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Relative Weight at Age 12 and Risk of Postmenopausal Breast Cancer

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Abstract

Background—Early adolescent weight may impact the risk of postmenopausal breast cancer, and this association may be modified by a family history of breast or ovarian cancer in a first degree relative, and/or estrogen (ER) and progesterone (PR) receptor status of the disease.

Methods—Relative weight at age 12 (above, below, or average weight compared to peers) and family history were ascertained using a mailed questionnaire in 1986, in the Iowa Women's Health Study, a prospective cohort study of postmenopausal women. Incident breast cancer cases (including ER and PR status) were identified using the Iowa SEER Cancer Registry. Relative risks (RR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression, and were adjusted for breast cancer risk factors including body mass index (BMI) at age 18 and BMI at study baseline.

Results—Through 2003, 2503 cases of postmenopausal breast cancer were identified among 35,941 women in the analytic cohort. Compared to women with average weight at age 12, there was no association of below average weight with risk of breast cancer (RR=1.02, 95% CI: 0.92, 1.13), while women with above average weight had a lower risk (RR=0.85, 95% CI: 0.74, 0.98). There was no evidence of an interaction between weight at age 12 and family history (p=0.44). The inverse association of above average weight with risk of breast cancer was strongest for PR– tumors (RR=0.62; 95% CI 0.43, 0.89), intermediate for ER+ (RR=0.80; 95% CI 0.67, 0.96) and ER– (RR=0.77; 95% CI 0.50, 1.19) tumors, and weakest for PR+ tumors (RR=0.90; 95% CI 0.74, 1.09). These associations were not modified by a family history (all p>0.18). In a joint ER/PR analyses, the strongest inverse association with above average weight at age 12 was seen for ER+/PR– (RR=0.49; 95% 0.29, 0.85)

Conclusion—Above average weight at age 12 was inversely associated with risk of postmenopausal breast cancer, and was not modified by a family history of the disease. The inverse association was strongest for ER+/PR– tumors.

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Introduction

Breast cancer is the most common non-cutaneous cancer among women and the second leading cause of cancer death among women in US (1). Most studies suggest that higher adult body mass index (BMI) is associated with elevated risk of postmenopausal breast cancer, presumably due to increased estrogen levels produced by excess adipose tissue (2,3). However, among pre-menopausal women, where the major source of endogenous estrogens is the ovary, higher body mass index (BMI) has consistently been inversely associated with the risk of premenopausal breast cancer. While the mechanism underlying this observation is not known, lower estrogen levels among obese premenopausal women has been suggested (2,4–6).

In contrast, greater BMI in later adolescence (age 15–18 years) has been inversely associated with both premenopausal (4,7–13) and postmenopausal (4,8–10,14–16) breast cancer risk, although there are exceptions for premenopausal (17) and postmenopausal (7,11,17) breast cancer risk. More limited data suggest that this inverse association extends into earlier adolescence (ages 9 to 14 years) as well for premenopausal (8,10,12,18–20) and postmenopausal (8,10,18,19,21,22) breast cancer risk, although there are a few exceptions (17,23). Early life obesity may also be modified by a family history of breast cancer (21,24, 25). Finally, risk factors may differ for biologic subtypes of breast cancer defined by estrogen and progesterone receptor (ER/PR) status (26,27), but this has not been evaluated for early adolescent weight.

We evaluated the association of relative weight at age 12 with postmenopausal breast cancer risk in the Iowa Women's Health Study. In addition, we investigated whether these associations differ by family history of breast cancer and/or biologic subtypes of breast cancer defined by estrogen and progesterone receptor (ER/PR) status.

Materials and Methods

The Iowa Women's Health Study is a prospective cohort study of women aged 55–69 years at study baseline in 1986 (28). Briefly, a mailed survey was returned by 41,836 women in 1986 from a random sample of women with a valid Iowa driver's license. The baseline survey included questions on a variety of potential breast cancer risk factors including medical and family history, anthropometrics, reproductive factors, and lifestyle characteristics. Participants were also asked: "Think back to when you were in 6^{th} grade- or about the age of 12. Would you say at that time your weight was: below average for your age and height, about average for your age and height, or above average for your age and height".

