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BODY SIZE AND BREAST CANCER RISK ASSESSED IN WOMEN PARTICIPATING IN THE BREAST CANCER DETECTION DEMONSTRATION PROJECT

CHRISTINE A. SWANSON,[1] LOUISE A. BRINTON,[2] PHILIP R. TAYLOR,[1]
LISA M. LICITRA,[3] REGINA G. ZIEGLER,[2] AND CATHERINE SCHAIRER[2]

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In a case-control study that included 2,560 breast cancer cases and 2,679 controls, the authors examined the association between body size and breast cancer with the use of measured height and weight of white US women. The subjects were women aged 26–93 years recruited between 1973 and 1975 for participation in the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. After controlling for the effect of potential confounders, the relative risks of breast cancer across increasing quartiles of height were 1.00, 1.07, 1.15, and 1.27 (p = 0.001, test for trend). The effect of weight independent of height was evaluated using indices of relative weight (e.g., weight/height$^{1.5}$, weight/height^2), and the authors identified excess weight as a risk factor for breast cancer among women who had experienced natural menopause and among women aged 50 years or older at diagnosis. Among women aged 50 years or older, for example, the relative risks of breast cancer for increasing quartiles of weight/height$^{1.5}$ were 1.00, 1.04, 1.40, and 1.29 (p = 0.0006, test for trend). An inverse association between relative weight and breast cancer risk was suggested for women younger than age 50 years at diagnosis. However, the apparent protective effect of high relative weight was restricted to women with small tumors, suggesting a detection bias.

anthropometry; body height; body weight; breast neoplasms; retrospective studies

Migration studies provide evidence that breast cancer is determined, in part, by environmental exposures. Buell (1), for example, reported that risk of breast cancer was increased dramatically among Japanese women who reside in Hawaii or California. De Waard et al. (2) were among the first to suggest that the changes in breast cancer rates that occur with migration are related to dietary factors which in turn are reflected by changes in body size.

Body size is an ill-defined term usually described by measures of skeletal dimension (height, frame size), body mass (weight), and variables derived from height and weight (e.g., relative weight). As reviewed by others (3, 4), the literature is

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[1] Cancer Prevention Studies Branch, Cancer Prevention Research Program, Division of Cancer Prevention and Control, National Cancer Institute, NIH, 9000 Rockville Pike, EPN Room 211, Bethesda, MD 20892. (Send reprint requests to Dr. Christine A. Swanson at this address.)

[2] Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, NIH, Bethesda, MD.

[3] Information Management Services, Inc., Silver Spring, MD.

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replete with contradictory findings, but large body size is generally considered to be a breast cancer risk factor. The most consistent finding is an increased disease risk among heavy postmenopausal women (3). The association is biologically plausible given that both aging and obesity are associated with enhanced estrogen production by adipocytes (5), and estrogen exposure has been linked to the pathogenesis of breast cancer (3). Conventionally, excess weight is thought to represent obesity, but weight is also correlated with height. Because a number of investigators (2, 6–9) have reported a direct association between height and breast cancer risk, weight should be corrected for height. Relative weight (weight adjusted for height) has been associated with increased risk of the disease in some studies (2, 6, 10) but not in all studies (9, 11, 12).

The relation between anthropometry and breast cancer may be modified by menstrual status. For example, some investigators (13–15) have reported that relative weight was inversely associated with breast cancer risk among premenopausal women. This inverse association among premenopausal women requires confirmation, and the biology has not been explained. Willett et al. (14) suggest that excess risk of breast cancer among lean premenopausal women results in part from easier diagnosis and earlier detection of small tumors.

In the study reported here, we examined the relation between breast cancer risk and body size as reflected by height, weight, and relative weight. Additionally, our data set included a large number of women diagnosed with breast cancer prior to menopause and allowed us to evaluate effect modification due to menopausal status.

Materials and Methods

This case-control study involved participants in the Breast Cancer Detection Demonstration Project, a multicenter breast cancer screening program involving over 280,000 women at 29 centers. Project participants were recruited between 1973 and 1975 for a five-year program of annual breast examinations by the combined modalities of clinical examination, mammography, and thermography. Height and weight were measured at each yearly examination.

