Relative Weight, Weight Change, Height, and Breast Cancer Risk in Asian-American Women

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Background: **Breast cancer incidence rates have historically been four to seven times higher in the United States than in China or Japan, although the reasons remain elusive. When Chinese, Japanese, or Filipino women migrate to the United States, their breast cancer risk rises over several generations and reaches that for white women in the United States, indicating that modifiable exposures are involved. In a previous report on this case–control study of breast cancer in Asian-American women, designed to take advantage of their diversity in risk and lifestyle, we demonstrated a sixfold gradient in risk by migration history, comparable to the international differences in breast cancer incidence rates.** ***Purpose:*** **In this analysis, we have examined the roles of adult height, adiposity, and weight change in breast cancer etiology.** ***Methods:*** **A population-based, case–control study of breast cancer was conducted among women of Chinese, Japanese, and Filipino ethnicities, aged 20-55 years, living in San Francisco–Oakland (CA), Los Angeles (CA), and Oahu (HI) during the period from April 1, 1983, through June 30, 1987. We successfully interviewed 597 (70%) of 852 eligible case subjects and 966 (75%) of 1287 eligible control subjects from August 1985 through February 1989. Subjects were asked about current height, usual adult weight, and usual weight in each decade of life, excluding the most recent 3 years and any periods of pregnancy.** ***Results:*** **Height, recent adiposity (weight in the current decade of life/height$^{1.5}$), and recent weight change (between the current and preceding decades of life) were strong predictors of breast cancer risk after adjustment was made for accepted breast cancer risk factors. Risk doubled (relative risk [RR] = 2.01; 95% confidence interval [CI] = 1.16-3.49) over the 7-inch (17.8-cm) range in height (two-sided *P* for trend = .003), with comparable effects in both premenopausal and postmenopausal women. Except for reduced risk in the heavy, younger women (weight/height$^{1.5}$ >29 kg/m$^{1.5}$ and <40 years old), risk was positively associated with usual adult adiposity. Trends in risk became more striking as adiposity in each succeeding decade of adult life was considered. Women in their 50s and in the top quintile of adiposity for their age group had twice the breast cancer risk (RR = 2.13; 95% CI = 1.17-3.87) of women in the bottom quintile (two-sided *P* for trend = .004). Women in their 50s, above the median adiposity for their age group, and with a recent gain of more than 10 pounds had three times the risk (RR = 3.01; 95% CI = 1.45-6.25) of women below the median adiposity and with no recent weight change. Recent weight loss was consistently associated with reduced risk (RRs of approximately 0.7) relative to no recent weight change.** ***Conclusions:*** **Adult adiposity, weight change, and height are critical determinants of breast cancer risk. Increased adiposity and weight gain in the decade preceding diagnosis are especially influential, suggesting that excess weight may function as a late stage promoter.** ***Implications:*** **Weight maintenance and/or reduction as an adult, possibly accompanied by specific changes in diet and physical activity, may have a significant and rapid impact on breast cancer risk. [J Natl Cancer Inst 1996; 88:650-60]**

Breast cancer incidence varies widely among countries; rates have historically been approximately four to seven times higher in the United States and many other Western countries than in Asia (*1*). Numerous studies have established that, when Chinese, Japanese, or Filipino women migrate to the United States, their risk of breast cancer rises over several generations and approaches that for white women living in the United States [cited in (*2*)]. Thus, modifiable exposures related to lifestyle or environment are believed to play a major role in the etiology of breast cancer. However, the specific causal factors remain elusive.

To identify these causal factors, we designed a population-based case–control study of breast cancer among Chinese, Japanese, and Filipino women living in San Francisco–Oakland (CA), Los Angeles (CA), and Oahu (HI). Failure to attain sufficient heterogeneity in exposure and risk has been a repeated criticism of case–control and cohort studies of breast cancer (*3*). Within these ethnic populations, we were able to demonstrate a

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sixfold gradient in breast cancer risk by migration patterns (*2*). Asian-American women who had recently migrated to the United States from rural communities in Asia and who had all four grandparents also born in Asia were at the lowest risk, whereas Asian-American women born in the United States and who had three or four grandparents also born in the United States were at the highest risk. This sixfold difference in risk that we observed is comparable to the international differences in breast cancer incidence rates and implies that the diversity in lifestyle among these Asian-American women is adequate to elucidate causes of breast cancer.

In this analysis, we investigated the relationship of height, relative weight or adiposity, and weight change to risk of breast cancer. Although height and weight have been evaluated in breast cancer studies for more than 20 years (*4*,*5*), their importance is still controversial. Early work frequently did not examine the influence of weight adjusted for height. More recently, excess weight has been presented to the medical community as a weak and clinically unimportant determinant of breast cancer in postmenopausal women, and height has been presented as a risk factor that is not yet firmly established (*6*). However, two recent discussions of body size and breast cancer relationships (*7*,*8*) have suggested that relative weight and height merit more careful consideration and may provide insights into the roles of endogenous hormones and diet.

Most case–control and cohort studies of breast cancer have utilized a single static measure of adult weight. In our study, we asked about usual weight during each decade of adult life; therefore, we could examine the impact of weight change on breast cancer risk, as well as the influence of adiposity at different periods over a lifetime and at different stages of carcinogenesis. In many women, weight fluctuates during adult life, and the timing and magnitude of such changes may be crucial in understanding their importance in cancer etiology (*7*).

Subjects and Methods

Study Design

Eligible case subjects were all women of Chinese, Japanese, or Filipino ethnicity diagnosed with histologically confirmed first primary breast cancer at ages 20 through 55 years during the period from April 1, 1983, through June 30, 1987, in the population-based cancer registries in the San Francisco–Oakland Metropolitan Statistical Area (MSA), the Los Angeles MSA, and Oahu. Older case subjects were excluded, since the study design required recall of childhood and adolescent diet and lifestyle. Potential control subjects were identified in the San Francisco–Oakland and Los Angeles study areas by random-digit dialing (*2*,*9*), with bilingual interviewers when necessary, and were frequency matched to the expected case subject distribution on study area, ethnicity, and year of birth (5-year groups), in a ratio of two control subjects to one case subject to the extent possible. Potential control subjects from Oahu were selected by using the Health Surveillance Program of the Hawaii Department of Health, which annually samples 2% of the households in the state. Hawaiian control subjects were individually matched to eligible case subjects on ethnicity and age (5-year groups), in a 2:1 ratio when possible. In general, a case or control subject had to be at least 50% Chinese, Japanese, or Filipino, or a mixture of these ethnicities, to be eligible for the study. Control subjects with previous breast cancer or double mastectomies were excluded.