Breast cancers and their ER/PR status were ascertained through linkage to the State Health Registry of Iowa, part of the Surveillance, Epidemiology and End Results (SEER) program (29). On an annual basis, cohort members were linked to the registry based on name (first, last, maiden), zip code, birth date, and social security number. Deaths were identified through follow-up surveys, annual linkage to Iowa death certificates, and linkage to the National Death Index.

For this analysis, we excluded women if they reported any of the following on the baseline survey: being premenopausal (n=569), having a history of any cancer other than skin cancer (n=3830), or ever having had a total or partial mastectomy (n=1884). An additional 1164 women were excluded due to missing data on relative weight at age 12. This left a total of 35,941 women in the analysis (exclusions were not mutually exclusive).

Each woman accrued person-years of follow-up from the completion of the baseline questionnaire until a diagnosis of breast cancer, death, or emigration from Iowa; if none of these occurred, cohort members were censored on December 31, 2003. Relative risks (RR) and

95% confidence intervals (CI) were estimated using Cox regression, controlling for potential confounding factors as included in Table 1. Incidence was modeled as a function of age (30). Initially, we examined the overall association of weight at age 12 with breast cancer risk. Formal assessments of risk were assessed using tests for trend, calculated by ordering the three-level weight variable and including it in the Cox proportional hazards model as a linear term.

We then investigated whether a family history of 1) breast or 2) breast or ovarian cancer in a first degree relative modified the association between weight at age 12 and risk of breast cancer. Results were similar, so we report results for a family history of breast or ovarian cancer in order to facilitate comparison with a previously published study (21). Formal tests of interaction were carried out by including the main effects of weight at age 12 (ordinal) and family history, and testing the statistical significance of the corresponding interaction term. Finally, we evaluated whether these associations varied by breast cancer subtypes defined by ER and PR status. In these receptor-specific analyses, events not of that specific cancer type were considered censored observations. All analyses were performed on SAS 8.02 (SAS Institute, Inc., Cary, NC) and Splus 7.0.6 (Mathsoft, Inc., Seattle, WA) software systems.

Results

Of the 35,941 women in the analytic cohort, 22.5% reported below average weight at age 12, 64.3% reported average weight, and 13.2% reported above average weight. Table 1 reports breast cancer risk factors by relative weight at age 12 years. Compared to women reporting below average weight, women reporting above average weight had an earlier age at first menstrual cycle (13.3 versus 12.3 years); higher BMI at age 18 (19.6 versus 25.2 kg/m^2) and at study baseline in 1986 (25.8 versus 29.6 kg/m^2); lower use of hormone replacement therapy (42.2% vs. 35.9%); and were never smokers (68.4% versus 60.6%). Other breast cancer risk factors were similar across categories of relative weight at age 12.

During 548,567 person-years of follow-up (through 2003), 2503 breast cancers were identified. The mean age at diagnosis was 71.4 years (SD=6.2 years). ER status was available on 1901 (75.9%) of the cases, and 84.4% of these cases were ER+. PR status was available on 1825 (72.9%) of the cases, and 73.0% of these cases were PR+.

The association of weight at age 12 with breast cancer risk is reported in Table 2. Compared to women with average weight at age 12, there was no association of below average weight with risk of breast cancer, while women with above average weight had a lower risk of breast cancer (RR=0.85, 95% CI 0.74, 0.98) after adjustment for multiple risk factors including BMI at age 18 and BMI at study baseline. As shown in Table 1, while there was tracking of weight over the life course, this was not absolute. For example, of women reporting above average weight at age 12, 44% were overweight or obese at age 18 (but 56% had a BMI of <25) and 76% were overweight or obese at study baseline (but 24% had a BMI<25). As shown in Figure 1, results were unchanged when we stratified on BMI at age 18 (adjusting for baseline BMI) or BMI at baseline (adjusting for BMI at age 18).

The inverse association of weight at age 12 with breast cancer risk was not modified by a family history of breast or ovarian cancer in a first degree relative (p for interaction = 0.44) (Table 2). Similar results were seen if we restricted to a first degree relative with breast cancer only (data not shown).