Cases from 28 centers consisted of women aged 26–93 years whose breast cancer was detected during the period January 1973 through November 1980. Based on a standardized pathology reporting system, breast cancer cases were classified as in situ, invasive, or unknown. Invasive lesions were classified as small invasive tumors if each dimension of length, width, and depth was ≤1 cm; larger lesions were classified as large invasive tumors. Control subjects were selected from women who had not received either a recommendation for biopsy or a biopsy during the course of screening participation. The controls were chosen to be comparable with the cases on center, race (white, black, Oriental, other), age (same five-year group), time of entry (same six-month period), and length of continuation in the program (controls had as many years of screening as cases).

Home interviews were conducted by interviewers who received standardized training. During the interview, subjects provided information on known or suspected breast cancer risk factors including family history of the disease, age at menarche, menstrual history, age at first birth, parity, education, and income. Since cases were interviewed at variable times after diagnosis, exposure information was truncated at the time of diagnosis for cases or the equivalent period for controls.

Likewise, we used measurements of height and weight from the screening examination leading to a diagnosis of breast cancer; the comparable examination was selected for controls. (We also analyzed the data using height and weight at entry to the screening program; the results were similar.) Height was recorded to the nearest inch and converted to meters. Weight was recorded to the nearest pound and con-

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verted to kilograms. Several indices of relative weight or weight adjusted for height were constructed to identify the variable highly correlated with weight but independent of height (16). We evaluated weight/height, weight/height$^{1.5}$ (National Health and Nutrition Examination Survey (NHANES) (16) index for women), weight/height^2 (Quetelet index), and weight$^{0.33}$/height (ponderal index). As expected, all indices were highly correlated with weight, but only weight/height$^{1.5}$ was independent of height. Weight/height$^{1.5}$ appeared to be the most appropriate index, but we also evaluated weight/height^2, because the Quetelet index is more commonly reported as an index of relative weight.

Interviews were conducted during two different periods (January 1978 through November 1978 and June 1982 through July 1983). Completed interviews were obtained from 3,351 cases (77.9 percent of eligible subjects) and 3,583 controls (83.0 percent). Reasons for nonresponse included subjects being unlocatable or having moved too far away for interviews to be conducted (1.7 percent of cases vs. 4.3 percent of controls), refusals (5.0 percent vs. 7.8 percent), death (11.5 percent vs. 2.3 percent), and other miscellaneous reasons (3.9 percent vs. 2.6 percent). Women who were interviewed were not found to differ from those not interviewed with regard to a number of breast cancer risk factors (i.e., age, race, family income, and history of benign breast surgery) determined for each woman at the time of entry to the screening project. Based on data from the first screening examination, respondents were 1 cm taller than nonrespondents ($p < 0.02$), but the two groups did not differ significantly in weight.

A total of 134 cases and 38 controls reported a history of breast cancer prior to entering the project and were excluded. We further restricted the cohort to white subjects, eliminating 309 cases and 365 controls. Women without height and weight measurements at the screening examination leading to the diagnosis of breast cancer also were eliminated (348 cases and 501 controls). The final analytic cohort consisted of 2,560 cases of breast cancer and 2,679 controls.

In order to evaluate the effects of the anthropometry variables, the measure of association used was the relative risk, as estimated by the odds ratio. Subjects were divided into quartiles of height, weight, and relative weight using the distribution of these values for the controls. Adjustment for confounding variables was accomplished using multivariate logistic regression techniques (17), deriving maximum likelihood estimates of combined relative risks and 95 percent confidence intervals. Logistic regression was also used to test for statistical significance ($p < 0.05$) of interaction terms. Tests for trend in the logistic analysis were obtained by categorizing the exposure variable and treating the scored variable as a continuous variable.

