beyond current efforts.[7] Chronic psychosocial stressors impact psychological and physical health,[8] and increased risk for breast cancer might constitute a chronic stressor for parents and offspring.[9] The chronic stress of growing up in a breast cancer family could negatively impact immunologic host-responses,[10] and psychosocial distress can also be associated with greater risk behaviors (e.g., tobacco,

alcohol use). Health and risk behaviors in preadolescence relate to the adoption and maintenance of health and risk behaviors throughout life, which is of particular importance for individuals at increased risk for cancer.[11–13]

We describe the methods used to establish a cohort of 1,040 girls recruited at ages 6–13 years that is enriched with girls at increased risk of breast cancer due to their breast cancer family history. The aims of the LEGACY (Lessons in Epidemiology and Genetics of Adult Cancer from Youth) Girls Study are two-fold: We will investigate the role of early-life factors in pubertal development in the context of family history and genetic susceptibility. Specifically, we will characterize the growth and developmental trajectories (height, body mass index (BMI), pubertal timing and tempo) and differences in genetic and biomarker profiles across the spectrum of breast cancer risk and determine whether modifiable lifestyle factors can alter these growth and developmental trajectories. We will also examine how living in a family at increased breast cancer risk impacts the psychosocial adjustment and health and risk behaviors of girls as they mature, transitioning into and through pubertal development. Specifically, we will examine the onset and trajectory of girls' risk and preventive health behaviors, and how they are modified by family history, pubertal development, breast cancer worry, and perceived controllability as the LEGACY cohort ages into late adolescence.

METHODS

Pilot studies

We conducted several pilot studies to determine feasibility and develop study materials and protocols prior to establishing the LEGACY cohort. Initially, a sample of women participating in the Breast Cancer Family Registry[14] who had daughters ages 6–17 years were invited to participate in qualitative interviews about their willingness to enroll their daughters in a youth cohort.[15] Additional pilot studies demonstrated the feasibility of recruiting young girls ages 6–13 years and their mothers into a prospective youth cohort, collecting questionnaire data, anthropometric measurements and biospecimens, and retaining them for follow-up.

Study design

The LEGACY Girls Study (www.legacygirlsstudy.org) enrolled girls at five study sites in the U.S. (New York City, NY; Philadelphia, PA; Salt Lake City, UT; San Francisco Bay Area, CA) and Canada (Toronto, Ontario) that comprise the 5 North American sites of the Breast Cancer Family Registry (BCFR), a multigenerational cohort of breast cancer families (www.bcfamilyregistry.org).[14] All participating institutions obtained Institutional Review Board approval to conduct the study. Mothers/guardians provided written informed consent, and girls provided assent based on institutional standards.

The girls were primarily ages 6–13 years at recruitment, with about 5% outside of this age range. Some pilot study participants continued participation and were ≥13 years at baseline, and some younger siblings were nearly 6 years old and recruited at the same time as their older sibling(s). Recruited between August 2011 and July 2013, the cohort includes girls

with a family history of breast cancer, defined as having one or more first- or second-degree relatives diagnosed with breast cancer (hereafter referred to as family history positive girls), and girls without a breast cancer family history (family history negative girls). Participants also included a parent (usually the mother) or guardian (hereafter referred to as mother/guardian). Family history positive girls were identified through a parent who is enrolled in the BCFR, regional cancer registries, or family genetics and oncology clinics. Family history negative girls were recruited through friend referrals by families already enrolled, community outreach, and social media. Those found to have a breast cancer family history were classified as family history positive. We frequency-matched family history negative girls to family history positive girls by race/ethnicity and age at each site. The study involves follow-up every six months through 2015, either a clinic visit (at the four clinic-based sites) or a home visit (at the California site), with repeated collection of questionnaire data, biospecimens, and anthropometric measurements. Breast tissue characteristics are assessed by optical spectroscopy in the final year.

Given the potential vulnerability of the study participants and unanticipated risks, we elected to develop an independent Event Monitoring Committee to analyze and categorize anticipated (e.g., distress related to query about breast cancer knowledge, perceptions and experiences, breach of confidentiality, physical reactions to blood draw) and unanticipated adverse events (e.g., reports of bullying, sibling or peer events), to advise investigators on the significance of such events, and to recommend approaches to minimize study-related risks.[16]

Data collection

We assess changes in pubertal outcomes and exposures during the pubertal transition through questionnaires and measurements, with most items collected every six or 12 months (Table 1). Mothers/guardians complete questionnaires for girls of all ages, either online or by mail, except for the Early-life Questionnaire, which was administered by trained research staff at the baseline visit. Girls ages ≥10 years complete selected questionnaires online or by mail, except for the baseline Growth and Development Questionnaire and Behavioral Questionnaire which were completed during the visit. Except for the Behavioral Questionnaire, the questionnaires were translated into Spanish and administered by bilingual interviewers. The questionnaires are available at http://legacygirlsstudy.org/researchers and sources of questionnaire items are shown in eTable 1. Contact information to initiate collaborations is provided at http://legacygirlsstudy.org/researchers.