The inverse association of above average weight at age 12 with risk of breast cancer was observed for all subtypes defined by ER and PR status, and was strongest for PR– tumors (RR=0.62), intermediate for ER+ (RR=0.80) and ER– (RR=0.77) tumors, and weakest for PR + tumors (RR=0.90) (Table 2). These associations were not modified by a family history of breast or ovarian cancer (all p>0.18). In an analysis where ER and PR were jointly evaluated

(not reported in the table), an inverse association with above average weight was seen for ER +PR+ (RR=0.91, 95% CI 0.75, 1.10), ER+PR– (RR=0.49, 95% CI 0.29, 0.85), ER–PR+ (RR=0.74, CI 0.24, 2.26) and ER–PR– (RR=0.77, 95% CI 0.47, 1.26). There was insufficient sample size to evaluate the interaction of these subtypes by a family history of breast or ovarian cancer.

Discussion

We confirmed an inverse association between relative weight at age 12 and risk of postmenopausal breast cancer after adjustment for a wide variety of breast cancer risk factors, including BMI at age 18 and BMI at study baseline. However, we were not able to confirm the interaction between relative weight at age 12 and family history of breast or breast or ovarian cancer we had reported previously in a different population (21). We also found inverse associations for relative weight at age 12 with all breast cancer subtypes defined by ER and PR status, and this was strongest for ER+PR– tumors.

Strengths of this study include the prospective cohort design, excellent follow-up of the cohort, case identification using a SEER cancer registry, ability to assess multiple potential confounders, and assessment of associations for breast cancer subtypes defined by ER and PR status. There are also limitations. Relative weight at age 12 was self-reported and involved recalling a relative weight more than 4 to 6 decades in the past. Indeed, this is why we did not collect actual weight. Recall of childhood and adolescent body build by elderly subjects has been shown to have reasonable validity (31,32) and any bias introduced is expected to attenuate associations. Furthermore, we observed expected associations of relative weight at age 12 with age of first menstruation, which provided some internal consistency for our measure. Information about ER/PR status of breast cancer was obtained through multiple laboratories involved with SEER, rather than a single reference laboratory. However, the availability of receptor status and the ER/PR distribution in our study (ER+ 64.1%, ER– 11.9%, PR+ 53.2%, and PR– 19.7%) was similar to that reported by other studies (27,33).

Most studies have reported that greater weight or obesity in early adolescence (age 9 to 14 years) is associated with a lower risk of postmenopausal breast cancer (8,10,18,19,21,22), although there are exceptions (17,23). This association appears to be independent of adult obesity (which is positively associated with postmenopausal breast cancer risk), particularly as demonstrated in our multivariate-adjusted analyses and analyses stratified on adult BMI. However, we were not able to confirm results of a prior study which found a strong interaction ($p \leq 0.001$) between relative age at weight 12 with family history on the risk of postmenopausal breast cancer (15,21). The latter study, conducted among a historical cohort of 426 families of breast cancer probands diagnosed between 1944 and 1952, found that women with above average weight at age 12 had a lower risk of breast cancer if they had no family history of breast cancer (OR=0.75, 95% CI 0.26, 2.16), while women with a family history had a greatly increased risk of breast cancer (OR=4.25, 95% CI: 1.71, 10.5). These latter findings, different from our study results, could be due to difference in the genetic risk, as the study was based on a historical cohort of families of breast cancer probands with a higher genetic risk of breast cancer, while our study was based on a population cohort of average genetic risk.

We found that the inverse association of relative weight at age 12 with postmenopausal breast cancer risk was apparent for all tumor subtypes defined by ER or PR status, although results were strongest for ER+/PR- tumors. To our knowledge, no studies have evaluated the association between early adolescent obesity and postmenopausal breast cancer by ER/PR tumor subtype.