The regression analyses included family history of breast cancer in first-degree relatives (no, yes, unknown); benign breast disease (none, 1 biopsy, ≥2 biopsies, unknown); age at menarche (<12, 12, 13, 14, ≥15 years, unknown); menstrual status (premenopausal, natural menopause, surgical menopause with at least one ovary intact, surgical menopause with bilateral oophorectomy, unknown); age at first birth (<20, 20–24, 25–29, ≥30 years, nulliparous, unknown); and years of education (<12, 12, 13–16, ≥17 years, unknown). Family history was included in the regression anlayses because of its relatively strong association with breast cancer risk, but it was the only potential confounder not associated with at least one anthropometry measure. Parity and income were associated with a number of anthropometry variables but were not associated with risk of breast cancer after controlling for age at first birth and education, respectively. When parity and income were included in the logistic analysis with other potential confounders, the results were not materially altered. Age at diagnosis was included in the regression analysis as a continuous variable. When we modeled age as an indicator variable (five-year age intervals), the results were similar.

Results

Relative risk estimates for each anthropometry variable are shown in table 1. Height, weight, and weight/height$^{1.5}$ were directly associated with risk of breast cancer. Among women in the top quartile of height and weight, respectively, risk of breast cancer was increased 27 percent and 25 percent compared with women in the referent (lowest) quartile of each variable. The effect of weight on breast cancer risk was reduced, but not removed, when weight was adjusted for height, and weight/height$^{1.5}$ was slightly stronger as a risk predictor than was the Quetelet index (weight/height^2).

TABLE 1

Relative risks (and 95 percent confidence intervals (CIs)) for breast cancer, by quartiles of anthropometry variables, among white US women screened for breast cancer between 1973 and 1980: the Breast Cancer Detection Demonstration Project

Variable	Quartile	No. of cases	No. of controls	Relative risk*	95% CI
Height (m)					
1.55†	1	633	760	1.00	
1.60	2	339	374	1.07	0.89–1.29
1.64	3	783	800	1.15	0.99–1.34
1.70	4	805	745	1.27	1.10–1.48
Trend test (p value)				(0.001)	
Weight (kg)					
52†	1	554	658	1.00	
59	2	659	688	1.15	0.98–1.35
66	3	678	652	1.26	1.08–1.48
80	4	669	681	1.25	1.06–1.47
Trend test (p value)				(0.004)	
Weight/height$^{1.5}$					
26†	1	618	672	1.00	
29	2	586	668	0.98	0.84–1.15
31	3	713	670	1.23	1.05–1.44
38	4	643	669	1.15	0.98–1.35
Trend test (p value)				(0.014)	
Weight/height^2					
20†	1	629	670	1.00	
22	2	603	669	0.98	0.84–1.15
25	3	692	672	1.17	1.00–1.37
30	4	636	668	1.11	0.95–1.31
Trend test (p value)				(0.058)	

* Regression analysis included age, family history of breast cancer, benign breast disease, age at menarche, menstrual status, age at first birth, and education.

† Quartile mean. Weight in kg and height in meters.

To consider menstrual effects, we limited the analysis to premenopausal women (n = 1,484) and women who experienced natural menopause (n = 2,128). Additionally, we divided women into two age categories (<50 years and ≥50 years). In the age-specific analyses, we made use of the full data set (n = 5,239) including women with surgical menopause.

Height was similarly associated with increased breast cancer risk among both pre- and postmenopausal women. The relation of breast cancer risk and relative weight, however, was significantly modified by menstrual status (table 2). Relative weight, regardless of index, was not associated with risk of breast cancer among premenopausal women. Among women who experienced natural menopause, weight/height$^{1.5}$ was directly associated with risk of breast cancer; this association was only slightly less pronounced when weight/height^2 was used.

The direct association between height and breast cancer risk was not affected by age (<50 years and ≥50 years), but the trends associated with relative weight were significantly modified (table 3). While breast cancer risk decreased (although insignificantly) with increasing relative weight among younger women, risk was directly associated with breast cancer among older women. Again, the risk estimates were not materially altered when weight/height^2 rather than weight/height$^{1.5}$ was used as the index of relative weight.