Outcomes assessment—Pubertal development, including sexual maturation using drawings showing five Tanner stages of breast and pubic hair development,[17] is assessed through the Growth and Development Questionnaire, completed every six months by mothers/guardians for girls of all ages and by girls ages ≥10 years. We also perform clinical breast Tanner staging at two clinical LEGACY sites in New York and Utah; these data will be used to help interpret and calibrate the self-reported measures across all sites. Trained research staff or a physician perform standardized clinical breast Tanner staging by completing a visual check of breast development, scored from 1 to 5. If it is difficult to distinguish between breast bud development and fat tissue, the breast is palpated with the

girl's permission, and a second score based on both visualization and palpation is recorded. To ensure consistency, Tanner staging is performed by two independent reviewers whenever possible.

Breast tissue characteristics are measured in girls ages ≥10 years using optical spectroscopy, a novel experimental technique developed[18] and modified in Ontario pilot studies. Optical spectroscopy captures variation in the amount of lipid, water, total hemoglobin, and hemoglobin oxygen saturation, as well as overall cellular and connective tissue density in breast tissue. These components have been associated with mammographic density in adult women,[19] a consistently strong breast cancer risk factor.[20] Optical spectroscopy can also detect breast tissue differences associated with age and parity in premenopausal women.[21] Ithas been performed in studies involving hundreds of women.[19,21] A newer technique is used in the LEGACY study (eFigures 1–3) and takes about 10–15 minutes to complete. Following a pilot study with LEGACY girls from the Ontario site that performed optical spectroscopy measurements every 12 months, it was implemented at all sites in late 2014. All girls ages ≥10 years who consent will receive one set of optical spectroscopy measurements by the end of 2015.

Psychosocial adjustment and health and risk behaviors are assessed in the Behavioral Questionnaire. It is completed by girls ≥10 years and evaluates psychosocial adjustment and breast cancer-specific distress,[22] adapted measures of knowledge and perceptions of breast cancer risk and family cancer history,[23,24] general family function and communication,[25] and preventive health and risk behaviors.[26] Mothers/guardians complete parallel measures evaluating their daughter's[22] and their own psychosocial adjustment,[27] their own health and risk behaviors,[28] family functioning and communication,[25] and knowledge and perceptions of breast cancer risk.[24] Specific domains covered are shown in Table 1. The development of the Behavioral Questionnaire was informed by a theoretical model grounded in Self-Regulation Theory of Health Behavior and developmental theory[13] and preliminary semi-structured interviews with girls ages 11–19 years.[29]

Exposures assessment—We assess early-life exposures relevant to the pubertal outcomes by questionnaire using validated constructs. Specific domains include daughter's cancer family history, family *BRCA1* and *BRCA2* mutation status if tested, birth and perinatal exposures, medical history, home environment, physical activity, dietary intake, neighborhood characteristics, social and physical environment, and health and risk behaviors (Table 1).

Anthropometric measurements are taken every six months by trained research staff, including height (fixed stadiometer attached to a scale or a Harpeden pocket stadiometer), weight (digital Tanita HD-314 scale), percent body fat by bioimpedence (Omron Handheld HBF-360C), waist and hip circumferences (Irwin Shore Canister linen tape), and foot size (Euro Junior or Euro Adult Brannock device). Height, weight, waist and hip circumferences, and percent body fat are measured twice and averaged.

Biospecimen collection

Girls of all ages are invited to provide a urine sample (every six months) and a blood sample (every 12 months), or a saliva sample if they decline the blood sample. We use a common protocol for collecting, processing and storage within 48 hours of biospecimen collection. Blood is collected into one EDTA tube and two serum tubes. White blood cells are frozen at −80°C until DNA is extracted using the organic solvent method (or equivalent), and DNA is stored at 4°C. Urine samples are aliquoted and stored in −80° C freezers. Multiple aliquots of biospecimens are kept in long-term storage for future analyses.