Of 852 eligible case subjects, 597 (70%) participated. Of 1287 eligible control subjects, 966 (75%) participated. Major reasons for not participating were subject refusal (19% and 23% of eligible case and control subjects, respectively), death of subject (6% of case subjects), and physician refusal (4% of case subjects). Participation rates were similar for the three ethnicities and the three study centers and have been previously reported (*2*).

Assessment of Exposure

Case and control subjects were interviewed in their homes by use of structured questionnaires during the period from August 1985 through February 1989. The subject chose the language of the interview (i.e., English, Chinese, or Japanese). For the case subjects, the median difference between date of diagnosis and date of interview was 1.3 years; 5% were interviewed less than 0.5 year after diagnosis, and 5% were interviewed more than 2.6 years after diagnosis.

Subjects were asked their current height and usual weight as an adult, excluding the most recent 3 years and any periods of pregnancy. Three years were excluded, since case subjects ascertained up to 2 years prior to the start of the study were eligible. Subjects were also asked their usual weight in their 20s, 30s, 40s, and 50s, excluding any periods of pregnancy and, for the current decade, the most recent 3 years. Adult weight change was defined as the difference between usual weight in the oldest decade for which a weight was reported and usual weight in the 20s. Recent weight change was defined as the difference between usual weight in the oldest decade for which a weight was reported and usual weight in the preceding decade.

Because practically all the women answered the anthropometry questions, no imputation was necessary for height, usual adult weight, adult weight change, recent weight change, or decade-specific weights, other than weight in the current decade. For 21% of the women, weight in the current decade had to be extrapolated from weight in the preceding decade. Specifically, 29% of the women aged 50 years or above at diagnosis were in their early 50s at interview and thus too young to report usual weight in their 50s once the 3 years preceding the date of interview were excluded. For each of these women, both the case and control subjects, usual weight in the 50s was imputed by adding 3 pounds to the usual weight reported for the 40s. The median of the difference between the weights reported for the 50s and for the 40s was 4 pounds for all women in the study in their 50s at diagnosis and was assumed to be slightly less for the women in their early 50s. Similarly, for the 23% of the women aged 40-49 years at diagnosis who were too young to report usual weight in their 40s and for the 13% of women aged 30-39 years at diagnosis who were too young to report usual weight in their 30s, once the 3 years preceding the date of interview were excluded, weight in the current decade was imputed, for both case and control subjects, by adding 4 pounds to the weight reported for the preceding decade. For all women in the study, the median of the difference between the weights reported for the 40s and for the 30s and of the difference between the weights reported for the 30s and for the 20s were each 5 pounds. Simply excluding from the pertinent analyses those subjects who could not report usual weight for the decade in which diagnosis of breast cancer occurred gave similar, but less stable, results; thus, results using the imputation approach are presented.

The median age at diagnosis of breast cancer was 47 years for all case subjects; 45, 49, and 45 years were the median ages for Chinese, Japanese, and Filipino case subjects, respectively. An age comparable to the age at diagnosis of breast cancer for the case subjects was assigned to each of the control subjects. First, all subjects were concurrently stratified by ethnicity, study area, year of birth (5-year groups), and age at interview (above or below the median for the case subjects). Then the mean difference between age at interview and age at diagnosis for the case subjects in each stratum was subtracted from the age at interview for each control subject in the stratum to generate an assigned age at diagnosis for each control subject.

Women who reported that a first-degree relative (mother or sister) or a second-degree relative (grandmother or aunt) had been diagnosed with breast cancer were considered to have a family history of breast cancer. Women who reported a biopsy or aspiration for a breast lump or cyst at least 2 years before the date of diagnosis were considered to have a history of benign breast disease.

A woman was considered to have been premenopausal at diagnosis if her menstrual periods had not ended before her diagnosis date (1086 women). For women whose periods had ended by date of diagnosis, ovarian function was based on self-report of the reason(s) for menopause and of the reproductive organs removed in any pertinent surgeries. Natural menopause was reported by 266 women; surgical menopause with loss of ovarian function, by 92 women; and surgical menopause without loss of ovarian function, by 99 women. The menopausal status of 20 women was unclear. Women experiencing natural

menopause or surgical menopause with loss of ovarian function by date of diagnosis were combined to form the postmenopausal category.

Analytic Methods

The relative risk (RR), as estimated by the odds ratio, was the measure of association used to evaluate the effect of height, relative weight, and weight change on breast cancer risk. Logistic regression was performed to obtain maximum likelihood estimates of the odds ratios and 95% confidence intervals (CIs), adjusted for confounding variables (*10*). Two-sided tests for linear trend were applied by assigning the median value in each category of an exposure to the category and then treating the categorical variable as continuous. Effect modification was assessed by comparing stratum-specific RRs and by examining the statistical significance of appropriate interaction terms.

Published research on anthropometry and breast cancer suggested that (*a*) adult height would be positively associated with risk, (*b*) usual adult adiposity and adult weight gain would probably be positively associated in the women diagnosed at older ages, and (*c*) usual adult adiposity would probably be inversely associated with risk in the women diagnosed at younger ages (*7,8*). However, our analysis of adiposity and weight change by decade of adult life was exploratory, since most other studies of breast cancer have treated weight as a constant during adult life (*7*). Multiple analyses were conducted and focused on a wide variety of potential relationships. The relationships highlighted in the tables and text were the strongest and most persuasive. Similarly, several ways of stratifying the anthropometric variables were tried. Those chosen for presentation emphasized the differences in risk between extremes. This approach generated the strongest trends in risk and, in addition, assigned RRs to heights and adiposities that characterize Asian women living in Asia and white women living in the United States.

Two models are presented in the tables and text. The first model includes the matching variables used in study design (i.e., ethnicity, study area, and age at diagnosis). The second model, referred to as the "multivariate" model, adds age at first live birth, family history of breast cancer, and history of benign breast disease, which are acknowledged breast cancer risk factors. Age at menarche, menopausal status, and parity, also accepted breast cancer risk factors, are not routinely included in the multivariate model, since adding them individually did not noticeably alter the patterns observed.