We further examined the association between relative weight (weight/height$^{1.5}$) and breast cancer risk for pre- and postmenopausal women grouped by age cate-

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TABLE 2

Relative risks (and 95 percent confidence intervals (CIs)) for breast cancer, by quartiles of relative weight and menstrual status, among white US women screened for breast cancer between 1973 and 1980: the Breast Cancer Detection Demonstration Project

Variable	Quartile	Menstrual status							
		Premenopausal				Postmenopausal (natural)			
		No. of cases	No. of controls	Relative risk*	95% CI	No. of cases	No. of controls	Relative risk*	95% CI
Weight/height$^{1.5}$									
26†	1	231	211	1.00		192	257	1.00	
29	2	192	199	0.86	0.65–1.15	216	268	1.08	0.83–1.40
31	3	168	174	0.91	0.68–1.23	318	291	1.51	1.18–1.95
38	4	160	149	1.02	0.75–1.39	291	295	1.41	1.09–1.82
Trend test (p value)				(0.90)				(0.0009)	
Weight/height^2									
20†	1	246	214	1.00		191	249	1.00	
22	2	190	203	0.82	0.62–1.10	228	272	1.08	0.83–1.41
25	3	159	165	0.86	0.63–1.16	312	293	1.44	1.11–1.85
30	4	156	151	0.95	0.70–1.30	286	297	1.34	1.03–1.73
Trend test (p value)				(0.72)				(0.006)	

* Regression analysis included age, family history of breast cancer, benign breast disease, age at menarche, age at first birth, and education.

† Quartile mean. Weight in kg and height in meters.

TABLE 3

Relative risks (and 95 percent confidence intervals (CIs)) for breast cancer, by quartiles of anthropometry variables and age group, among white US women screened for breast cancer between 1973 and 1980: the Breast Cancer Detection Demonstration Project

Variable	Quartile	Age group (years)							
		<50				≥50			
		No. of cases	No. of controls	Relative risk*	95% CI	No. of cases	No. of controls	Relative risk*	95% CI
Weight/height$^{1.5}$									
26†	1	237	236	1.00		381	436	1.00	
29	2	173	198	0.90	0.67–1.19	413	470	1.04	0.85–1.26
31	3	158	185	0.89	0.66–1.20	555	485	1.40	1.16–1.69
38	4	134	169	0.84	0.62–1.14	509	500	1.29	1.06–1.56
Trend test (p value)				(0.27)				(0.0006)	
Weight/height^2									
20†	1	249	245	1.00		380	425	1.00	
22	2	175	193	0.92	0.69–1.22	428	476	1.03	0.85–1.26
25	3	153	183	0.84	0.63–1.13	539	489	1.34	1.10–1.62
30	4	125	167	0.80	0.59–1.09	511	501	1.26	1.04–1.53
Trend test (p value)				(0.12)				(0.002)	

* Regression analysis included age, family history of breast cancer, benign breast disease, age at menarche, menstrual status, age at first birth, and education.

† Quartile mean. Weight in kg and height in meters.

TABLE 4

Relative risks (and 95 percent confidence intervals (CIs)) for breast cancer, by quartiles of relative weight, age group, and menstrual status, among white US women screened for breast cancer between 1973 and 1980: the Breast Cancer Detection Demonstration Project

Variable	Quartile	Age group (years) <50 No. of cases	No. of controls	Relative risk*	95% CI	≥50 No. of cases	No. of controls	Relative risk*	95% CI
				Premenopausal					
Weight/height$^{1.5}$									
26†	1	180	165	1.0		51	46	1.0	
29	2	129	146	0.8	0.6–1.1	63	53	1.1	0.6–2.0
31	3	109	122	0.8	0.6–1.2	59	52	1.3	0.7–2.3
38	4	96	112	0.8	0.6–1.2	64	37	1.8	1.0–3.3
Trend test (p value)				(0.26)				(0.06)	
				Postmenopausal (natural)					
Weight/height$^{1.5}$									
20†	1	10	19	1.0		182	238	1.0	
22	2	13	9	3.4	0.8–15	203	259	1.0	0.8–1.3
25	3	14	19	1.3	0.4–4.9	304	272	1.5	1.2–2.0
30	4	11	15	1.1	0.3–4.2	280	280	1.4	1.1–1.8
Trend test (p value)				(0.90)				(0.001)	

* Regression analysis included age, family history of breast cancer, benign breast disease, age at menarche, age at first birth, and education.