Blood samples (15–20 ml) are collected by trained phlebotomists from girls of all ages (non-fasting at baseline, fasting at 1st follow-up and every 12 months thereafter). If a baseline blood sample was declined, saliva was collected as an alternative source of DNA using an Oragene kit. At least one saliva sample was also requested from each girl who provided a blood sample to have a uniform source of DNA from all girls in the cohort. In addition, at least two biospecimens of the same type (blood or saliva) one year apart are collected from each girl for studies of methylation markers, as we have previously shown that they differ by source of DNA.[30] The New York site collected both blood and saliva at the same visit for a subset of girls to facilitate biomarker pilot studies. We also collected a saliva sample from the mother unless a stored sample is available in the Breast Cancer Family Registry biorepositories. The girls' DNA will be used for methylation studies, and the plasma will be used for analyses of vitamin D, folate, insulin and leptin (the latter two from fasting samples). Both the daughter's and mother's DNA and the daughter's plasma will be stored for future analyses.

A first morning urine sample is collected from girls of all ages every six months. These samples will be used for analyses for hormones and environmental chemicals, and stored for future assays.

Follow-up and retention

We use several strategies to encourage continued study participation of both girls and mothers/guardians, including newsletters, birthday and holiday cards, certificates of appreciation, credit for community service hours, modest monetary incentives, and small gifts. All sites have developed local activities to enhance retention and specific examples include a five-member teen board at the Utah site that meets twice a year and provides feedback on newsletters, website, incentives and study processes, and a junior scientist program developed at the Ontario site which provides educational activities.

Study cores

We have established five cores to facilitate the integration and analysis of data and storage of biospecimens. A Data Core develops questionnaires for online data collection using Qualtrics; maintains data in a central database; performs quality control and derives core variables; and distributes analytic data sets for approved analyses. A Behavioral Core performs the same activities for the behavioral questionnaires. The Biospecimen Core coordinates all blood, saliva and urine collection and storage; the Methylation Core performs

DNA methylation related assays; and the Optical Spectroscopy Core coordinates the measurements across sites.

Statistical analyses

We computed response rates to specific study components as the number of girls or mothers/guardians completing the component by the number of girls or mothers/guardians eligible for that component to summarize the available resources in the LEGACY cohort.

RESULTS

Characteristics of cohort

The LEGACY cohort comprises 1,040 girls from 821 families, including families with one (n=623), two (n=177) or three (n=21) daughters. Most girls participated with their biological mother (97%) or biological father (1.5%). Half of the girls had a family history of breast cancer, either in both their mother and second-degree relatives (16%), their mother only (25%), or second-degree relatives only (59%) (Table 2). The mean age of the girls was 9.6 years, 62% of girls were non-Hispanic white, and the majority of parents had a college or graduate degree.

Participation in baseline and follow-up visits

At baseline, mothers/guardians provided information on cancer family history and completed the Early-life Questionnaire for all 1,040 girls enrolled in the cohort (Table 3). Completion rates were 96% for the Growth and Development Questionnaire and 91% for the Behavioral Questionnaire. Most girls (98%) participated in the anthropometric measurements. For girls ages ≥10 years, completion rates were 95% for the Growth and Development Questionnaire 91% for the Behavioral Questionnaire. Urine and blood or saliva was collected for nearly all girls (98%). Blood collection was higher for girls ages ≥10 years (49%) than younger girls (33%).

At the first follow-up visit at 6 months, 12 (1%) girls withdrew from the study, including some who had moved from the study areas, 1,003 (96%) completed the visit, and 25 girls or mothers/guardians were not available for the visit, but open to future participation (Table 3). At the second follow-up visit at 12 months, an additional 12 girls withdrew from the study and 977 (94%) completed the visit. As girls entered the cohort until July 2013, follow-ups for the 3rd to 7th visit are currently in progress. A total of 54 girls have withdrawn from the study, with 95% remaining in the cohort.

Clinical breast Tanner staging and optical spectroscopy measurements

Baseline clinical Breast Tanner staging was completed for 83% of girls to whom it was offered to at the Utah and New York sites (Table 3), with a greater participation by girls ages <10 years (88%) than girls ages ≥10 years (77%). Participation was similarly high at the first (85%) and second (82%) follow-up visit. Baseline optical spectroscopy measurements have been collected for 279 girls ages ≥10 years who were invited to participate in this study component. At the four sites where it is part of the clinic visit, 83% of invited girls participated in optical spectroscopy. At the California site, this study component requires a

visit at the study center, unlike previous 6-month assessments that involved home visits only. Of eligible families that did not decline a visit at the study center, 70% of girls completed or are scheduled for optical spectroscopy. At the clinic-based site in Ontario, optical spectroscopy measurements were obtained annually, with consistently high participation rates (92%–93%) at the baseline, second, and third measurement.

