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STAGE OF BREAST CANCER IN RELATION TO BODY MASS INDEX AND BRA CUP SIZE

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Most studies on women with breast cancer indicate that obesity is positively associated with late-stage disease. Some results have shown a similar relationship between breast size and stage. A recent study found that the association between body mass index (BMI) and stage was limited to cancers that were self-detected, suggesting that the BMI-stage relation may be due to delayed symptom recognition. We examined the relationships between stage and both BMI and breast (bra cup) size, stratified by method of detection, using data from a population-based case-control study of 1,361 women (ages 20–44 years) diagnosed with breast cancer during 1990–1992. Height and weight measurements and information on bra cup size, method of cancer detection and other factors predictive of stage at diagnosis were collected during in-person interviews. A case-case comparison was conducted using logistic regression to estimate odds of regional or distant stage rather than local stage in relation to BMI and bra size. Odds of late-stage disease were increased with higher BMI [adjusted odds ratio (OR) for highest to lowest tertile = 1.46, 95% confidence interval (CI) 1.10–1.93] and larger bra cup size (OR for cup D *vs.* cup A = 1.61, 95% CI 1.04–2.48). These relationships were not modified by the method of detection. Differences in etiologic effects, rather than differences in detection methods, may explain the relations observed between stage and both BMI and breast size. *Int. J. Cancer* 82:23–27, 1999.

Among women with breast cancer, those who weigh more or have a higher body mass index (BMI) are more likely to have larger tumors and more advanced-stage cancers at their initial diagnosis than those who weigh less or have a lower BMI (Greenberg *et al.*, 1985; Ingram *et al.*, 1989*b;* Jones *et al.*, 1997; London *et al.*, 1989; Senie *et al.*, 1992; Shapira *et al.*, 1991; Verreault *et al.*, 1989). Heavier women with breast cancer are also more likely to have higher breast cancer recurrence rates and poorer survival after diagnosis (Senie *et al.*, 1992; Lees *et al.*, 1989; Tretli, 1989). Reeves *et al.* (1996) observed that the positive association between BMI and stage was confined to cancers that were self-detected; BMI was unrelated to stage among women whose cancers were detected by mammography or clinical breast examination (CBE). These findings suggested that the greater likelihood of late-stage breast cancer in heavier women may be largely a consequence of delayed detection. Larger women with larger breasts may be less able to feel breast lumps, the most common symptom of breast cancer. This possibility is supported by 2 studies, which found that women with larger breasts are more likely to have larger tumors at diagnosis (Ingram *et al.*, 1989*a*; Hoe *et al.*, 1993). An implication of these results was that heavier women may particularly benefit from regular mammography, not because of greater efficacy of mammography in heavier women, but because of the reduced likelihood of having early detection by other means. The implication could be increasingly important given the growing prevalence of overweight in the U.S. population (Kuczmarski *et al.*, 1994).

There is less information available about the positive association between BMI and stage in younger women, and the hypothesis that delayed detection may explain that relation has not been addressed. In addition, no study, in younger or older women, has examined the relation between BMI and stage of disease while taking breast size into account. If large breast size and delayed detection mediate the relation between BMI and stage, then including breast size in the multivariate model may eliminate the association.

The purpose of our study was to examine relations between both BMI and breast size, as estimated by bra cup size, and the stage of disease at diagnosis among younger women newly diagnosed with invasive breast cancer. In addition, we determined whether relations between stage and both BMI and bra cup size varied according to method of detection. Finally, we determined whether the relation between BMI and later-stage disease remained after breast size was taken into consideration.

MATERIAL AND METHODS

Using data from a population-based case-control study of breast cancer etiology, we conducted a case-case comparison of BMI and bra cup size of women diagnosed with regional or distant stage *vs.* women with local stage cancer. The study was conducted in 3 geographic areas: the metropolitan areas of Atlanta, GA, and Seattle-Puget Sound, WA, and 5 counties of central New Jersey. The study protocol was approved by institutional review boards at each collaborating institution. All women ages 20–44 years who were newly diagnosed with breast cancer during May 1, 1990, through December 31, 1992, were identified through rapid ascertainment systems. Completeness of ascertainment was established by periodically checking the data against population-based registries (Atlanta and Seattle-Puget Sound) or hospital discharge data (New Jersey). Women who had a prior diagnosis of breast cancer were not eligible.