More speculative causes of breast cancer—specifically, diet, alcohol, physical activity, and endogenous hormone levels, measures of which have been weakly and/or inconsistently associated with risk of breast cancer—were also not included in the models. How best to assess the pertinent exposures is not clear. More importantly, anthropometry and these factors may well share common causal pathways. Their complex interrelationships will be carefully considered in our future work.

Correlations between anthropometric measures are expressed as Pearson correlation coefficients for continuous forms of the variables.

Results

The median height of the control subjects in this study of Asian-American women was 62 inches (1.57 m); the median heights for the Chinese, Japanese, and Filipino control subjects were 62, 61 (1.55 m), and 61 inches, respectively. Adjusted RRs of breast cancer increased steadily with height; women reporting a height of 66 inches or more (≥1.66 m) were at twice the risk (RR = 2.01; 95% CI = 1.16-3.49) of women reporting a height of 59 inches or less (≤1.51 m) (Table 1). The influence of height on breast cancer risk was similar in premenopausal and postmenopausal women (Table 1). In addition, a strong positive association between height and risk was noted in women aged 20-39 years, 40-49 years, and 50-55 years and in all three ethnicities (data not shown). Among the Asian-American women of intermediate height, the increase in breast cancer risk associated with each incremental inch in height was more modest than between extremes. Thus, the RR and multivariate RR, both adjusted as in Table 1, for height as a continuous variable, in inches, were 1.08 (95% CI = 1.03-1.13) and 1.06 (95% CI = 1.01-1.12), respectively.

The median usual adult weight reported by the control subjects in our study was 115 pounds (52.2 kg); the median weights reported by the Chinese, Japanese, and Filipino control subjects were 115, 112 (50.8 kg), and 115 pounds, respectively. In these Asian-American women, as in many other female populations (*11,12*), weight/height$^{1.5}$ was more strongly correlated with weight (r = .93) and concurrently less strongly correlated with height (r = –.0003) than weight/height$^{2.0}$ (Quetelet's index) (r with weight = .88; r with height = –.12) or weight/height (r with weight = .97; r with height = .12). Thus, weight/height$^{1.5}$ was selected as a better measure of adiposity, or weight adjusted for height, than Quetelet's index.[1]

Table 1. Relative risk (RR) of breast cancer by height in Asian-American women 20-55 years of age

	Height, inches*						*P* for trend
	≤59	60-61	62-63	64	65	≥66	
			***All women*†**				
RR‡	1.0 (referent)	1.12	1.45	1.56	1.64	2.25	.0002
Multivariate RR§ (95% CI‖)	1.0 (referent)	1.15 (0.80-1.64)	1.47 (1.04-2.08)	1.49 (0.95-2.35)	1.44 (0.77-2.69)	2.01 (1.16-3.49)	.003
No. of case subjects/control subjects	69/141	170/323	223/335	65/89	24/32	41/41	
			Premenopausal women				
Multivariate RR§ (95% CI‖)	1.0 (referent)	1.08 (0.69-1.69)	1.32 (0.85-2.04)	1.36 (0.78-2.38)	1.27 (0.60-2.71)	1.90 (1.00-3.61)	.03
No. of case subjects/control subjects	45/79	120/220	161/242	47/63	17/24	34/33	
			Postmenopausal women				
Multivariate RR§ (95% CI‖)	1.0 (referent)	1.17 (0.58-2.39)	1.48 (0.72-3.04)	1.72 (0.64-4.64)	1.67 (0.39-7.23)	1.68 (0.46-6.21)	.17
No. of case subjects/control subjects	17/49	35/87	39/75	13/18	4/7	6/7	

*Stratified at the 15, 48, 83, 92, and 96 percentiles of the frequency distribution in all control subjects. Cutpoints correspond to 1.51, 1.56, 1.61, 1.64, and 1.66 m, respectively.

†The numbers of premenopausal and postmenopausal women do not add up to the number of all women, since the women with unclear menopausal status and the women with surgical menopause without loss of ovarian function were not included in either menopausal category.

‡Adjusted for age at diagnosis, ethnicity, and study center.

§Adjusted for age at diagnosis, ethnicity, study center, age at first live birth, family history of breast cancer, and history of benign breast disease.

‖CI = confidence interval.

Table 2. Relative risk (RR) of breast cancer by usual adult relative weight in Asian-American women 20-55 years of age

	Usual adult weight/height$^{1.5}$, kg/m$^{1.5}$*						*P* for trend
	<22.9	22.9-24.7	24.8-26.2	26.3-28.0	28.1-31.3	>31.3	
			***All women*†**				
RR‡	1.0 (referent)	1.05	1.34	1.16	1.20	1.35	.24
Multivariate RR§ (95% CI‖)	1.0 (referent)	1.13 (0.73-1.75)	1.48 (0.96-2.27)	1.31 (0.85-2.01)	1.44 (0.93-2.22)	1.60 (0.98-2.61)	.05
No. of case subjects/control subjects	50/96	105/194	129/184	120/195	116/184	66/95	
			Premenopausal women				
Multivariate RR§ (95% CI‖)	1.0 (referent)	1.18 (0.71-1.95)	1.70 (1.03-2.80)	1.16 (0.70-1.92)	1.46 (0.88-2.44)	1.60 (0.87-2.94)	.17
No. of case subjects/control subjects	39/73	79/144	99/120	84/140	82/125	38/54	
			Postmenopausal women				
Multivariate RR§ (95% CI‖)	1.0 (referent)	1.19 (0.39-3.64)	1.11 (0.37-3.33)	1.48 (0.49-4.48)	1.39 (0.47-4.14)	1.78 (0.57-5.58)	.19
No. of case subjects/control subjects	6/18	19/44	22/55	21/42	24/49	20/29	
			Women in their 20s and 30s				
Multivariate RR¶ (95% CI‖)	1.0 (referent)	1.07 (0.51-2.24)	1.65 (0.77-3.54)	0.93 (0.40-2.13)	1.19 (0.52-2.73)	0.45 (0.12-1.66)	.39
No. of case subjects/control subjects	19/33	36/80	36/48	19/49	22/40	4/18	
			Women in their 40s				
Multivariate RR¶ (95% CI‖)	1.0 (referent)	1.58 (0.78-3.20)	1.70 (0.86-3.36)	1.33 (0.67-2.66)	1.86 (0.94-3.71)	2.31 (1.08-4.94)	.05
No. of case subjects/control subjects	20/40	45/60	57/74	47/81	53/77	34/42	
			Women in their 50s				
Multivariate RR¶ (95% CI‖)	1.0 (referent)	0.96 (0.39-2.36)	1.33 (0.56-3.17)	1.88 (0.81-4.37)	1.51 (0.64-3.56)	1.94 (0.78-4.84)	.05
No. of case subjects/control subjects	11/23	24/54	36/62	54/65	41/67	28/35	

*Stratified at the 10, 30, 50, 70, and 90 percentiles of the frequency distribution in all control subjects.