Characteristics of participating girls and parents/guardians

At enrollment, mothers/guardians reported that 77% of girls were pre-menarcheal and 49% were at breast Tanner stage T1. The distribution of these indices of pubertal development differed by family history status (Table 4). A lower proportion of girls was pre-menarcheal among those with a first-degree family history (75%) compared to girls with a second-degree family history (81%) or those without a family history (83%). Differences across the three groups of girls were also seen for breast Tanner stage, with T1 (i.e., no signs of breast development) reported for 47%, 53% and 60% respectively, and for pubic hair Tanner stage, with T1 reported for 50%, 63%, and 60%, respectively. Height, weight, and BMI for age and waist-to-hip ratio and percent body fat were similar across the three groups.

DISCUSSION

The prevailing causal theory of breast cancer has focused on adult risk factors. However, accumulating evidence from both human and animal studies strongly supports that breast cancer susceptibility begins much earlier in life.[1] Prior studies of early-life factors and breast cancer have faced a number of methodologic challenges, including long latency periods between exposures and breast cancer diagnosis, lack of relevant intermediate markers of risk, and reliance on retrospective recall for exposure assessment.[31] Long-established risk factors, such as earlier age at menarche and taller adult height, confirm the importance of early-life events in altering breast cancer risk.[32] Other events during the pubertal window, including age at onset of breast development and pubic hair development, may also be important in breast cancer etiology, but have been less studied given recall difficulty. One notable exception, however, is a recent report from a large, prospective cohort study that is the first to show that women who experienced breast development at age <10 years had a 20% increased breast cancer risk;[4] importantly, this association was independent of age at menarche and height. Because information on pubertal timing was retrospectively recalled, but before breast cancer was diagnosed, the increased risk is likely an underestimate due to non-differential misclassification of exposure.

Disentangling the effects of pubertal timing, growth rate in height, and onset of menarche needs to be addressed prospectively by enrolling girls into pubertal cohorts. As a recent prospective study has shown that early breast development, age at peak height attainment, and age at menarche are each independently associated with breast cancer risk,[4] it is crucial to have cohorts that prospectively measure each through clinic- and questionnaire assessment. There are several prospectively recruited female youth cohorts (e.g.,[33,34]) with data on some of the same pubertal measures we are collecting in the LEGACY Girls Study. Our cohort differs from some of the larger pubertal cohorts in that we are collecting anthropometric measures and pubertal development outcomes every six months. We

consider height growth, age at onset of breast development, and age at menarche as separate, but interrelated outcomes. Importantly, we will be able to integrate these outcomes by examining outcomes related to time between events (or tempo, e.g., between onset of breast development and age at menarche). Our study is also the first to specifically recruit girls with a family history of breast cancer, making it the only study among girls to have sufficient statistical power to test for interactions by family history. For example, in the Growing Up Today Study of girls ages 9–15 years who are daughters of participants in the Nurses Health II Study, only a small proportion of girls had a mother (3.8%) or aunt (3.5%) with breast cancer at baseline.[35] Furthermore, the collection of detailed pedigree data from all families allows the estimation of an absolute breast cancer risk score using algorithms such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)[36] model and classification of girls both by BOADICEA risk score and family history status, and thus we can examine risk across the spectrum of underlying familial risk as proxied by BOADICEA scores.

Unlike other pubertal cohorts, we recruited across a range of ages. This design allows us to address the timing of exposures in relation to windows surrounding several outcomes, including age at onset of breast development, age at menarche, and breast tissue characteristics during thelarche, menarche, and post-menarche. Studies like ours, which have the ability to address several outcomes using the same cohort and exposure assessments, are needed to thoroughly examine whether there are differential effects across outcomes or whether previous inconsistent findings were driven by selection and/or measurement differences.