Information on reproductive history, screening history, demographic factors, medical history, family history of breast cancer, smoking and alcohol consumption was collected during structured, in-person interviews. All exposure information was truncated at the date of cancer diagnosis.

During the interview, standing height was measured using a stadiometer and weight was measured using a portable digital scale (Seca, Columbia, MD). BMI [weight (kg)/height squared (m^2)] (Najjar and Rowland, 1987) was calculated and categorized into approximate tertiles based on all cases. Each participant was also asked what her usual bra cup size had been during her adult life, not counting times when she was pregnant or nursing. Cup A is approximately 2.5 cm, cup B 5.0 cm, cup C 7.5 cm and cup D 10.0 cm.

To determine the method of detection, each subject was asked, "Who first noticed the problem which led to the discovery of your

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breast cancer?'' Response categories included ''routine physical examination by a doctor,'' which we labeled CBE for this report, and ''routine mammography''. We grouped as self-discovered the categories ''routine self-examination,'' ''accidental self-discovery'' and ''accidental discovery by a partner'' because they had nearly identical stage distributions. Cancers that had been detected in ''some other way'' included those detected by a variety of symptoms and signs, including breast pain, swelling, dimpling and nipple discharge or bleeding, some of which were detected during treatment of another medical problem, and were not included in the analyses investigating method of detection.

Of the 1,940 eligible case subjects identified, interviews were completed with 1,668 (86.0%). Reasons for non-interview included subject refusal (6.7%), physician refusal (5.8%), death or illness (0.8%) and other (0.7%). Eighty-five percent of the subjects were interviewed within 6 months of cancer diagnosis, 11% within 6 months to 1 year of diagnosis and 4% 1 year or more after diagnosis.

The stage of the cancer at diagnosis and estrogen receptor status were obtained from the Surveillance, Epidemiology and End Results (SEER) program cancer registry records in Seattle and Atlanta. In New Jersey, stage and estrogen receptor status were obtained from subjects' medical records. Stage of disease was defined as *in situ* if the neoplasm was non-infiltrating (n = 227), localized if the invasive neoplasm was confined entirely to the breast tissue (n = 797), regional if the tumor had extended into the lymph nodes or exhibited both direct extension and regional lymph node involvement (n = 580) and distant if the tumor had spread to parts of the body remote from the primary tumor by direct extension or by discontinuous metastases (n = 32). Because less than 2% of the interviewed subjects had presented with distant tumors, a combined category was created of regional and distant tumors (*i.e.*, later-stage). We excluded 32 cases for whom no stage information was available. We also excluded the 227 *in situ* cases because it is unclear what proportion might have progressed to invasive cancer (Bodian, 1993). We further excluded 48 cases for whom information on height, weight or method of detection was not available. This resulted in a sample of 1,361 case subjects: 774 with local disease and 587 with regional or distant disease.

Multivariate logistic regression was used to estimate the odds that cases were diagnosed with regional/distant disease compared with local disease, with odds ratios comparing those with higher BMI and larger bra size to those with the smallest BMI or bra size (referent). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with adjustment for potential confounders. All analyses included adjustment for study site. We evaluated as potential confounders height (Michels *et al.*, 1998) and several factors found to be associated with breast cancer stage at diagnosis including age, ethnicity, history of breast disease (in this analysis, whether a previous breast biopsy had been performed), screening history (number of mammograms during the 5-year period prior to 1 year before the interview), method of cancer detection, parity and 2 measures of socio-economic status (education level and poverty status). A poverty index was calculated by dividing the household income by the 1991 poverty level incomes, taking into consideration the number of people in the household. Tests for linear trend in regression coefficients were obtained by ordering a categorical variable and entering the measure as a continuous variable. To determine whether the associations between stage and both BMI and breast size varied by method of tumor detection, we stratified by method of detection and assessed statistical significance using the likelihood ratio test.