† Quartile mean. Weight in kg and height in meters.

gory (table 4). Relative weight was directly associated with breast cancer risk among older women regardless of menopausal status, but there was no clear association among younger women.

Although the downward trend of relative weight among women less than age 50 years (table 3) was not statistically significant, we explored the possibility that an inverse association could be produced artificially if there was a detection bias. Among younger women, the relation between relative weight and breast cancer risk was modified by tumor size. The apparent protective effect of high relative weight was restricted to the in situ and small invasive tumors (figure 1). High relative weight did not exhibit an apparent protective effect among older women diagnosed with such tumors (figure 2).

DISCUSSION

Our data support the concept that large body size defined either by height or relative weight is a breast cancer risk factor. The adverse effect of high relative weight was limited to women with natural menopause and to women aged 50 years or older. The magnitude of the elevated risks associated with large body size was modest and our ability to detect an association was facilitated by the large sample size.

In the study reported here, risk of breast cancer was increased about 30 percent in the tallest group of women. The literature is not consistent, but stronger associations (relative risk >2.0) between height and breast cancer risk have been reported (2, 8, 9). We considered the possibility that our results were due to response bias. Responders were taller than nonresponders but that difference was not distributed such that we preferentially included tall women with breast cancer. We controlled for several potential confounders, and the observed association between height and breast cancer was not explained by the association of height to other breast cancer

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	≥50	
No. of controls	Relative risk*	95% CI
46	1.0	
53	1.1	0.6–2.0
52	1.3	0.7–2.3
37	1.8	1.0–3.3
	(0.06)	
238	1.0	
259	1.0	0.8–1.3
272	1.5	1.2–2.0
280	1.4	1.1–1.8
	(0.001)	

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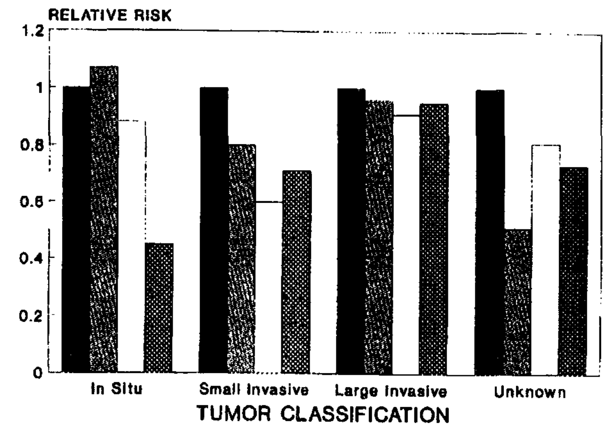

Figure 1. Relative risk of breast cancer across increasing quartiles of relative weight (weight/height$^{1.5}$) according to tumor size classification among women aged less than 50 years at diagnosis in the Breast Cancer Detection Demonstration Project: in situ tumors (n = 103), small invasive tumors (n = 71), large invasive tumors (n = 417), tumor size unknown (n = 111), compared with controls (n = 788). Tests for trend (p values) for in situ, small invasive, large invasive, and unknown tumor classification were 0.05, 0.22, 0.70, and 0.42, respectively. Regression analyses included age, family history of breast cancer, benign breast disease, age at menarche, menstrual status, age at first birth, and education.

