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13. ABSTRACT (Maximum 200 Words)

Breast development and structure is influenced most during the following stages of life - intrauterine, menarche, and pregnancy and lactation. Much of breast cancer risk is still unexplained perhaps because many investigations focus on exposures after critical breast development periods. In particular, studies examining the intrauterine period and later breast cancer risk are scant. *In utero* exposures may increase breast cancer risk by increasing the number of mammary cells and rate of cell division, increasing the number of *in utero* mutations, and/or through imprinting the fetal ovary. This study is a prospective follow-up study of children who were part of a perinatal prospective cohort recruited during 1959-1963 in New York City. We are examining associations between maternal exposures during fetal development, fetal growth and childhood growth with the following factors known to be important to breast cancer risk -- age at menarche, insulin-like growth factors, and mammographic density in a sample of 200 Hispanic, African American and white, premenopausal women aged 38 to 42. After the first year of work, we have collected questionnaire information on 137 women. We are currently collecting blood and mammogram information and study recruitment is ongoing.

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Introduction

Breast development and structure is influenced most during the following stages of life – intrauterine, menarche, and pregnancy and lactation. The success of traditional breast cancer epidemiology has been to uncover the relationship of factors such as menarche, parity, and menopause on breast cancer risk. However, much of breast cancer risk is still unexplained perhaps because many investigations focus on exposures after critical breast development periods. In particular, studies examining the intrauterine period and later breast cancer risk are scant. *In utero* exposures may increase breast cancer risk by increasing the number of mammary cells and rate of cell division, increasing the number of *in utero* mutations, and/or through imprinting the fetal ovary. We hypothesize that early life factors are important to breast cancer risk, particularly premenopausal breast cancer, and also that they may help to explain the higher breast cancer risk in African Americans as compared to whites in the premenopausal period. This study is a prospective follow-up study of children who were part of a perinatal prospective cohort recruited during 1959-1963 in New York City. Specifically, we are examining associations between maternal exposures during fetal development, fetal growth and childhood growth with the following factors known to be important to breast cancer risk -- age at menarche, insulin-like growth factors, and mammographic density in a sample of 200 Hispanic, African American and white, premenopausal women aged 38 to 42. After the first year of work, we have collected questionnaire information on 137 women. We are currently collecting blood and mammogram information and study recruitment is ongoing.

Body:

We have just completed the first year of a three year grant. The status of our progress is listed by task following our approved statement of work

Task 1: To complete interviewing of 265 women using a mailed health questionnaire.

a. Continue to trace women, efforts began in May 2001 as part of National Cancer Institute K-07 grant. We expect 40% of cohort will be traced by start of this project in Feb 2002. After start of Army grant, we will be able to trace full-time so we expect to trace the remaining cohort within 9 months (Months 1-9).

b. Continue to send out mailed interviews, efforts will begin in July 2001 as part of National K-07 grant. (Months 1-12)

c. Enter data from mailed questionnaires; ongoing as questionnaires are received (Months 1-15)

- As of June 30, 2003, we have completed interviewing 137/265 women using a mailed health questionnaire. 41% (318/784) of mothers have been traced successfully. This group includes women that have provided information on their daughter, are deceased or refused participation. 33% (262/784) of daughters have been traced. This group includes those women who are willing to participate, deceased, too ill to participate and those who have refused to participate.

- As of June 30, 2003, 226 health questionnaires have been mailed out at least 1 time to the daughter participants. We have received 140 completed questionnaires, however we are only able to use 137, due to missing questionnaire consent forms.

- As of June 30, 2003, 137 have been entered in to the questionnaire database.

We are continuing this task in Year 2.

Task 2: To collect blood samples from 212 women and perform genotyping and IGF-1 assays.

a. Send out blood collection kits; send after collection of questionnaire data as women are enrolled. (Months 1-20)

b. Aliquot and send samples to Nichols for IGF-1 and IGFBP-3 testing (Months 22-25)

c. Perform genotyping in Dr. Santella's laboratory for the following 3 genes – AIB1, IGF1, CYP3A4; after genotyping assay is validated using 96-well plates and the Florescence Polarization method (Months 21-29)

- As of June 30, 2003, we have received blood collection consent forms form 29 daughter participants. We have sent out 26 blood collection kits.