To evaluate more fully the possibility that the case-case ORs relating BMI and breast size to stage might reflect differences in etiology, we reexamined these associations in the case-control data. This study has been described elsewhere (Swanson *et al.*, 1996). Briefly, control subjects in the 3 geographic areas were ascertained through random digit telephone dialing and age-matched to the anticipated age distribution of cases. Interviews were completed with 1,500 controls, with a 71.2% response rate. For this analysis, we used 1,396 controls after applying similar exclusion criteria as for cases. Using variable definitions from the current study, we recalculated the case-control ORs: OR_L, the OR indicating risk of local stage disease associated with increased BMI and bra cup size, and OR_R, the OR indicating risk of regional/distant disease. These case-control ORs were then used to calculate the case-case OR, OR_C, which is equivalent to OR_R/OR_L (Begg and Zhang, 1994).

RESULTS

Few of the factors we examined as potential confounders were strongly related to stage (Table I). Women with mammography-detected cancers were much less likely to have been diagnosed with regional/distant cancers (OR = 0.39), and there was an inverse association between stage and the number of prior mammograms. The odds of regional/distant stage cancer were increased with the number of live births. Women with regional/distant stage disease were also somewhat more likely to be taller, but CIs were wide, including the possibility of no association. There was little or no relation between stage and previous biopsy, education, poverty status and other factors we examined, including smoking, alcohol consumption, estrogen receptor status and menopausal status (data not shown).

BMI and bra cup size were positively associated with cancer stage (Table II). Women in the highest tertile of BMI and those who wore a bra cup size D had an odds of regional/distant disease that was 50% greater than the odds among women in the lowest BMI tertile and those who wore size A. Significant trends were observed for the levels of BMI or bra cup size and stage. Adjustment for a variety of possible confounders, including age, race, height, number of full-term births, number of mammograms and method of detection, had little effect on these associations. BMI and bra cup size were correlated (Spearman's $r = 0.36$, $p < 0.01$). When both BMI and bra cup size were included in the logistic regression model the associations were attenuated, but the ORs for both remained elevated and a significant trend remained in the ORs.

The strengths of the relationships between stage and BMI and between stage and bra cup size varied by method of detection (Table III). Yet for all methods of detection, the odds of regional/distant stage breast cancer increased as BMI and bra cup size increased. The relationships were statistically significant only for self-detected cancers, most likely because of the much larger sample size for self-detection.

Relations between stage and both BMI and bra cup size did not vary by ethnicity, and although the relations appeared somewhat stronger for estrogen receptor positive than for estrogen receptor negative cancers, differences were not statistically significant (data not shown).

The analyses with the case-control data indicated heterogeneity in the etiology of the different stage cancers (Table IV). That is, BMI, as previously reported (Swanson *et al.*, 1996), was inversely associated with risk of local stage disease but was unrelated to risk of regional/distant disease. In contrast, bra cup size was positively related to risk of regional/distant disease, but was unrelated to risk of local disease. The reduced risk of local stage cancer with a BMI in the highest tertile ($OR_L = 0.66$) combined with no difference in risk of regional/distant cancer ($OR_R = 1.00$) resulted in a positive association in the case-case comparison between BMI and regional/distant disease ($OR_C = 1.00/0.66 = 1.51$). Similarly, the increased risk of regional/distant cancer with a D bra cup size combined with no difference in risk of local disease resulted in a positive association in the case-case comparison (1.51/0.94 = 1.59). Since the case-control ORs in Table IV were adjusted for geographic site as were the case-case ORs in the first column of Table II, these ORs are identical.