The biological mechanisms for a putative inverse relationship between relative weight at age 12 and postmenopausal breast cancer risk is not known. In a 7-year longitudinal study of 286 girls initially aged 8 to 9 years, adiposity was associated with higher circulating concentrations of dehydroepiandrosterone sulfate (DHEAS) and lower concentrations of sex hormone-binding globulin (SHBG), but there were no consistent associations for circulating levels of estrogen or progesterone (34). The lack of an association for estrogen would suggests that early adolescent obesity is not likely to influence postmenopausal breast cancer risk through estrogen signaling, consistent with the similar association for ER+ (RR=0.80) and ER– (RR=0.77) tumors in our study. We did observe larger differences for PR+ (RR=0.90) versus PR– (RR=0.62) tumors, however, which is inconsistent with the finding of no differences in progesterone concentrations noted above. Obese adolescent and preadolescent girls also have elevated levels of insulin and insulin-like growth factor I (IGF-I), and this leads to impaired ovarian steroid metabolism and anovulation (35). Fewer ovulatory cycles are expected to protect against breast cancer (36,37), although one recent study found that the inverse relationship between adult BMI and premenopausal breast cancer incidence was not likely to be explained by menstrual cycle characteristics of the women (38). However, the impact of fewer ovulatory cycles could be more pronounced during the time frame before first full-term pregnancy, and particularly in adolescence, due to the greater susceptibility to carcinogens of undifferentiated breast tissue (39,40). There may also be other aspects of the hormonal milieu associated with obesity in the early teenage years that protects against breast cancer, and this requires further evaluation (34,35).

We confirmed an inverse association between relative weight at age 12 and risk of postmenopausal breast cancer, and this was independent of adult BMI. The inverse association was strongest for ER+/PR– tumors. We did not find any interaction between relative weight at age 12 and family history of cancer as suggested in previous studies.

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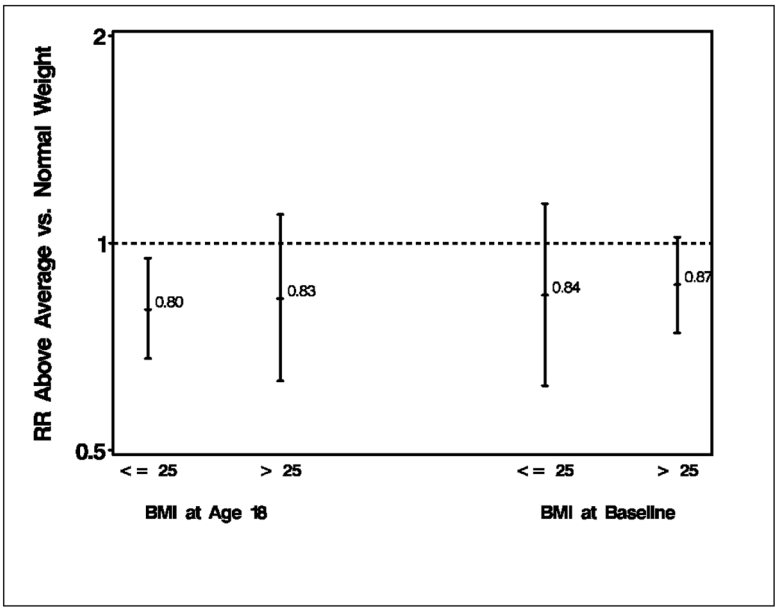

Figure 1.
Multivariate-adjusted relative risks and 95% CI intervals of post-menopausal breast cancer for above average weight at age 12 (compared to average weight), stratified by Body Mass Index (BMI) at age 18 (including adjustment for BMI at study baseline) and study baseline in 1986 (including adjustment for BMI at age 18)

Table 1

Distribution of breast cancer risk factors by relative weight at age 12, Iowa Women's Health Study, 1986