Body (continued):

Task 3: To collect mammograms from 150 women and scan the mammograms for mammographic density measures.
a. Attend training on use of density scanning software in Toronto with Drs. Boyd and Yaffe (June 2001, as part of program project work on mammographic density)
b. Collect mammograms (Months 13-25)
c. Scan mammograms as they come in and perform density readings (Months 13-29)

This task is currently being accomplished in year 2.

Task 4: To analyze the data using the methods described in the body of the proposal.
a. Cleaning and editing the data (Month 30-31)
b. Performing analyses as described for the 3 aims (Months 32-35)
c. Manuscript preparation (Months 35-36)

This task will start in the third year.

Key Research Accomplishments After one year of work, our key accomplishments are:

- We have trained our research staff on our protocol.
- We have developed and tested all study instruments.
- As of June 30, 2003, we have completed interviewing 137/265 women using a mailed health questionnaire. 41% (318/784) of mothers have been traced successfully. This group includes women that have provided information on their daughter, are deceased or refused participation. 33% (262/784) of daughters have been traced. This group includes those women who are willing to participate, deceased, too ill to participate and those who have refused to participate.
- As of June 30, 2003, 226 health questionnaires have been mailed out at least 1 time to the daughter participants. We have received 140 completed questionnaires, however we are only able to use 137, due to missing questionnaire consent forms.
- As of June 30, 2003, 137 have been entered in to the questionnaire database.
- As of June 30, 2003, we have received blood collection consent forms form 29 daughter participants. We have sent out 26 blood collection kits.

Reportable Outcomes

In the past year, we have presented preliminary data at the Second World Congress on Fetal Origins of Adult Disease. The conference goal was to bring new insights in to pathogenesis of adult disease including cancer, coronary heart disease, hypertension, diabetes, osteoporosis and some neurological disorders. Views from various disciplines were presented, ranging from epidemiology to molecular biology.

We presented 2 posters at the conference is Brighton, England. One poster was entitled, "" Validity of Self-Report of Birthweight"; the other" Early Life Growth and its Influence on Age at Menarche and Adult Body Size." (To view to posters, please see appendices.)

Conclusions

We have had a very busy and productive first year. We have recruited and received questionnaires on 137 study subjects and are in the process of recruiting more subjects. We have started collecting blood and are now set up to retrieve the mammograms which will be collected this year. We presented two posters at an international meeting summarizing some preliminary findings (see Appendix).

References
N/A

Appendices

1. Poster – " Validity of Self-Report of Birthweight."
2. Poster – " Early Life Growth and its Influence on Age at Menarche and Adult Body Size."

Validity of Self-Report of Birthweight

Columbia University MAILMAN SCHOOL OF PUBLIC HEALTH
MB Terry, P Tehranifar, D Shah*, E Susser
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Background

Accumulating evidence suggests that birthweight is associated with a number of adult health outcomes, including breast cancer.

In many countries it is difficult to obtain birth record data retrospectively so investigators must rely on self-report of birthweight.

Research Question

Can birthweight be reliably recalled to justify the use of self-reported birthweight in epidemiological studies?

Subjects

The subjects are daughters of the former participants of the New York site of the National Collaborative Perinatal Project (NCPP).

NCPP was initiated over 40 years ago to learn about pregnancy, childbirth and childhood growth.

13 university affiliated medical centers participated in NCPP and over 55,000 pregnant women were enrolled and followed through pregnancy, labor and delivery.

809 daughters from the New York site, born between 1959 and 1966, were followed until the age of 7 and are currently being recruited into a follow-up study of adult health.

To date, we have adult questionnaire data on 130 daughters from the NCPP.

Data

Self-reported birthweight was obtained from 111 subjects after 36-43 years, via a postal questionnaire.