TABLE I – DISTRIBUTION OF CHARACTERISTICS BY STAGE OF DISEASE AND ORs OF REGIONAL/DISTANT STAGE *VS.* LOCAL STAGE BREAST CANCER, WOMEN AGES 20–44, GEORGIA, NEW JERSEY AND WASHINGTON, 1990–1992

Characteristic	Stage of disease		OR[1]	95% CI	*p*
	Local number (%)	Regional/ distant number (%)			
Age (years)					
20–34	130 (16.8)	103 (17.6)	1.0		
35–39	230 (29.7)	181 (30.8)	1.00	0.73–1.39	
40–44	414 (53.5)	303 (51.6)	0.93	0.69–1.26	0.57[2]
Ethnicity					
White	618 (79.8)	456 (77.7)	1.0		
Black	107 (13.8)	103 (17.5)	1.21	0.88–1.67	0.24
Other	49 (6.3)	28 (4.8)	0.80	0.49–1.29	0.35
Previous breast biopsy					
No	706 (91.2)	539 (91.8)	1.0		
Yes	68 (8.8)	48 (8.2)	1.12	0.76–1.65	0.57
Education					
High school or less	199 (25.7)	161 (27.4)	1.0		
Technical school	53 (6.9)	40 (6.8)	0.96	0.60–1.52	0.84
Some college	201 (26.0)	161 (27.4)	1.00	0.74–1.34	0.99
College graduate	200 (25.8)	137 (23.3)	0.84	0.62–1.12	0.26
Postgraduate work	121 (15.6)	88 (15.0)	0.90	0.64–1.27	0.53
Income[3] (% of poverty index)					
≤200	103 (13.6)	86 (14.9)	1.0		
201–400	208 (27.4)	180 (31.3)	1.09	0.78–1.52	
>400	448 (59.0)	310 (53.8)	0.85	0.63–1.16	0.10[2]
Number of births					
0	207 (26.7)	121 (20.6)	1.0		
1	163 (21.1)	114 (19.4)	1.20	0.86–1.66	
2	261 (33.7)	231 (39.4)	1.55	1.16–2.07	
≥3	143 (18.5)	121 (20.6)	1.49	1.07–2.07	0.004[2]
Method of detection					
Self	534 (69.0)	460 (78.4)	1.0		
CBE	68 (8.8)	44 (7.5)	0.75	0.51–1.13	0.17
Mammography	138 (17.8)	46 (7.8)	0.39	0.27–0.56	0.001
Symptoms[4]	34 (4.4)	37 (6.3)	1.29	0.80–2.10	0.30
Number of mammograms[5]					
0	353 (45.6)	314 (53.5)	1.0		
1	169 (21.8)	132 (22.5)	0.89	0.67–1.17	
2	118 (15.3)	60 (10.2)	0.58	0.41–0.81	
≥3	134 (17.3)	81 (13.8)	0.68	0.49–0.93	0.001[2]
Height (cm)					
≤161.1	268 (34.6)	193 (32.9)	1.0		
161.2–166.8	270 (34.9)	179 (30.5)	0.92	0.71–1.20	
166.9+	236 (30.5)	215 (36.6)	1.26	0.97–1.64	0.08[2]

[1]Adjusted for study site.–[2]Test for trend.–[3]Poverty index is the household income divided by 1991 poverty level incomes, taking into consideration the number of people in the household. Includes only women for whom this information was available.–[4]Breast pain, swelling, dimpling and nipple discharge or bleeding or cancer detected during treatment of another medical problem.–[5]Number of mammograms during the 5-year period prior to 1 year before interview.

DISCUSSION

Our findings of positive relationships between stage and both BMI and breast size add to the growing body of evidence that these patient characteristics are associated with more advanced disease at diagnosis, in younger as well as older women. Most published studies (Ingram *et al.*, 1989*b*; Shapira *et al.*, 1991; Verreault *et al.*, 1989), including those that examined this relationship among younger women (Greenberg *et al.*, 1985; Jones *et al.*, 1997; London *et al.*, 1989), have found that body weight and/or BMI is associated with later-stage disease. There is much less information about the relationship between breast size and stage. Ingram *et al.* (1989*a*) found that women with larger breasts were more likely to have both larger tumors and node positive tumors. Hoe *et al.* (1993), studying women with early-stage disease, found those with larger breasts more likely to have larger tumors but not more likely to have node positive tumors. Neither of these studies presented information specifically on younger women or included BMI measurements.