†The numbers of premenopausal and postmenopausal women do not add up to the number of all women, since the women with unclear menopausal status and the women with surgical menopause without loss of ovarian function were not included in either menopausal category.

‡Adjusted for age at diagnosis, ethnicity, and study center.

§Adjusted for age at diagnosis, ethnicity, study center, age at first live birth, family history of breast cancer, and history of benign breast disease.

‖CI = confidence interval.

¶Adjusted for ethnicity, study center, age at first live birth, family history of breast cancer, and history of benign breast disease.

Both weight/height$^{1.5}$ (Table 2) and weight/height$^{2.0}$ exhibited similar relationships to breast cancer risk; women in the top decile of usual adult relative weight were at 1.5-1.6 the risk of women in the bottom decile, after adjustment was made for other risk factors (RR = 1.60 [95% CI = 0.98-2.61] and RR = 1.51 [95% CI = 0.92-2.47] for weight/height$^{1.5}$ and weight/height$^{2.0}$, respectively). When Quetelet's index was stratified at the 10, 30, 50, 70, and 90 percentiles of the frequency distribution in all control subjects, comparable to the cut-points for weight/height$^{1.5}$ in Table 2, multivariate RRs rose from 1.0 (≤18.26 kg/m$^{2.0}$) to 1.17 (18.27-19.77 kg/m$^{2.0}$), 1.31 (19.78-20.99 kg/m$^{2.0}$), 1.14 (21.00-22.43 kg/m$^{2.0}$), 1.31 (22.44-24.88 kg/m$^{2.0}$), and 1.51 (≥24.89 kg/m$^{2.0}$); the *P* for the trend test was .12.

Breast cancer risk was positively associated with usual adult relative weight in all three ethnicities (data not shown) and in premenopausal and postmenopausal women (Table 2). However, further analysis suggested that the increase in risk with increasing relative weight was restricted to women in their 40s and 50s (Table 2). Among these women, risk doubled when women in the top decile of usual adult relative weight were compared with women in the bottom decile (RR = 2.31 [95% CI = 1.08-4.94] and RR = 1.94 [95% CI = 0.78-4.84] for women in their 40s and 50s, respectively). However, for women in their 20s and 30s, risk was decreased in the heaviest women (RR = 0.45; 95% CI = 0.12-1.66). In these younger women, once relative weight was greater than approximately 29 kg/m$^{1.5}$, risk dropped below that of the lightest women (<22.9 kg/m$^{1.5}$) (data not shown).

The effects of height and usual adult relative weight on breast cancer risk were essentially independent. Multivariate RRs for height were unchanged, and multivariate RRs for usual adult weight/height$^{1.5}$ were slightly reduced when both parameters were incorporated into the same model (data not shown). Risk increased with height at all levels of usual adult relative weight and with relative weight at all levels of height (Table 3). The tallest, heaviest women had 2.6 times the risk of the shortest, lightest women (RR = 2.62; 95% CI = 1.08-6.32), as predicted by the addition of two independent effects.

Among the women in our study, weight increased steadily with age. The median weights reported for the second, third, fourth, and fifth decades of life by the Asian-American control subjects, aged 20-55 years, were 108 pounds (49.0 kg), 112 pounds (50.8 kg), 115 pounds (52.2 kg), and 118 pounds (53.5 kg), respectively. No clear differences in weight gain between the three ethnicities emerged.

The usual adult weight that the women in our study reported reflected recent weight. For the women in their 50s, correlations between usual adult weight and usual weight reported for their 50s, 40s, 30s, and 20s were .92, .93, .84, and .69, respectively. For the younger women, those in their 40s, 30s, and 20s, the correlation between usual adult weight and the weight reported for the current decade of life varied from .92 to .99, whereas weights for earlier decades of life were less correlated.

Table 3. Relative risk (RR)* of breast cancer by height and usual adult relative weight in Asian-American women 20-55 years of age

Usual adult weight/ height$^{1.5}$, kg/m$^{1.5}$	Height, inches				
	≤59	60-61	62-63	64	≥65
≤24.7					
RR (95% confidence interval)	1.0 (referent)	1.15 (0.58-2.29)	1.71 (0.87-3.36)	1.40 (0.58-3.36)	1.56 (0.61-4.04)
No. of case subjects/control subjects	18/41	46/109	62/95	16/27	13/18
24.8-28.0					
RR (95% confidence interval)	1.01 (0.46-2.19)	1.55 (0.80-3.00)	1.94 (1.02-3.71)	2.17 (0.99-4.77)	2.30 (1.05-5.03)
No. of case subjects/control subjects	22/53	70/121	99/138	28/33	30/34
≥28.1					
RR (95% confidence interval)	1.77 (0.83-3.79)	1.64 (0.83-3.25)	1.90 (0.97-3.73)	1.92 (0.83-4.43)	2.62 (1.08-6.32)
No. of case subjects/control subjects	28/46	53/90	61/96	20/28	20/19

*Adjusted for age at diagnosis, ethnicity, study center, age at first live birth, family history of breast cancer, and history of benign breast disease.

In order to examine the importance of adiposity at different periods of adult life, decade-specific weights, like usual adult weight, were divided by adult height$^{1.5}$. This approach reduced their correlations with height and maintained their high correlations with decade-specific weights more effectively than dividing by height$^{2.0}$ or height. The resulting relative weights for each decade of life were stratified according to the distribution of relative weight for that specific decade. Thus, the adiposity of a woman at a particular age was based on the relative weights of other women in the same decade of life.