The LEGACY Girls Study has a behavioral component, employing an innovative model to assess psychosocial and behavioral constructs, which will be critical to the successful translation of the study's basic and epidemiologic science discoveries in childhood and adolescence into improvements in health outcomes in adulthood.[13] Although genetic testing and breast cancer risk reduction interventions are not currently indicated during childhood and adolescence for offspring in families at high risk for breast cancer,[37] it is possible that adolescent girls are impacted by growing up in a family with a history of breast cancer or an identified *BRCA1* or *BRCA2* mutation.[29] Studies of youth who have a parent with cancer have found greater internalizing and externalizing problems, stress response, anxiety, and lower self-esteem compared to peers with healthy parents, and particularly among daughters of mothers with breast cancer.[38] Few studies have directly evaluated psychosocial adjustment in children and adolescents from families at familial or genetic risk for breast cancer. We and others have shown that the majority of adolescents in high risk families learn of their hereditary risk at a young age.[39] Some evidence suggests that the majority of adolescent girls from breast cancer families as well as other girls have misperceptions about breast cancer risk.[29,40] The LEGACY Girls Study will provide a better understanding of the longitudinal impact of awareness and perceptions of breast cancer risk on psychosocial adjustment and health and risk behaviors as young girls develop into adulthood, which is critically important in individuals at familial or genetic risk.

We faced several challenges in the initial recruitment of this cohort. For example, we had initially attempted to use the friend control approach to recruit family history negative girls.

This was inefficient and we were more successful using community outreach methods. For biospecimen collection we found that initial reluctance to donate blood was lessened by use of topical anesthetic and becoming comfortable with study staff. Participation in fasting blood collection at the first follow-up was enhanced by discussions before a visit with parents and daughters about their willingness to donate, and by offering weekend appointments. Despite these initial challenges in cohort recruitment, we achieved high retention and participation at the 6- and 12-month follow-up visits, which will ensure the overall internal validity of our study.

We achieved high participation (range 91%–98%) across the various baseline study components (questionnaires, anthropometry, urine, and DNA collection), regardless of breast cancer family history or age, although the girls, particularly those at younger ages, were less willing to donate blood. An additional strength of the study is the high retention rate, with only 2% of girls withdrawing 12 months after recruitment. Lastly, the LEGACY cohort will be large enough to independently replicate findings from other youth cohorts that included mostly girls at average risk of breast cancer, and robust enough to formally test interactions across the spectrum of breast cancer risk.

In conclusion, the data and biospecimens collected in the multi-center LEGACY cohort are a resource for a wide range of scientific aims focused on prevention. Information on early-life exposures, growth and development, and psychosocial well-being in the context of family history will be essential in developing successful interventions during this key developmental period in which there may be a heightened susceptibility to carcinogenesis, and will have the potential to enhance cancer prevention across the lifespan and reduce the morbidity and mortality of breast cancer for those with and without a family history of breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of financial support:

This work was supported by the National Cancer Institute at the National Institutes of Health (Grants CA138638 to E.M. John, CA138819 to M.B. Daly and A.R. Bradbury, CA138822 to M.B. Terry, and CA138844 to I.L. Andrulis) and the Canadian Breast Cancer Foundation (I.L. Andrulis). The work at the New York site was also supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number UL1 TR000040, formerly the National Center for Research Resources, Grant Number UL1 RR024156. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. I.L. Andrulis holds the Anne and Max Tanenbaum Chair in Molecular Medicine at Mount Sinai Hospital and the University of Toronto.

The authors thank the LEGACY girls and their family members for their continuing contributions to the study and our colleagues at the participating family genetics and oncology clinics. We also thank the staff at each LEGACY study site, including Alex Blacker, Connie Cady, Jocelyn Koo, Lisa Moy, Meera Sangaramoorthy, Enid Satariano (California site); Ann Johnson, Jasmine MacDonald, Melissa White (New York site); Gordon Glendon, Danielle Hanna, Teresa Selander (Ontario site); Colleen Sands (Philadelphia site); and Briar Doi, Karen O'Toole (Utah site). The authors also thank the members of the Scientific Advisory Board (Drs. Tim A. Ahles, Christopher K. Daugherty, Michele Forman, Marcia E. Herman-Giddens, Robert Hiatt, Lawrence H. Kushi, Mary S. Wolff, Susan L. Teitelbaum, Martin J. Yaffe) and the Event Monitoring Committee (Drs. Jeffrey Botkin, Christopher K. Daugherty, Branlyn DeRosa, Malcolm Pike, and Ms. Cheryl Schuman).

The authors thank the contributing clinical centers for their efforts in recruiting our LEGACY participants (Ontario site: Clinical Genetics at Trillium Health Partners – Credit Valley Hospital, The Cancer Risk Assessment Centre at the Juravinski Cancer Centre, The Princess Margaret Hospital Familial Breast and Ovarian Cancer Clinic, The Mount Sinai Familial Breast Cancer Clinic and The Granovsky Gluskin Family Medicine Centre of Mount Sinai Hospital; Philadelphia site: the Clinical and Translational Research Center (CTRC) and the Pediatric Research Consortium (PeRC) at The Children's Hospital of Philadelphia).