The BMI effect on stage appears not to be mediated by breast size as the risk relation for bra cup size was not substantially stronger than the relation between BMI and stage. In addition, the relation between BMI and stage was not eliminated after adjustment for breast size.

Our findings of positive relations between BMI and risk of late-stage cancer for all 3 methods of detection are inconsistent with the findings of the only other study to examine this issue (Reeves *et al.*, 1996). Reeves *et al.* (1996) found that high BMI was related to late-stage disease only for breast cancers that were self-detected, not those detected by mammography or CBE. If the BMI-stage relation was due to delayed detection, the strongest effect should have been observed for the self-detected cancers; this was not the case in our study. We also found a positive relation between BMI and stage even after adjustment for breast size. Hypotheses other than difficulty in detecting a lump should be considered possible explanations for the relation between stage and both BMI and breast size.

Our findings suggest that, at least in young women, the relations between stage and both BMI and breast size may be due to differences in etiology of breast cancer of different stages. Potential reasons for the differences in etiology by stage are unclear, just as are reasons for differences by menopausal status in relations

TABLE II – ORs FOR BMI AND BRA CUP SIZE FOR REGIONAL/DISTANT STAGE *VS.* LOCAL STAGE BREAST CANCER AMONG WOMEN AGES 20–44 YEARS, GEORGIA, NEW JERSEY AND WASHINGTON, 1990–1992

Characteristic	Cancer stage[1]		OR								
			Site-adjusted[2]			Multivariate model[4]			BMI/cup-adjusted[5]		
	Local (%)	Regional/distant (%)	OR	95% CI	p^3	OR	95% CI	p^3	OR	95% CI	p^3
BMI (kg/m²)											
<22.5	36.9	30.2	1.0			1.0			1.0		
22.5–26.6	33.1	32.7	1.21	0.93–1.58		1.19	0.91–1.60		1.16	0.89–1.53	
≥26.7	30.0	37.1	1.51	1.16–1.96	<0.01	1.46	1.10–1.93	0.01	1.34	1.00–1.81	0.05
Bra cup size (cm)											
A (2.5)	16.8	15.4	1.0			1.0			1.0		
B (5.0)	50.8	45.5	0.98	0.72–1.33		0.97	0.70–1.33		0.92	0.67–1.27	
C (7.5)	23.4	26.0	1.20	0.85–1.69		1.20	0.84–1.71		1.09	0.76–1.58	
D (10.0)	9.0	13.2	1.59	1.04–2.42	0.01	1.61	1.04–2.48	0.01	1.40	0.88–2.21	0.09

[1]There were 774 cases with local and 587 cases with regional/distant breast cancer.–[2]Adjusted for study site.–[3]Test for trend.–[4]Adjusted for study site, age, ethnicity, height, number of births, number of mammograms and method of detection.–[5]Adjusted as in footnote 4, as well as bra cup size for BMI and BMI for bra cup size.

TABLE III – ORs FOR BMI AND BRA CUP SIZE FOR REGIONAL/DISTANT STAGE *VS.* LOCAL STAGE BREAST CANCER, BY METHOD OF DETECTION, AMONG WOMEN AGES 20–44 YEARS, GEORGIA, NEW JERSEY AND WASHINGTON, 1990–1992

Risk factor	Method of detection								
	Self[1]			Mammography[1]			CBE[1]		
	OR[2]	95% CI	p^3	OR[2]	95% CI	p^3	OR[2]	95% CI	p^3
BMI (kg/m²)									
<22.5	1.0			1.0			1.00		
22.5–26.6	1.20	0.87–1.63		1.57	0.62–3.97		1.85	0.68–5.04	
≥26.7	1.47	1.06–2.02	0.02	1.63	0.65–4.06	0.31	2.27	0.74–6.98	0.13
Bra cup size (cm)									
A (2.5)	1.0			1.00			1.00		
B (5.0)	1.03	0.72–1.47		0.77	0.26–2.24		0.84	0.22–3.26	
C (7.5)	1.14	0.76–1.73		1.31	0.41–4.17		1.18	0.30–4.67	
D (10.0)	1.66	1.00–2.74	0.05	1.91	0.43–8.50	0.19	1.72	0.29–10.27	0.45

[1]A total of 994 cases were self-detected, 112 were detected by CBE and 184 were detected by mammography.–[2]Adjusted for study site, age, ethnicity, height, number of births and number of mammograms.–[3]Test for trend.