Subjects reported their birthweight using the following categories*:

< 5.5 lbs.

5.5 - 6.9 lbs.

7.0 - 8.4 lbs.

8.5 – 9.9 lbs.

10 lbs. and over

True birthweight was measured and recorded at delivery and is available in the NCPP database.

Self-reported birthweights were compared to birthweight recorded at delivery.

**All weights were converted to grams.*

Statistical Analyses

Kappa as a measure of agreement.

$$\text{Kappa} = \frac{\%\ \text{Agreement} - \%\ \text{Chance}}{1 - \%\text{Chance}}$$

Sensitivity by birthweight category.

$$\text{Sensitivity (by birthweight category)} = \frac{\text{Self-Reported Weight}}{\text{Recorded Weight}}$$

Results

Histogram of Sample birthweights(g)

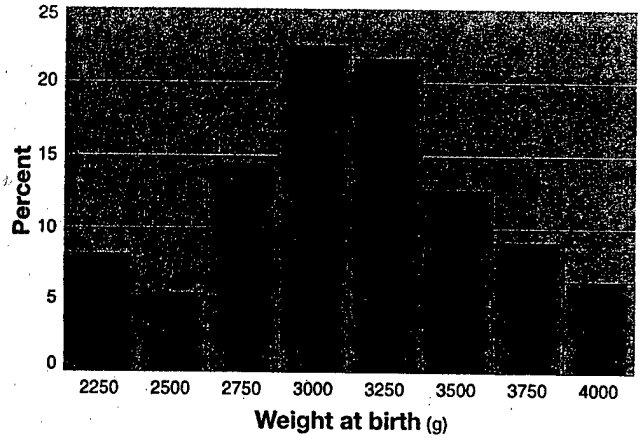

Table 1

Sample Description

Birthweight (g)

Mean	=3128.3
SD	= 448.2
Median	=3146.5
Min-Max	=2155.0-3997.0

Race/ethnicity

White	=30%
African American	=28%
Hispanic	=24%
Multiracial	=16%
Other	=2%

Current Educational Attainment

High school graduate or less	=16%
Technical or some college	=42%
College graduate or more	=42%

Table 2

Self-Reported Birthweight vs. Recorded Birthweight (g)

Recorded Birthweight (g)	Self-Reported Birthweight (g) < 2500	2500 – 3199	3200 – 3899	> 3900	Total
< 2500	7	4	0	1	12
2500 – 3199	3	33	9	1	46
3200 – 3899	0	7	34	6	47
> 3900	0	0	0	6	6
Total	10	44	43	14	111

Weighted Kappa = 0.64, 95% CI (0.52 – 0.75)

Table 3

Measurement of agreement between self-reported birthweight and recorded birthweight records for total sample and by educational level

	Total sample N=111	Less than college N=64	College graduate N=46
Spearmen correlation	0.71	0.63	0.81
Weighted Kappa	0.64(0.52-0.75)	0.53(0.37-0.70)	0.75(0.60-0.90)
Sensitivity			
<2500	7/12=58%	3/7=43%	3/4=75%
2500-3199	33/46=72%	17/26=65%	16/20=80%
3200-3899	34/47=72%	22/30=73%	12/17=71%
>=3900	6/6=100%	1/1=100%	5/5=100%

**1 subject has missing educational data*

Results

Only 14 participants did not report their birthweight. These participants did not differ significantly from those who reported their birthweight in terms of recoded birthweight, ethnicity or educational attainment.

Overall Kappa is 0.64, 95% CI (0.52 – 0.75), however sensitivity varied by birthweight category and increased with increasing birthweight

When stratified by educational level, highest agreement was seen in women who were college graduates and above.

Within educational strata, sensitivity also increased with increasing birthweight.

Conclusion

Results suggest that self-reported birthweight is measured with error. The magnitude of the error depends on the initial birthweight and also varies by educational status.

This amount of measurement error is of concern as many associations between birthweight and adult health outcomes are modest (< 2-fold).