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Epidemiology. Author manuscript; available in PMC 2017 March 08.

Table 1

Collection of Questionnaire and Clinical Data and Biospecimens at Baseline and Follow-up, LEGACY Girls Study, 2011 – 2015

Participants	Baseline	F1[a]	F2[a]	F3[a]	F4[a]	F5[a]	F6[a]	F7[a]
Mothers	Growth and Development[b]	Growth and Development	Growth and Development	Growth and Development	Growth and Development	Growth and Development	Growth and Development	Growth and Development
	Behavioral Questionnaire[c]		Behavioral Questionnaire		Behavioral Questionnaire		Behavioral Questionnaire	
	Cancer Family History[d]							
	Update on Cancer Family History: In year 5 of the study							
	Early-life Questionnaire[e]		Update on Home Environment and Medical History[f]		Update on Home Environment and Medical History		Update on Home Environment and Medical History	
		History of Chronic Conditions						
		Recent Physical Activity[g]		Recent Physical Activity		Recent Physical Activity		Recent Physical Activity
		Recent Dietary Intake[h]		Recent Dietary Intake		Recent Dietary Intake		Recent Dietary Intake
						Nutrition[i]		Nutrition
		Neighborhood Characteristics.[j]						Neighborhood Characteristics
			Cosmetics				Cosmetics	
			Physical and Social Environment[k]				Physical and Social Environment	
								Medical History and Infections
	Saliva sample[l]							
Daughters ages ≥10 years	Growth and Development[b]	Growth and Development	Growth and Development	Growth and Development	Growth and Development	Growth and Development	Growth and Development	Growth and Development
		Recent Physical Activity[g]		Recent Physical Activity		Recent Physical Activity		Recent Physical Activity
		Recent Dietary Intake[h]		Recent Dietary Intake		Recent Dietary Intake		Recent Dietary Intake
						Nutrition[i]		Nutrition
		Neighborhood Characteristics.[j]						Neighborhood Characteristics
			Cosmetics				Cosmetics	
			Social Environment[m]				Social Environment	
	Behavioral Questionnaire[n]		Behavioral Questionnaire		Behavioral Questionnaire		Behavioral Questionnaire	
	Optical Spectroscopy Measurements: In year 5 of the study							
Daughters of all ages	Anthropometry[o]	Anthropometry	Anthropometry	Anthropometry	Anthropometry	Anthropometry	Anthropometry	Anthropometry
	Clinical Breast Tanner Staging[p]	Clinical Breast Tanner Staging	Clinical Breast Tanner Staging	Clinical Breast Tanner Staging	Clinical Breast Tanner Staging	Clinical Breast Tanner Staging	Clinical Breast Tanner Staging	Clinical Breast Tanner Staging
	Urine Sample	Urine Sample	Urine Sample	Urine Sample	Urine Sample	Urine Sample	Urine Sample	Urine Sample
	Non-fasting Blood or Saliva Sample	Fasting Blood or Saliva Sample		Fasting Blood Sample		Fasting Blood Sample		Fasting Blood Sample

[a] F1: Follow-up 1 at 6 months; F2: Follow-up 2 at 12 months; F3: Follow-up 3 at 18 months; F4: Follow-up 4 at 24 months; F5: Follow-up 5 at 30 months; F6: Follow-up 6 at 36 months; F7: Follow-up 7 at 42 months.

[b] **Growth and Development:** Signs of puberty (growth spurt, body hair, breast development, skin changes); menses; Tanner stage of breast and pubic hair development; comparative body size (height, weight) currently and at age 6 years; current body shape (drawing).

[c] **Behavioral Questionnaire:** Daughter's psychosocial adjustment; maternal anxiety, depression, breast cancer-specific distress, perceived stress, knowledge and perceptions of breast cancer risk, breast cancer and genetic testing experiences, family functioning and communication and health behaviors.

[d] **Cancer Family History:** Cancer in daughter's 1st, 2nd, and 3rd degree relatives; familial relationship, type of cancer diagnosed, age at diagnosis.

[e] **Early-life Questionnaire:** Daughter's demographic background; parents' background (demographics, income, occupation, country of birth, migration to US/Canada, language); parents' height; parents' physical activity; grandparents' country of birth; home environment (primary residence, language spoken, household composition); siblings (Age, gender, age at menarche for sisters); pregnancy and birth outcomes (weight gain, physical activity, smoking, alcohol consumption, use of prenatal vitamins, duration of pregnancy, medical conditions, birth weight and length, breast-feeding); medical history (medication use, medical conditions, chronic conditions); daughter's physical activity level at ages 3–5 years; lifetime history of organized sports and exercise activities.