Recent adiposity was more influential than earlier adiposity (Table 4). For women in their 50s, the pattern of increasing breast cancer risk with increasing relative weight became steadily more evident as relative weights at older ages were examined. Women in their 50s and in the top quintile of adiposity for their age group had twice the breast cancer risk of women in the bottom quintile (RR = 2.13; 95% CI = 1.17-3.87); a typical Asian-American woman 62 inches tall would weigh more than 134 pounds to be in the top quintile and less than 111 pounds to be in the bottom quintile. For women in their 40s, relative weight in the 40s was more predictive of risk than relative weight in the 30s or 20s. For women in their 30s, risk seemed to increase with relative weight in the 30s as long as the women were not especially heavy. However, women in their 30s and in the highest quintile of adiposity while in their 30s or 20s were clearly at reduced risk, relative to those in the lowest quintile (RRs = 0.64 and 0.49; 95% CIs = 0.30-1.38 and 0.22-1.10, respectively).

The high correlation between relative weights at similar ages limited our ability to evaluate independent effects. However, for women in their 50s, relative weight in the 50s and relative weight in the 20s (each stratified, as in Table 4, at the 20, 50, and 80 percentiles) were both entered into the multivariate model. The increase in risk with increasing adiposity in the 50s was marginally enhanced (RRs = 1.0, 1.19, 2.08, and 2.32), whereas the weak positive association with adiposity in the 20s disappeared (RRs = 1.0. 0.88, 0.89, and 0.84). Similarly, for women in their 40s, introducing relative weight in the 40s and relative weight in the 20s into the same multivariate model left the positive trend with increasing adiposity in the 40s unchanged, but it eliminated the weak positive association with adiposity in the 20s (data not shown).

Adult weight gain, the difference between current weight and weight in the 20s, is often used as a measure of adiposity. For Asian-American women in their 50s or 40s, adult weight gain was associated with increased breast cancer risk, relative to women with no net change in weight or a net weight loss; but clear trends were not apparent (Table 5). For women in their 30s, weight gain as an adult was associated with a decreased risk of breast cancer (Table 5). Adult weight gain was not divided by adult height$^{1.5}$, since the correlation between the two variables was only .06, substantially smaller than the correlation of .35 for usual adult weight and height.

The increase in breast cancer risk with adult weight gain among women in their 50s was totally eliminated when adjusted for recent relative weight (weight in 50s/height$^{1.5}$) in the multivariate model; the RRs for weight gains of 1-5, 6-15, 16-25, and 26 or more pounds, relative to no change in weight, became 1.0, 0.82, 1.23, and 1.07, respectively. However, the RRs by recent relative weight were only marginally reduced by adjustment for adult weight change. Similarly, for women in their 40s, entering both adult weight change and recent relative weight into the multivariate model erased the association with adult weight gain, but it did not weaken the positive trend with recent relative weight (data not shown). Thus, although women with a sizable weight gain during adult life were more likely to be currently heavy, adult weight change was not an independent determinant of breast cancer risk.

Among women in their 50s, recent weight change (weight change between the current and preceding decade) was more predictive of breast cancer risk (P for trend = .002, Table 6) than weight change during adult life (P for trend = .04, Table 5). Relative to women of the same age who reported that their weight was unchanged, women in their 50s who had lost weight since the preceding decade had 0.7 times the risk (RR = 0.69; 95% CI = 0.29-1.66), whereas women with a recent weight gain of 11 or more pounds had 2.3 times the risk (RR = 2.26; 95% CI = 1.21-4.21) (Table 6). Among women in their 40s and 30s also, risk was reduced (RRs of approximately 0.7) in women with a recent weight loss (Table 6).

Unlike net weight change during adult life, the effect of more recent weight change was somewhat independent of adiposity. For women in their 50s, introducing both recent weight change and relative weight in the 50s into the multivariate model at-

Table 4. Relative risk (RR)* of breast cancer by relative weight during specific decades of adult life in Asian-American women 20-55 years of age

	Decade-specific relative weight†				*P* for trend
	Lowest 20%	21%-50%	51%-79%	Highest 20%	
		Women in their 50s			
Weight in 50s/height$^{1.5}$					
RR (95% confidence interval)	1.0 (referent)	1.14 (0.63-2.09)	1.96 (1.13-3.40)	2.13 (1.17-3.87)	.004
No. of case subjects/control subjects	32/68	38/85	75/92	51/61	
Weight in 40s/height$^{1.5}$					
RR (95% confidence interval)	1.0 (referent)	1.21 (0.68-2.16)	1.72 (0.97-3.04)	1.92 (1.01-3.66)	.02
No. of case subjects/control subjects	29/59	57/104	71/94	40/48	
Weight in 30s/height$^{1.5}$					
RR (95% confidence interval)	1.0 (referent)	1.34 (0.77-2.35)	1.63 (0.93-2.87)	1.70 (0.89-3.24)	.08
No. of case subjects/control subjects	31/63	63/101	66/90	36/49	
Weight in 20s/height$^{1.5}$					
RR (95% confidence interval)	1.0 (referent)	1.06 (0.60-1.87)	1.28 (0.73-2.26)	1.32 (0.69-2.51)	.29
No. of case subjects/control subjects	30/55	60/98	66/96	36/51	
		Women in their 40s			
Weight in 40s/height$^{1.5}$					
RR (95% confidence interval)	1.0 (referent)	1.01 (0.61-1.67)	1.22 (0.74-1.99)	1.51 (0.89-2.56)	.08
No. of case subjects/control subjects	49/76	64/101	80/111	61/87	
Weight in 30s/height$^{1.5}$					
RR (95% confidence interval)	1.0 (referent)	1.25 (0.75-2.07)	1.01 (0.60-1.70)	1.55 (0.89-2.69)	.21
No. of case subjects/control subjects	44/69	84/108	68/115	58/84	
Weight in 20s/height$^{1.5}$					
RR (95% confidence interval)	1.0 (referent)	1.25 (0.75-2.09)	1.23 (0.74-2.04)	1.35 (0.77-2.34)	.36
No. of case subjects/control subjects	48/74	73/102	77/114	55/84	
		Women in their 30s			
Weight in 30s/height$^{1.5}$					
RR (95% confidence interval)	1.0 (referent)	1.30 (0.69-2.46)	0.95 (0.49-1.84)	0.64 (0.30-1.38)	.13
No. of case subjects/control subjects	29/50	45/72	36/69	18/51	
Weight in 20s/height$^{1.5}$					
RR (95% confidence interval)	1.0 (referent)	0.99 (0.52-1.88)	1.18 (0.63-2.24)	0.49 (0.22-1.10)	.18
No. of case subjects/control subjects	30/48	42/77	42/70	14/47	

*Adjusted for ethnicity, study center, age at first live birth, family history of breast cancer, and history of benign breast disease.

†Stratified according to the frequency distribution of each decade-specific weight/height$^{1.5}$ among all the control subjects. The 20, 50, and 80 percentiles for control subjects in their 50s, 40s, 30s, and 20s, respectively, were 25.3, 27.3, and 30.8 kg/m$^{1.5}$; 24.7, 27.0, and 30.3 kg/m$^{1.5}$; 23.5, 25.9, and 28.7 kg/m$^{1.5}$; and 22.5, 24.7, and 27.1 kg/m$^{1.5}$. These relative weights imply, for a woman at the median height in this Asian-American population of 62 inches, weights of 110, 119, and 134 pounds for women in their 50s; weights of 108, 118, and 132 pounds for women in their 40s; weights of 103, 113, and 125 pounds for women in their 30s; and weights of 98, 108, and 118 pounds for women in their 20s.

Table 5. Relative risk (RR)* of breast cancer by weight change during adult life in Asian-American women 20-55 years of age

	Weight loss	No weight change	Weight gain, pounds†				*P* for trend
			1-5	6-15	16-25	≥26	
Women in their 50s							
RR (95% confidence interval)	0.99 (0.37-2.64)	1.0 (referent)	1.00 (0.43-2.37)	1.00 (0.47-2.14)	1.71 (0.77-3.83)	1.63 (0.72-3.71)	.04
No. of case subjects/control subjects	12/25	15/25	23/43	58/109	46/51	37/46	
Women in their 40s							
RR (95% confidence interval)	0.95 (0.44-2.04)	1.0 (referent)	1.30 (0.67-2.51)	1.46 (0.79-2.69)	1.26 (0.64-2.47)	1.35 (0.65-2.82)	.43
No. of case subjects/control subjects	25/35	24/46	45/74	87/107	42/65	30/45	
Women in their 30s							
RR (95% confidence interval)	0.72 (0.29-1.81)	1.0 (referent)	0.87 (0.42-1.82)	0.58 (0.28-1.21)	0.77 (0.32-1.89)‡		.43
No. of case subjects/control subjects	13/27	22/36	29/52	30/73	14/27		

*Adjusted for ethnicity, study center, age at first live birth, family history of breast cancer, and history of benign breast disease.

†Cutpoints correspond to 2.5, 7.0, and 11.6 kg, respectively.

‡For women in their 30s, weight gains of 16-25 pounds and ≥26 pounds were combined to generate a more stable risk estimate.

Table 6. Relative risk (RR)* of breast cancer by recent weight change in Asian-American women 20-55 years of age

	Weight loss	No weight change	Weight gain, pounds†			*P* for trend
			1-5	6-10	≥11	
Women in their 50s						
RR (95% confidence interval)	0.69 (0.29-1.66)	1.0 (referent)	1.01 (0.61-1.67)	1.38 (0.78-2.44)	2.26 (1.21-4.21)	.002
No. of case subjects/control subjects	9/27	46/82	60/103	44/57	37/35	
Women in their 40s						
RR (95% confidence interval)	0.72 (0.36-1.46)	1.0 (referent)	1.20 (0.74-1.94)	1.28 (0.74-2.22)	1.12 (0.66-1.89)	.36
No. of case subjects/control subjects	19/36	51/90	75/107	52/61	57/81	
Women in their 30s						
RR (95% confidence interval)	0.73 (0.29-1.82)	1.0 (referent)	0.87 (0.42-1.83)	0.54 (0.24-1.22)	0.72 (0.33-1.56)	.39
No. of case subjects/control subjects	13/27	22/36	29/52	18/47	26/53	

*Adjusted for ethnicity, study center, age at first live birth, family history of breast cancer, and history of benign breast disease.
†Cutpoints correspond to 2.5 and 4.8 kg, respectively.

tenuated, but did not eliminate, the effect of each anthropometric measure. The RRs for recent weight change (stratified as in Table 6) were reduced to 0.72, 1.0, 0.92, 1.19, and 1.77 for weight loss, no weight change, and weight gains of 1-5, 6-10, and 11 or more pounds, respectively. The RRs for relative weight in the 50s (stratified as in Table 4) were reduced to 1.0, 1.10, 1.73, and 1.74 for women in the lowest 20%, 21%-50%, 51%-79%, and highest 20% of relative weight, respectively.

The joint effect of recent weight change and recent adiposity on breast cancer risk for women in their 50s is illustrated in Table 7. Risk increased steadily with recent weight gain in women above and below median adiposity (119 pounds for a woman 62 inches in height), and heavier women were consistently at an increased risk of breast cancer, whatever the magnitude and direction of recent weight change. Women currently above median adiposity with a recent weight gain of more than 10 pounds (i.e., cutpoint set at 10.5 pounds or 4.8 kg) were at three times the risk of women below median adiposity with no recent change in weight (RR = 3.01; 95% CI = 1.45-6.25).

The influence of recent adiposity (Table 4) and of recent weight change (Table 6) on risk of breast cancer among women in their 50s was not altered by the addition of adult height to the multivariate models. Similarly, the relationship between height and breast cancer risk (Table 1) was not changed by adjusting for recent adiposity or recent weight change.

In these Asian-American women, migration history—which took into account the birthplaces (whether in the East or West) of the woman and her grandparents, whether she had lived in rural or urban areas while in the East, and the number of years she had lived in the West—was associated with a sixfold gradient in breast cancer risk (*2*). Even incorporating this strong predictor of risk into the models for height, recent adiposity, and recent weight change did not noticeably attenuate their effects.

We considered the possibility that bias could have generated the associations between breast cancer and recent adiposity and recent weight change among women in their 50s. Case subjects could have exaggerated their weight in the current decade because of weight gain due to adjuvant therapy (*13,14*), even though we asked them to exclude any weight change in the most recent 3 years. However, the correlations between weight in the 50s and weight in the 40s, 30s, and 20s were similar for case subjects (r = .94, .83, and .69) and control subjects (r = .93, .81, and .65), suggesting no unusual bias in recall of recent weight by the case subjects. In addition, the relationships between breast cancer risk and recent relative weight (Table 4) and recent weight gain (Table 6) were not noticeably different for the case subjects treated with surgery only and those treated with surgery plus adjuvant chemotherapy and/or hormone therapy.

Bias due to identification of potential control subjects by random-digit dialing in the San Francisco–Oakland and Los An-

Table 7. Relative risk (RR)* of breast cancer by recent weight change and recent relative weight in Asian-American women in their 50s

Relative weight in 50s, kg/m$^{1.5}$	Recent weight change					Relative weight in 50s, adjusted for recent weight change
	Loss	No change	Gain of 1-5 pounds	Gain of 6-10 pounds	Gain of ≥11 pounds	
≤27.3						
RR (95% confidence interval)	0.73 (0.24-2.27)	1.0 (referent)	1.00 (0.49-2.02)	1.40 (0.58-3.41)	2.81 (0.66-11.90)	1.0 (referent)
No. of case subjects/control subjects	5/19	25/55	23/51	13/22	4/5	
>27.3						
RR (95% confidence interval)	1.37 (0.35-5.36)	1.98 (0.90-4.33)	1.64 (0.85-3.20)	2.04 (1.00-4.18)	3.01 (1.45-6.25)	1.64
No. of case subjects/control subjects	4/8	21/27	37/52	31/35	33/30	
Recent weight change, adjusted for relative weight in 50s	0.71	1.0 (referent)	0.93	1.20	1.78	

*Adjusted for ethnicity, study center, age at first live birth, family history of breast cancer, and history of benign breast disease.

geles study areas was also of concern. However, only one of the participating case subjects from these areas (and one of the participating control subjects) reported, at the time of the home interview, not having a telephone regularly available for personal use, suggesting that the study design was reasonable. We wondered whether diagnosis of breast cancer might have prompted case subjects to install phones; however, 3 years prior to interview, only three case subjects (and six control subjects) did not have access to a phone.

Discussion

Height was a strong predictor of breast cancer risk among the Asian-American women in our study; effects were apparent in both premenopausal and postmenopausal women. Breast cancer risk doubled over the 7-inch (17.8-cm) range in height, even after we controlled for acknowledged breast cancer risk factors.

Other studies of breast cancer among U.S. women, with primarily Caucasian participants, have demonstrated comparable associations with height. Two early retrospective studies (*15,16*) noted RRs of 2.1 and 1.7 for 13- and 18-cm increases in height, respectively. More recently, adjusted RRs of 1.9 and 1.5-1.8 for an approximately 15-cm increase in height were reported in two prospective studies (*17,18*), although other retrospective and prospective studies conducted in the United States have reported modest (*19,20*) or no (*21,22*) associations. Striking associations between breast cancer risk and height have also been observed in women living in Japan (*23,24*), in Japanese women living in Hawaii (*25*), and in women living in Singapore (*26*).

It has been frequently postulated that height is related to breast cancer risk primarily in those populations where inadequate caloric intake in childhood and adolescence limits growth (*20,27-29*). However, an enhanced risk of breast cancer among taller women has been demonstrated in populations in which energy or nutrient deficiency is not evident and tallness is determined primarily by genetic factors (*7,8,15,16,18,30,31*). Thus, it is possible that inherited patterns in endogenous hormones and growth factors contribute to the height attained prior to epiphyseal closure at puberty and also to the promotion of breast carcinogenesis, either at puberty when breast tissue is rapidly developing or at a later stage in the life cycle. Estrogen and progesterone are generally believed to be the hormones that determine breast cancer risk (*32,33*); but androgens, growth hormones, insulin, and insulin-like growth factors deserve consideration (*34*). In our population of Asian-American women, height probably reflects a combination of genetics and environment; its striking relationship to breast cancer risk is mediated by as yet unidentified patterns in endogenous hormones, growth factors, and/or diet.

In addition to height, usual adult relative weight or adiposity was also a strong predictor of breast cancer risk among the Asian-American women in our study. Although there was evidence of reduced risk in heavy women (weight/height$^{1.5}$ >29 kg/m$^{1.5}$) younger than 40 years of age, the dominant pattern was increasing risk with increasing adiposity. Breast cancer risk rose with usual adult relative weight in both premenopausal and postmenopausal women, in women in their 40s and 50s, and even in the leaner, younger women. Among women in their 40s and 50s, risk more than doubled with increasing adiposity, after controlling for established risk factors.

A complex relationship with adiposity has been demonstrated in many of the epidemiologic studies of breast cancer conducted in Western countries; an inverse association has been found in younger, premenopausal women, and a positive association has been seen in older, postmenopausal women (*7,8*). The positive association between relative weight and risk that we observed among the Asian-American women in our study was stronger and apparent at younger ages than in other U.S. studies of breast cancer. In these studies, RRs by adiposity generally ranged from 1.0 to 1.5 in postmenopausal women (*17,18,20-22,35-44*).

There are several possible explanations for why adiposity is so strongly associated with risk in the Asian-American population whom we studied. Asian-American women are, in general, leaner than other U.S. women. The median usual adult adiposity among the control subjects in our Asian-American population was 26.2 kg/m$^{1.5}$; the median adiposities for participants in the Breast Cancer Detection Demonstration Project (*45*) and the first National Health and Nutrition Examination Survey Follow-up Study (*17*) were approximately 30 and 31 kg/m$^{1.5}$, respectively. In addition, the dietary and physical activity patterns that characterize levels of adiposity may be different in Asian-American women. Finally, in our Asian-American population, the positive association between excess weight at older ages and breast cancer risk would not have been attenuated by a protective effect of adiposity at younger ages. Our findings are consistent with a meta-analysis of case–control data from countries at high (United States and Wales), moderate (Brazil, Greece, and Yugoslavia), and low (Japan and Taiwan) risk for breast cancer, which demonstrated that breast cancer incidence rates increased with weight/height$^{2.0}$ among both premenopausal and postmenopausal women, except for premenopausal women from high-risk countries where an inverse relationship was noted (*46*). Adiposity is reported to be strongly associated with breast cancer risk in both premenopausal and postmenopausal women in Japan (*24*).

Because in our interviews we asked about usual weight during each decade of adult life, we had the opportunity to analyze weight as a dynamic process. Most other epidemiologic studies have utilized a static measure of adult weight: current, recent, or usual adult weight in retrospective studies or weight at base line in prospective studies.

When adiposity in each decade of adult life was evaluated in our study, trends in risk became more striking as the decade in which breast cancer was diagnosed was approached. Women in their 50s in the top quintile of relative weight for their age group had twice the risk of breast cancer as women in the bottom quintile; their relative weight at successively younger ages was decreasingly predictive of risk. In addition to recent adiposity, recent weight change was also a major determinant of breast cancer risk. For women in their 50s, a recent weight gain (between the current and preceding decade) of more than 10 pounds was associated with a doubling of risk, relative to no recent weight change. Recent weight loss was associated with a reduced risk of breast cancer in all age groups, relative to no change in weight. Although the effects of recent adiposity and

recent weight change were not totally independent, neither measure fully explained the impact of the other.

We wanted to determine whether the remarkable impact of excess weight in the years immediately preceding breast cancer diagnosis that we observed in Asian-American women was suggested in other studies and in other populations. However, we have been unable to find other analyses focused on recent adiposity and recent weight change and breast cancer risk in older women with which to compare our results. We did note that in the Nurses' Health Study Cohort the strongest associations between adiposity and breast cancer risk were seen among postmenopausal women 55 years of age or older when the most recent Quetelet's index was used (*20*).

The critical importance of excess weight in the years preceding diagnosis is consistent with three relatively recent findings. First, adiposity at the time of breast cancer diagnosis is generally associated with an increased probability of recurrence and a decreased survival time, even after adjusting for stage and treatment (*7,47,48*). If adiposity can enhance tumor growth after diagnosis, it should be expected to promote tumor development and growth also in the late stages of breast carcinogenesis prior to clinical detection.

Second, weight gain during adult life is increasingly recognized as a striking predictor of breast cancer risk in older, postmenopausal women (*7,18,20,22,35,39,42,44,49-51*). In our study also, adult weight gain was a clear risk factor. However, its effect was eliminated by adjusting for recent relative weight, suggesting that adult weight gain may be important to the extent that it determines adiposity in the years preceding diagnosis. In two prospective studies (*20,51*), adult weight gain up to base line has predicted an increased risk of breast cancer in postmenopausal women more reliably than base-line adiposity, possibly because it indicated continued weight gain and thus obesity at later ages.

Third, as noted in recent reviews (*7,8*), retrospective studies (*22,25,35,36,38,43,44*) have reported stronger and more consistent associations between adiposity and breast cancer in older, postmenopausal women than prospective studies (*17,20,41*). A partial explanation may be that retrospective studies asking about current, recent, or usual adult weight are, in general, assessing adiposity at an age closer to diagnosis than prospective studies asking about weight at base line. The only prospective study of breast cancer in the United States to observe a positive association with adiposity was the Iowa Women's Cohort, an older cohort with limited years of follow-up (*52*), for whom base-line weight probably reflected weight in the years immediately preceding diagnosis. In several cohorts, weight is being assessed periodically during adult life; analyses taking advantage of these sequential data should be able to evaluate our hypotheses.

Although we propose that adiposity and weight gain influence the late stages of breast carcinogenesis, we cannot exclude the possibility that the impact of excess weight in the years preceding diagnosis, noted primarily among the women in their 50s in our study, is restricted to the perimenopausal years. Weight gain during periods of hormonal change, such as menopause, pregnancy, and menarche, may have distinct biologic effects (*7*); in addition, the perimenopausal years are often characterized by substantial weight gain (*53*). Our study did not include women in their 60s and 70s, among whom the breast cancer risk associated with excess weight acquired after menopause could be evaluated.

At present, we can only speculate on the mechanisms underlying the striking relationship between recent adiposity and weight change and breast cancer risk observed in our study. Estrogen production in adipose tissue from circulating androgens is elevated in heavy women, may promote tumor growth, and becomes increasingly important as ovarian estrogen production diminishes with age (*7,32,33*). The effect could be localized, with especially high estrogen levels near breast adipose tissue. In addition, the decreased sex hormone-binding globulin levels and the increased triglyceride levels associated with excess weight increase the bioavailability of estrogen (*7*). Alternatively, the elevated levels of insulin and growth factors associated with adiposity may promote tumor growth, either directly or by modulating steroid activity (*7,34,54*).

Whether our findings in Asian-American women can be generalized to other U.S. women is not a simple question. As previously noted, the positive associations with adiposity observed in our study are stronger and apparent at younger ages than in other U.S. studies—possibly because Asian-American women are leaner, possibly because they adhere to distinctive dietary and physical activity patterns, and possibly because the protective influence of adiposity in early adult life is minimal in this population. Genetics is not the explanation for our results, since we have demonstrated that these Asian-American women acquire the high breast cancer rates of U.S. whites after several generations of acculturation (*2*). We deliberately conducted this study in Asian-American women. Within these migrant populations, one can find not only the elevated breast cancer rates characteristic of many Western countries but also the substantially reduced rates that U.S. women seek. If we can identify what explains the striking increase in breast cancer risk associated with added weight in the years immediately preceding diagnosis, then U.S. women may choose to modify their lifestyles accordingly.

Thus, these findings may have important clinical and public health implications. The twofold to threefold changes in breast cancer risk noted in our study are at least as strong as those associated with established breast cancer risk factors (*6*) and are definitely stronger than those reported for specific dietary factors or endogenous hormones (*8,33*). Further examination of the complex interrelationships between body size and shape, diet, physical activity, and endogenous hormone levels is warranted. Ultimately, intervention trials will be needed to test whether weight loss and/or maintenance can indeed reduce breast cancer incidence and whether weight loss and/or maintenance must be accompanied by specific dietary patterns or levels of physical activity. In the meantime, it is important to emphasize that adiposity is potentially modifiable. In contrast to other approaches to reducing breast cancer risk, weight loss and/or maintenance does not require long-term use of medications or difficult decisions about whether and when to bear children. Our results suggest that weight loss might have a relatively rapid impact, possibly within a decade, on breast cancer risk. This possibility should encourage women seeking a realistic way to

reduce their risk of developing the most common cancer affecting women in many Western societies.

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Notes

[1]Although it would have been possible to control weight for height by multivariate modeling, such an approach would have precluded a stratified analysis focused on women of low, intermediate, and high adiposity and the estimation of RRs for these subgroups.

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