ARIC Manuscript Proposal # 1512

PC Reviewed: 5/12/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Candidate-gene/SNP association study of age at menarche genes and breast cancer risk

b. Abbreviated Title (Length 26 characters): Menarche genes and breast cancer risk

2. Writing Group: Ellen Demerath, Nora Franceschini, Aaron Folsom, Eric Boerwinkle, Alanna Morrison, Gerardo Heiss, other welcome

Collaboration within CHARGE Consortium will be explored.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. NF____ **[please confirm with your initials electronically or in writing]**

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Address: same as above for first author

3. Timeline: Analyses will begin immediately upon approval of this proposal.

4. Rationale:
Age at menarche is associated with adult stature and obesity [1, 2, 3, 4], and influences the risk for several diseases in women, including breast cancer [5]. Menarche occurs at a mean age of approximately 13 years in individuals of European descent, and approximately 2 years after the onset of puberty. Secular chances of age of menarche have also been documented [6, 7].

Early age at menarche is a risk factor for breast cancer [8] and these effects are linked to greater time exposure to estrogens. Age at menarche has also a significant impact on breast cancer prognosis and survival among post-menopausal women[9]. In one study, age at menarche of 11 years or younger had a more than twofold excess risk of medium-grade (odds ratio [OR] = 2.05; 95% confidence interval [CI] 1.00 to 4.18) and high-grade (OR = 2.04; 95% CI 1.01 to 4.16) tumors. Survival was poorest in women with the earliest age at menarche, with a 72% increased risk of dying within 5 years after diagnosis (hazard ratio = 1.72; 95% CI 1.02 to 2.89) [9].

Several recently genome-wide studies (GWAS) have identified single nucleotide polymorphisms (SNPs) in genes for age of menarche [10](Perry et al, 2009, *in press*). Liu et al. identified associations of SNPs in the *SPOCK* gene with age of menarche [10]. In our own GWAS within the CHARGE Consortium involving a sample size of 17,510 women of European descent, we identified two genes associated with age of menarche (Nature Genetics, under review). The strongest signal was at 9q31.2 ($P = 1.7x10^{-9}$) where the nearest genes include *TMEM38*B, *FKTN*, *FSD1L*, *TAL2* and *ZNF462*. The next best signal was near the *LIN28B* gene (rs7759938; $P = 7.0x10^{-9}$), which also influences adult height. We were unable to replicate the association findings from the study of Liu et al.

5. Main Hypothesis/Study Questions:
To explore if genes associated with menarche timing also contribute to the susceptibility to breast cancer outcomes, we will perform a candidate gene/SNP association analysis using published genome-wide associated SNPs and these events in race-stratified samples of women of European and African ancestry.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).
Subjects: Women of European and African ancestries with available self-reported information regarding age at menarche, breast cancer and the candidate SNPs.
Variables (phenotype): breast cancer incident and prevalent cases.
Inclusion: all white and African American women with available phenotypes
Exclusions: women having a breast cancer or any cancer diagnosis at the baseline visit for analysis of incident data.
Exposure: candidate SNPs from the Affymetrix 6.0 SNP chip previously identified in GWAS for age of menarche.

Models:

Primary analysis: We will use imputed and genotyped data (using the HapMap Caucasian information) for all white women and only genotyped data for African American women. We will use Cox proportional models with additive genetic effects to model the association of candidate SNPs with time to breast cancer events and will use logistic regression to assess the association between genotype at candidate loci and case/control status (prevalent and incident breast cancer cases). We will perform analysis using all available SNPs that pass QC, with adjustment for age and center/site within race-stratified cohort, age of menarche, and other risk factors for the events. We will also adjust for number of pregnancies, use of hormone therapy, presence or absence of unilateral oophorectomy, and age of menopause, body mass index, smoking and will consider stratifying on age at diagnosis (pre-menopausal vs post-menopausal). Population stratification will be assessed using principal components (PC) analysis where PCs that are significantly associated with the trait will be included.

We will use the Framingham Heart Study as replication for our analysis and will consider extending the analysis to other cohorts within CHARGE in a meta-analysis. The following studies may participate in a meta-analysis: ARIC, Framingham Heart Study, Rotterdam Study I and II, TwinsUK, InCHIANTI, HAPI Heart Study (Amish study).

Covariates: (listed above)

Statistical significance: We will correct for the number of independent tests performed using Bonferroni correction.

Meta-analyses: We will conduct meta-analysis of cohort-specific p-values within the CHARGE Aging and Longevity—Reproductive Health WG, using fixed or random effects (if number of participant studies is more than 5) using STATA or SAS.

For African Americans, we will follow the procedures for CARe.

7.a. Will the data be used for non-CVD analysis in this manuscript?
__ __ Yes _X__ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?
____ Yes ____ No
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? __X__ Yes __ __ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
__X__ Yes ____ No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

____X__ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

ARIC Manuscript Proposal # 1472. Genome-wide association analysis of age of menarche: the CHARGE Consortium

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes _ ___ No

11.b. If yes, is the proposal

_X_ A. primarily the result of an ancillary study (list number* 2006.03 (Stampede and Geneva genotype funding in Caucasians) and 2007.02 (CARe, genotyping in African Americans).

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References:

1. Biro FM, McMahon RP, Striegel-Moore R, et al. Impact of timing of pubertal maturation on growth in black and white female adolescents: The National Heart, Lung, and Blood Institute Growth and Health Study. J Pediatr 2001;138:636-43.
2. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. Pediatrics 2002;110:e43.
3. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of menarcheal age to obesity in childhood and adulthood: the Bogalusa heart study. BMC Pediatr 2003;3:3.
4. Dunger DB, Ahmed ML, Ong KK. Early and late weight gain and the timing of puberty. Mol Cell Endocrinol 2006;254-255:140-5.
5. Rockhill B, Moorman PG, Newman B. Age at menarche, time to regular cycling, and breast cancer (North Carolina, United States). Cancer Causes Control 1998;9:447-53.

6. Varea C, Bernis C, Montero P, Arias S, Barroso A, Gonzalez B. Secular trend and intrapopulational variation in age at menopause in Spanish women. J Biosoc Sci 2000;32:383-93.
7. Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. Pediatrics 2008;121 Suppl 3:S172-91.
8. Clavel-Chapelon F. Differential effects of reproductive factors on the risk of pre- and postmenopausal breast cancer. Results from a large cohort of French women. Br J Cancer 2002;86:723-7.
9. Orgeas CC, Hall P, Rosenberg LU, Czene K. The influence of menstrual risk factors on tumor characteristics and survival in postmenopausal breast cancer. Breast Cancer Res 2008;10:R107.
10. Liu YZ, Guo YF, Wang L, et al. Genome-wide association analyses identify SPOCK as a key novel gene underlying age at menarche. PLoS Genet 2009;5:e1000420.