TABLE IV – ORs[1] FROM A CASE-CONTROL ANALYSIS INDICATING RISK OF LOCAL STAGE BREAST CANCER AND RISK OF REGIONAL/DISTANT STAGE BREAST CANCER IN RELATION TO BMI AND BRA CUP SIZE, AND THE CASE-CASE ORs CALCULATED FROM THE CASE-CONTROL ORs, WOMEN AGES 20–44 YEARS, GEORGIA, NEW JERSEY AND WASHINGTON, 1990–1992

Characteristic	Case-control analysis					Case-case (OR_c)[4]
	Control[2] (%)	Cases[3]				
		Local stage		Regional/distant stage		
		%	OR_L	%	OR_R	
BMI (kg/m²)						
<22.5	29.1	36.9	1.0	30.2	1.0	1.0
22.5–26.6	35.2	33.1	0.74	32.7	0.91	1.21
≥26.7	35.7	30.0	0.66	37.1	1.00	1.51
Bra cup size (cm)						
A (2.5)	17.3	16.8	1.0	15.4	1.0	1.0
B (5.0)	47.4	50.8	1.13	45.5	1.11	0.98
C (7.5)	25.2	23.4	0.98	26.0	1.19	1.20
D (10.0)	10.1	9.0	0.94	13.2	1.51	1.59

[1]Adjusted for study site.–[2]Includes 1,396 controls.–[3]Includes 774 cases of local and 587 cases of regional/distant breast cancer.–[4]$OR_c = OR_R/OR_L$.

between BMI and risk of breast cancer. Differences in relations by stage may be related to differences in tumor aggressiveness: the inverse relation between BMI and risk of breast cancer in young women has been found to be limited not just to early stage but to lower grade tumors (Willett *et al.*, 1985).

Compared with earlier studies on relations between stage and BMI and breast size among women newly diagnosed with breast cancer, this study has a number of strengths as well as specific limitations. The availability of data for controls from the case-control study allowed us to examine the issue of etiologic heterogeneity. The sample size of young women was larger than most earlier studies. Stage was standardized according to the method used by the SEER program. Information was available on both BMI and bra cup size. The population-based nature of the study allows greater generalizability. Finally, we were able to consider effects of many other factors that predict stage at diagnosis, including screening history and method of detection. A limitation of the study was that for some stratified analyses the sample size was small, resulting in wide CIs and limited power. There may have been lower study participation among women with later-stage cancer, which may have led to an underestimation of risk if non-participation among women with later-stage cancer was related to higher BMI or bra size measurements.

Weight and height were measured at interview providing more accurate information than was likely to have been recalled. However, weight may have been influenced by the disease and by treatment. Weight gain is common in women with breast cancer (Demark-Wahnefried *et al.*, 1997), and the magnitude of the ORs relating BMI with stage could have been affected by whether later- or earlier-stage cases gained more weight because of breast cancer or treatment. We assessed the influence of time between diagnosis and interview and chemotherapy treatment on weight and BMI measurements and ORs, and found no systematic bias. Other studies (Taioli *et al.*, 1995), including 2 cohort studies (Tretli, 1989; Willett *et al.*, 1985), also found an inverse relation between BMI and breast cancer risk in young women and that this relation was confined to early-stage cancers. It is unclear whether usual bra cup size during adult life would be affected by diagnosis, treatment or stage.

In conclusion, our results indicate that among young women newly diagnosed with breast cancer, breast size and BMI are positively associated with stage. The results suggest that the reason for the association is not likely to be delayed detection, but rather differing effects of BMI and breast size on risk of breast cancers of different types. Our findings also suggest that other studies conducting case-case comparisons to examine issues related to early detection should consider possible differential effects of factors on risk.

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