	Relative Weight for Age and Height in 6th Grade or About the Age of 12		
	Below Average (N=8,082)	**Average (N=23,127)**	**Above Average (N=4,732)**
		Mean ± standard deviation	
Age at study entry (years)	61.7 ± 4.2	61.8 ± 4.2	61.2± 4.2
Age of first menstruation (years)	13.3 ± 1.6	12.8 ± 1.4	12.3 ± 1.4
Age at menopause (years)	47.6 ± 6.4	47.6 ± 6.4	47.8 ± 6.4
Body mass index at age 18 (kg/m^2)	19.6 ± 2.3	21.6 ± 2.5	25.2 ± 4.1
Body mass index in 1986 (kg/m^2)	25.8 ± 4.6	26.9 ± 4.8	29.6 ± 6.1
		Percent distribution	
Body mass index at age 18 (kg/m^2)			
<18.0	30.0%	6.6%	2.2%
18.0–24.9	67.9%	85.6%	53.6%
25.0–29.9	1.9%	7.0%	32.0%
30.0+	0.3%	0.8%	12.2%
Body mass index in 1986 (kg/m^2)			
<18.0	1.6%	0.9%	0.4%
18.0–24.9	47.3%	38.7%	23.6%
25.0–29.9	35.6%	37.9%	34.7%
30.0+	15.5%	22.5%	41.4%
Education greater than high school	41.0%	37.1%	44.5%
Family history of breast or ovarian cancer in a first degree relative	14.0%	13.6%	12.8%
Any live births	90.3%	91.5%	89.3%
Age at first live birth <20 years	18.5%	20.6%	18.4%
Ever used oral contraceptives	20.6%	17.9%	18.7%
Ever used hormone replacement therapy	42.2%	36.8%	35.9%
Did not drink alcohol in 1986	56.7%	55.8%	58.8%
Never smoker	68.4%	66.0%	60.6%
Physical activity index			
Low	47.3%	47.1%	48.5%
Medium	27.4%	27.9%	26.2%
High	25.3%	25.0%	25.3%

Table 2

Multivariate-adjusted relative risks of postmenopausal breast cancer by relative weight at age 12, overall and stratified by first degree family history of breast or ovarian cancer, and by breast cancer subtype based on ER and PR status

		All				No Family History				Family History			
Type of Breast Cancer	**Relative Weight at age 12**	**Cases**	**RR**	**95% CI**	***P* trend**	**Cases**	**RR**	**95% CI**	***P* trend**	**Cases**	**RR**	**95% CI**	***P* trend**
All	Below	596	1.02	0.92,1.13		465	0.99	0.88,1.11		112	1.10	0.87,1.38	
	Average	1635	1.00	reference		1309	1.00	reference		282	1.00	reference	
	Above	272	0.85	0.74,0.98	0.08	220	0.86	0.73,1.01	0.02	43	0.84	0.60,1.17	0.05
								P Interaction (family history and weight 12) = 0.44					
ER+	Below	383	1.01	0.89,1.16		296	0.95	0.82,1.11		72	1.25	0.94,1.67	
	Average	1055	1.00	reference		859	1.00	reference		165	1.00	reference	
	Above	166	0.80	0.67,0.96	0.08	137	0.82	0.68,1.00	0.06	24	0.77	0.49,1.22	0.03
								P Interaction (family history and weight 12) = 0.21					
ER–	Below	76	1.10	0.81,1.48		62	1.17	0.84,1.63		12	0.78	0.38,1.60	
	Average	190	1.00	reference		147	1.00	reference		35	1.00	reference	
	Above	31	0.77	0.50,1.19	0.20	26	0.81	0.50,1.30	0.11	5	0.81	0.31,2.09	0.71
								P Interaction (family history and weight 12) = 0.73					
PR+	Below	315	1.00	0.86,1.16		240	0.94	0.80,1.11		63	1.27	0.93,1.74	
	Average	868	1.00	reference		701	1.00	reference		139	1.00	reference	
	Above	149	0.90	0.74,1.09	0.48	122	0.91	0.73,1.12	0.31	23	0.94	0.59,1.48	0.06
								P Interaction (family history and weight 12) = 0.19					
PR–	Below	123	1.08	0.85,1.37		100	1.08	0.83,1.40		18	0.91	0.52,1.59	
	Average	328	1.00	reference		264	1.00	reference		54	1.00	reference	
	Above	42	0.62	0.43,0.89	0.24	36	0.69	0.47,1.01	0.02	6	0.53	0.21,1.34	0.45
								P Interaction (family history and weight 12) = 0.81					

* Cox proportional hazards regression analysis, accounting for age, education status, age at menopause. age at menarche, parity, age at first birth body mass index at age 18, body mass index in 1986, oral contraceptive use, hormone replacement therapy, smoking status, alcohol use, and physical activity level.