[f] **Update on Home Environment and Medical History:** Home environment; parents' occupation; medical history.

[g] **Recent Physical Activity:** Physical education (PE) at school, transportation to school, organized sports and activities in past year, organized sports and activities in past week, other physical activities in past week, sedentary activities and sleeping on prior day.

[h] **Recent Dietary Intake:** Food Frequency Questionnaire on intake in past week (frequency, portion size).

[i] **Nutrition:** Intake of organic food, soy food, fast-food and restaurant food, family meals, special diet.

[j] **Neighborhood Characteristics:** Type of housing, walkability, safety, availability of healthy foods.

[k] **Physical and Social Environment:** Chemical exposure in home and community environment; attitudes about daily life; place in society.

[l] **Saliva:** Collected unless DNA is already available in the Breast Cancer Family Registry biorepositories.

[m] **Social Environment:** Place in society; future hopes.

[n] **Behavioral Questionnaire:** Daughter's psychosocial adjustment, breast cancer-specific distress, perceived stress, knowledge and perceptions of breast cancer risk, breast cancer experiences, family functioning and communication, health and risk behaviors.

[o] **Anthropometry:** Standing height, weight, percent body fat, waist and hip circumference, foot size.

[p] **Clinical Breast Tanner Staging:** Performed at New York and Utah study sites only.

Table 2

Baseline characteristics of participating girls, by breast cancer family history, LEGACY Girls Study, 2011 – 2015

	Breast cancer in 1st degree relatives (N=220)		Breast cancer in 2nd degree relatives only (N=313)		No breast cancer in 1st or 2nd degree relatives (N=507)	
	N	% [a]	N	% [a]	N	% [a]
Age at baseline (years)						
5	2	1	5	2	5	1
6	20	9	34	11	47	9
7	17	8	40	13	58	11
8	22	10	37	12	72	14
9	29	13	47	15	75	15
10	28	13	42	13	74	15
11	27	12	30	10	69	14
12	31	14	34	11	60	12
13	29	13	35	11	37	7
14	5	2	5	2	5	1
15	8	4	4	1	4	1
16	2	<1	0	0	1	<1
Race/ethnicity						
Non-Hispanic White	124	56	232	74	290	57
Hispanic White	45	20	40	13	83	16
Hispanic Black	13	6	2	1	10	2
African American or Black	13	6	16	5	49	10
Asian American or Pacific Islander	22	10	17	5	57	11
Mixed race/ethnicity	3	1	6	2	18	4
Education, mother or female guardian						
High school graduate or less	23	11	33	11	57	11
Some college or university	35	17	47	15	89	18
Bachelor’s degree	83	40	106	35	188	38
Graduate degree	64	31	121	39	168	34
Not reported	15		6		5	

	Breast cancer in 1st degree relatives (N=220)		Breast cancer in 2nd degree relatives only (N=313)		No breast cancer in 1st or 2nd degree relatives (N=507)	
	N	% [a]	N	% [a]	N	% [a]
Education, father or male guardian						
High school graduate or less	39	19	53	18	95	24
Some college or university	32	15	46	16	74	19
Bachelor's degree	72	34	96	33	128	32
Graduate degree	66	32	98	33	174	44
Not reported	11		20		36	
Annual family Income						
< $50,000	30	18	37	15	74	18
$50,000 – $74,999	19	11	21	8	50	12
$75,000 – $99,999	19	11	30	12	71	17
≥ $100,000 or more	103	60	163	65	235	55
Not reported	49		62		77	

[a]Percentages may not add up to 100 because of rounding. Missing data were not included in percentages.

Table 3

Participation [a] in baseline and first two follow-up visits, LEGACY Girls Study, 2011–2015

	Baselinevisit N (%)	Follow-up 1(at 6 months) N (%)	Follow-up 2 (at 12 months) N (%)
Visit completed	1,040 [b]	1,003 (96%) [c]	977 (94%) [c]
Withdrawal from study		12	12
Not available or declined visit		25	39
Questionnaires completed by mothers/guardians			
Growth and Development Questionnaire	999 (96%)	953 (92%)	900 (87%)
Behavioral Questionnaire	945 (91%) [d]	n/a	916 (88%) [e]
Questionnaires completed by daughters			
Daughters ages ≥10 years	530	604	686
Growth and Development Questionnaire	510 (96%)	546 (90%)	602 (88%)
Behavioral Questionnaire	481 (91%)	n/a	610 (89%)
Biospecimen collection			
Urine	1,014 (98%)	951 (91%)	915 (88%)
Blood	427 (41%)	404 (39%)	n/a
Saliva	587 (56%)	340 [f]	454 [f]
Anthropometry completed	1,020 (98%)	954 (92%)	923 (89%)
Clinical breast Tanner staging [g]			
Daughters offered Tanner staging	305	292	285
Tanner staging completed	254 (83%)	247 (85%)	234 (82%)