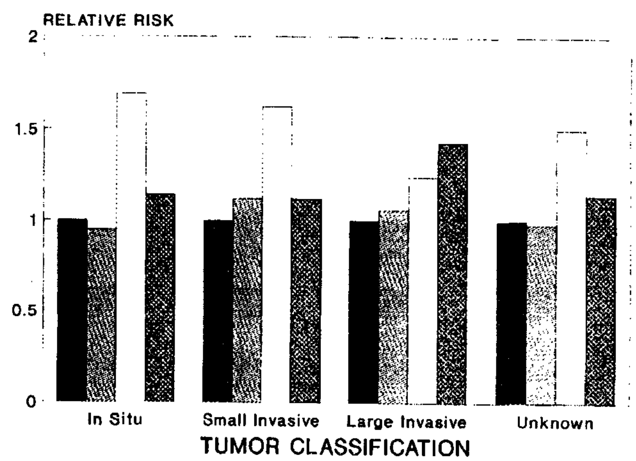

Figure 2. Relative risk of breast cancer across increasing quartiles of relative weight (weight/height$^{1.5}$) according to tumor size classification among women aged 50 years or older at diagnosis in the Breast Cancer Detection Demonstration Project: in situ tumors (n = 257), small invasive tumors (n = 271), large invasive tumors (n = 1,024), tumor size unknown (n = 306), compared with controls (n = 1,891). Tests for trend (p values) for in situ, small invasive, large invasive, and unknown tumor classification were 0.10, 0.23, 0.0006, and 0.15, respectively. Regression analyses included age, family history of breast cancer, benign breast disease, age at menarche, menstrual status, age at first birth, and education.

risk factors (i.e., higher socioeconomic status and later age at first birth).

Our findings support the concept that excess weight, and more specifically relative weight, is a risk factor in the development of breast cancer among older and postmenopausal women. The association may be related to the cessation of ovarian function. Our observation that relative weight was directly associated with breast cancer risk among older "premenopausal" women is not inconsistent with that hypothesis, because ovarian function undoubtedly decreases with age. The association between relative weight and breast cancer risk was not explained by the association of relative weight with other breast cancer risk factors. On the contrary, excess weight tended to be associated with protective factors (e.g., lower socioeconomic status and earlier age at first birth). Heavier women reported earlier menarche, but the direct association between relative weight and breast cancer risk was not limited to women with early menarche.

Relative weight is commonly used as a measure of obesity, but the index also reflects body proportions and frame size, and it does not in fact discriminate lean from adipose tissue (18). However, of all the factors that contribute to the composite of relative weight, adiposity is the only variable likely to have an effect post- but not premenopausally. Prior to the cessation of ovarian function, adiposity would not be expected to be associated with breast cancer risk because the estrogen contribution from adipose tissue is minimal relative to that from the ovaries.

Other investigators (13, 14) have reported an apparent protective effect of high relative weight among premenopausal women. We did not confirm that finding, but an inverse association was suggested among young women (ages <50 years). Following the example of Willett et al. (14), we examined the relation between relative weight, breast cancer risk, and tumor size among those young women. In agreement with Willett's finding, the protective effect of high relative weight was limited to women with small tumors. If high relative weight is related to poorer detection of small tumors, then excess weight in young women could be considered to be a risk factor for late diagnosis of breast cancer. We did not observe an apparent protective effect of high relative weight among older women with small tumors. It is possible that small tumors of older obese women are less likely to be missed because of age-associated changes in breast tissue structure which facilitate detection both by clinical examination and mammography. Alternatively, a direct association of relative weight and breast cancer risk might have masked a detection bias among older women.

In conclusion, large body size defined by height and relative weight was associated with increased breast cancer risk. Adult height is highly heritable, but identification of height as a breast cancer risk factor may also indicate a role for early nutrition in breast cancer etiology. In contrast to height, weight is influenced by nutrition and physical activity throughout life, and an attempt to maintain or achieve ideal body weight would be an acceptable goal. We identified several factors (i.e., menstrual status, age, and tumor size) which influenced the association between relative weight and breast cancer risk. However, we do not know precisely what relative weight measures. More direct measures of adiposity such as skinfold determinations are recommended. Excess weight probably represents adiposity and, as such, indicates an energy imbalance. We do not know whether that imbalance resulted from excess intake (i.e., calories), inadequate output (i.e., inactivity), or metabolic abnormality. Finally, it would be useful to know if the timing, pattern, and amount of weight gain were associated with breast cancer risk.

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le for early nutrition in
iology. In contrast to
influenced by nutrition
ity throughout life, and
ıintain or achieve ideal
l be an acceptable goal.
·eral factors (i.e., men-
and tumor size) which
›ciation between relative
;ancer risk. However, we
ıely what relative weight
rect measures of adipos-
l determinations are rec-
ı weight probably repre-
d, as such, indicates an
We do not know whether
ulted from excess intake
lequate output (i.e., in-
ıbolic abnormality. Fi-
useful to know if the
d amount of weight gain
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