Further, because these data suggest differences in accuracy by initial birthweight as well as education status, use of self-reported birthweight may create biases in associations between birthweight and adult outcomes

Studies using self-reported birthweight should consider the impact of this type of measurement error on their findings and the direction of expected bias.

Acknowledgements
This study was supported through the National Cancer Institute's K07 career development award and through a U.S. Army Breast Cancer Research Program Idea Grant.

We would like to thank the participants of the New York NCPP cohort for their continued support.

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Early Life Growth and its Influence on Age at Menarche and Adult Body Size

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Background

Accumulating evidence suggests that birthweight is positively associated with breast cancer.

Birthweight has also been associated with age at menarche and adult body size, both known risk factors for breast cancer.

Several studies suggest that the association between birthweight and age at menarche is influenced by other childhood growth measures, however the results are not consistent and few studies have examined populations that are racially and ethnically diverse.

Purpose

To determine if birthweight is associated with age at menarche and adult body size after accounting for potential mediation by childhood growth measures.

Subjects

The subjects are daughters of the former participants of the New York site of the National Collaborative Perinatal Project (NCPP).

NCPP was initiated over 40 years ago to learn about pregnancy, childbirth and childhood growth.

13 university affiliated medical centers participated in NCPP and over 55,000 pregnant women were enrolled and followed through pregnancy, labor and delivery.

809 daughters from the New York site, born between 1959 and 1966, were followed prospectively until the age of 7 and are currently being recruited into a follow-up study of adult health.

Of these 809 daughters: 28% are white, 43% are black and 29% are Puerto Rican, according to the racial/ethnic classification used in the original NCPP cohort.

To date, we have collected adult questionnaire data on 130 daughters from the NCPP.

Data

Height and weight were measured prospectively from birth throughout childhood until the age of 7.

The age of menarche and adult height and weight are self-reported from the adult follow-up questionnaire.

Body mass index (BMI) was calculated using information on weight and height (kg/m²).

Statistical Approach

Univariate statistics and analysis of variance (ANOVA) were used to compare means for continuous variables

Multivariate modeling was used to examine mediation between birthweight and menarche and adult BMI.

Age at Menarche

Polytomous logistic regression with 3 groups:
Early (less than or equal to 11 years)
Average (12 and 13 years)
Late (equal to or more than 14 years)

Adult Body Size

We used linear regression to analyze adult height and weight as continuous variables and logistic regression to analyze body mass index categorized into two groups:
Not overweight (BMI < 25)
Overweight (BMI ≥ 25)

Confounders considered:	**Mediators considered:**
Race	*Weight at age 1*
Socioeconomic status	*Height at age 1*
Maternal age at menarche	*BMI at age 1*
Maternal height	*Weight at age 7*
Gestational age	*Height at age 7*
Birth order	*BMI at age 7*

Confounding and mediation were considered by comparing parameters on birthweight before and after inclusion of these potential mediators/ confounders in the model.

Interaction between birthweight and body size at 7 years was explored through ANOVA but not in multivariate models

Results

Sample Description:

Race/Ethnicity (N = 125): Black = 36 (28.8%); White = 37 (29.6%); Hispanic = 31 (24.8%); Other or Multi-racial: 21 (16.8%)

Education (N = 124): High School Graduate or less = 24 (19.4%); Tech School or some College = 49 (39.5%); College graduate or more = 51 (41.1%)

Birthweight (g) (N =124): Mean = 3146.4; SD = 434.6; Median = 3175.0; Min - Max = 2155.0 – 3997.0

Weight at 1 year (kg) (N = 123): Mean = 9.6; SD =1.1; Median = 9.6; Min - Max = 6.4 – 12.3

Weight at 7 years (kg) (N = 124): Mean = 24.3; SD = 4.9; Median = 23.1; Min - Max = 16.2 – 37.4

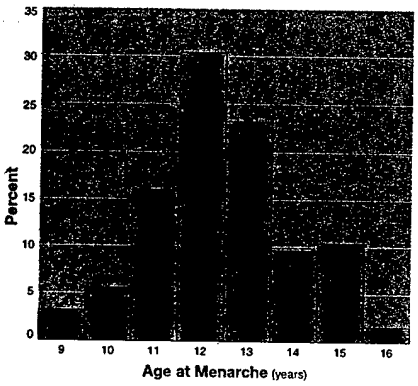
Weight at 30 years (kg) (N = 115): Mean = 65.9; SD = 17.4; Median = 59.9; Min - Max = 43.1 – 149.7

Age at Menarche (years) (N = 125): Mean = 12.4; SD = 1.5; Median = 12.0; Min - Max = 9.0 – 16.0

Menarche group (N = 125): Early (≤ 11 yrs) = 31 (24.8%); Average (12 – 13 yrs) = 67 (53.6%); Late (≥ 14 yrs) = 27 (21.6%)

Adult BMI at 30 years (kg/m²) (N = 114): Mean = 24.5; SD = 6.3; Median = 22.6; Min - Max = 16.6 – 58.5

Adult BMI-group (kg/m²) (N = 114): BMI < 25 = 76 (66.7%); BMI ≥ 25 = 38 (33.3%)



Univariate Statistics

Age at Menarche (years)

Race	N	Age at Menarche: Mean (SD)
Black	36	12.4 (1.5)
White	37	12.6 (1.4)
Hispanic	31	12.3 (1.5)
Other and multi-racial	21	12.5 (2.0)
		p-value = 0.85
Education		
High School graduate or less	24	12.3 (1.8)
Technical school or some college	49	12.4 (1.4)
College graduate or more	51	12.6 (1.5)
		p-value = 0.71
Birthweight (BWT)		
Low birthweight (≤ 3175 g)	63	12.6 (1.7)
High birthweight (> 3175 g)	61	12.3 (1.4)
		p-value = 0.38
Weight at 7 years (WT7)		
Low weight at 7 (≤ 23.10 kg)	62	12.8 (1.4)
High weight at 7 (> 23.10 kg)	62	12.1 (1.6)
		p-value = 0.01
Birthweight and weight at 7 years		
Low BWT + Low WT7	36	12.7 (1.5)
Low BWT + High WT7	27	12.4 (1.8)
High BWT + Low WT7	26	12.9 (1.3)
High BWT + High WT7	35	11.9 (1.3)
		p-value = 0.05

1) High (above median) weight at 7 but not birthweight was associated with earlier age at menarche.

2) Girls with high (above median) birthweight and high (above median) weight at 7 had the earliest age at menarche (11.9 years).

3) In contrast, girls with high (above median) birthweight and low (below median) weight at 7 years had the latest age at menarche (12.9 years).

Adult Body Mass Index (kg/m²)

Race	N	BMI at 30 years: Mean (SD)
Black	30	26.2 (7.5)
White	34	23.2 (5.8)
Hispanic	29	25.2 (6.7)
Other and multi-racial	21	23.3 (4.0)
		p-value = 0.19
Education		
High School graduate or less	22	27.3 (9.9)
Technical school or some college	46	23.7 (5.8)
College graduate or more	46	24.1 (4.2)
		p-value = 0.07

Birthweight (BWT)		
Low birthweight (≤ 3175 g)	57	24.7 (7.3)
High birthweight (> 3175 g)	56	24.3 (5.3)
		p-value = 0.75
Weight at 7 years (WT7)		
Low weight at 7 (≤ 23.10 kg)	55	22.7 (3.9)
High weight at 7 (> 23.10 kg)	58	26.2 (7.6)
		p-value < 0.01
Birthweight and weight at 7 years		
Low BWT + Low WT7	34	23.1 (4.2)
Low BWT + High WT7	23	27.0 (9.9)
High BWT + Low WT7	21	22.0 (3.2)
High BWT + High WT7	35	25.7 (5.8)
		p-value = 0.02

1) High (above median) weight at 7 but not birthweight is associated with higher BMI at age 30.

2) Girls with high (above median) birthweight and low (below median) weight at 7 had the lowest adult BMI (21.95).

3) In contrast, girls with low (below median) birthweight and high (above median) weight at 7 years had the highest adult BMI (26.98).

Multivariate Statistics:

Risk of early menarche relative to average

	OR per Kg (95% CI)	OR[a]	OR[b]
Birthweight	1.1 (0.4-3.0)	0.8 (0.3-2.5)	1.3 (0.4-4.6)
Birth length	1.1 (0.9-1.4)	1.0 (0.8-1.3)	1.2 (0.9-1.6)
BMI at birth	0.9 (0.6-1.3)	0.9 (0.6-1.3)	0.9 (0.6-1.4)

Risk of early menarche relative to late menarche

	OR per Kg (95% CI)	OR[a]	OR[b]
Birthweight	1.5 (0.5-4.9)	1.3 (0.4-4.6)	2.3 (0.5-10.0)
Birth length	1.2 (0.9-1.5)	1.1 (0.8-1.5)	1.3 (0.9-1.8)
BMI at birth	1.0 (0.6-1.6)	1.0 (0.6-1.6)	1.1 (0.6-1.8)

Risk of being overweight (BMI ≥ 25) versus not being overweight (BMI < 25)

	OR per Kg (95% CI)	OR[a]	OR[b]
BMI at birth	1.1 (0.7-1.5)	0.9 (0.6-1.4)	1.1 (0.7-1.9)
BMI at 1 year	1.0 (0.8-1.3)	0.8 (0.6-1.0)	0.7 (0.5-1.0)
BMI at 7 years	1.4 (1.2-1.7)	1.5 (1.2-1.8)	1.5 (1.2-1.9)

Association with adult weight at 30 years (in kg)

	β (Δ per Kg) (95% CI)	β[a]	β[b]
Birthweight	0.5 (-6.9-7.8)	-1.6 (-8.2-5.0)	2.7(-4.8-10.3)
Weight at 1 year	2.2 (-0.8-5.2)	-3.2 (-6.4-0.1)	-3.3 (-6.6-0.1)
Weight at 7 years	1.8 (1.2-2.4)	2.2 (1.5-2.9)	2.1 (1.4-2.9)

Association with adult height at 30 years (in kg)

	β (Δ per Kg) (95% CI)	β[a]	β[b]
Birth length	0.8 (0.2-1.3)	0.1 (-0.3-0.6)	0.3(-0.2-0.8)
Height at 1 year	1.1 (0.8-1.4)	0.5 (0.2-0.8)	0.5 (0.1-0.8)
Height at 7 years	0.9 (0.7-1.0)	0.7 (0.5-0.9)	0.7 (0.5-0.9)

[a] Adjusted for other body size measures (at birth, 1 and 7 years)
[b] Adjusted for other body size measures and confounders

Conclusion

Preliminary analyses suggest that birthweight by itself is not associated with age at menarche and adult body size but that measures of childhood growth including body size at age 1 and 7 years are associated with adult body size.

Birthweight in combination with weight at 7 is associated with age at menarche and adult body size in univariate analyses.

Multivariate analyses suggest that both BMI and weight at 7 are statistically significantly associated with adult body size.

After adjustment for age 7 weight and BMI at 7, the association between age 1 weight and BMI at 1 reverses direction and is inversely related to adult body size.

Height at age 1 and age 7 are both positively related to height at age 30, but the effect of birth length on adult height is fully mediated by height at age 1 and age 7.

These results suggest the importance of considering potential mediation and interaction by early childhood growth measures when examining the impact of birthweight on adult health.

Next steps

Continue to recruit subjects into the adult followup study.

Examine differences in the infant and childhood data between those participating in the adult followup and those not participating.

After data collection is complete, conduct growth curve analyses and perform statistical interaction testing by other childhood growth measures in multivariate models.

Acknowledgements

This study was supported through the National Cancer Institute's K07 career development award and through a U.S. Army Breast Cancer Research Program Idea Grant.

We would like to thank the participants of the New York NCPP cohort for their continued support.

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