[a] Participation rates are provided for the baseline cohort of 1,040 girls, unless specified otherwise.

[b] Number of girls enrolled in cohort.

[c] Completion of at least one component of follow-up visit.

[d] At baseline, the Behavioral Questionnaire was not offered to mothers/guardians of 67 girls who spoke Spanish only or due to delayed IRB approval.

[e] At the second follow-up, the Behavioral Questionnaire was not offered to mothers/guardians of 27 girls who spoke Spanish only.

[f] Includes repeat saliva samples for some girls.

[g] Clinical breast Tanner staging was performed at the New York and Utah study sites only.

Table 4

Growth and development of participating girls, by breast cancer family history, LEGACY Girls Study, 2011 – 2015

	Breast cancer in 1st degree relatives (N=220)		Breast cancer in 2nd degree relatives only (N=313)		No breast cancer in 1st or 2nd degree relatives (N=507)	
	N	% [a]	N	% [a]	N	% [a]
Menarche status						
Pre-menarcheal	156	75	245	81	404	83
Post-menarcheal	53	25	56	19	84	17
Not reported	11		12		19	
Age at menarche among post-menarcheal daughters (years)						
≤9	5	5	2	4	4	4
10	11	10	6	11	11	14
11	34	31	14	26	27	33
12	44	40	23	43	29	36
13	14	13	7	13	8	10
14	0	0	0	0	2	2
15	1	1	1	2	0	0
Not reported	1		0		3	
Breast Tanner stage [b]						
T1	90	47	150	53	267	60
T2	30	16	46	16	73	16
T3	41	21	54	19	60	13
T4	21	11	28	10	37	8
T5	10	5	4	1	11	2
Not reported	28		31		59	
Pubic hair Tanner stage [b]						
T1	99	50	180	63	277	60
T2	31	16	31	11	88	19
T3	20	10	27	9	35	8
T4	34	17	32	11	38	8

	Breast cancer in 1st degree relatives (N=220)		Breast cancer in 2nd degree relatives only (N=313)		No breast cancer in 1st or 2nd degree relatives (N=507)	
	N	% [a]	N	% [a]	N	% [a]
T5	14	7	16	6	21	5
Not reported	22		27		48	
Height for age (percentiles) [c]						
<5th	1	0	10	3	21	4
≥5th to <85th	153	71	216	72	360	73
≥85th to <95th	36	17	42	14	59	12
≥95th	24	11	31	10	56	11
Not available	1		14		11	
Not measured	0		12		8	
Weight for age (percentiles) [c]						
<5th	6	3	11	4	30	6
≥5th to <85th	164	75	235	78	369	74
≥85th to <95th	31	14	24	8	53	11
≥95th	19	9	31	10	47	9
Not available	0		12		8	
Body mass index for age (percentiles) [c]						
<5th	24	11	20	7	39	8
≥5th to <85th	148	68	226	76	371	75
≥85th to <95th	29	13	28	9	51	10
≥95th	18	8	25	8	35	7
Not available	1		14		11	
Waist-to-hip ratio						
< 0.79	55	25	57	19	121	24
0.80 – 0.83	63	29	89	30	147	30
0.84 – 0.87	42	19	78	26	112	22
≥0.88	60	27	76	25	118	24
Not measured	0		13		9	
Percent body fat						
< 22.5	56	26	77	26	111	23

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	Breast cancer in 1st degree relatives (N=220)		Breast cancer in 2nd degree relatives only (N=313)		No breast cancer in 1st or 2nd degree relatives (N=507)	
	N	% [a]	N	% [a]	N	% [a]
22.5 – 27.4	57	26	76	26	122	25
27.5 – 32.8	45	21	83	28	124	25
≥32.9	58	27	60	20	133	27
Not measured	4		17		17	

[a] Percentages may not add up to 100 because of rounding. Girls with missing data were not included in percentages.

[b] Assessed by the mother/guardian.

[c] Calculated from CDC growth charts http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm.