MINIREVIEW

The Role of Body Mass Index in the Relative Risk of Developing Premenopausal versus Postmenopausal Breast Cancer (44153B)

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Abstract. **Many women in industrialized countries are overweight. Excess body fat is associated with excess morbidity and mortality from atherosclerosis and diabetes. In some cases, overweight/obesity also is implicated with increased incidence of breast cancer, but the results of these studies are not consistent. Human breast cancer is usually distinguished as either premenopausal or postmenopausal. In this review, we focus on literature that presents body mass index (BMI, weight/height^2) ranges and identifies menstrual status. The majority of the relevant prospective studies support an inverse relationship between BMI and the relative risk (RR) of developing premenopausal breast cancer. In contrast, a positive relationship between BMI and the RR of developing postmenopausal breast cancer is reported in only half of all prospective studies on this topic. Those studies that do not show a positive RR, in general, have used younger postmenopausal women, and their body weights were obtained prior to menopause. Many case-control studies also report an inverse association between BMI and the RR of developing premenopausal breast cancer, and a positive association between BMI and the RR of developing postmenopausal breast cancer. Other studies do not find these associations, but a number of these studies have used small sample sizes and, for the postmenopausal subjects, have represented populations with low obesity and/or breast cancer rates. Other factors that might play a role in breast cancer development, such as body fat distribution, weight at earlier ages, and weight gain, are also addressed, as well as the effect of obesity in breast cancer prognosis. In addition, limited data available for animal studies related to this topic, as well as potential mechanisms by which body fat may play a role in breast cancer development, are discussed. Finally, the need for better animal models in which to perform controlled dietary and/or drug intervention studies to test rigorously the proposed mechanisms by which body fat may contribute to breast cancer development is addressed.** [P.S.E.B.M. 1997 Vol 216]

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Many adult women in the United States and other industrialized countries are overweight or obese (1–3). Metabolic abnormalities such as elevated serum cholesterol and insulin, and tissue insulin resistance have been associated with excess body fat (4–6). In addition, diseases such as diabetes and atherosclerosis have been found to be more prevalent in obese compared with normal weight individuals (4, 7, 8), and elevated body weights have been associated with shortened life expectancy (9). In a recent study of women, the relative risk (RR) of dying from any cause was increased as body mass index (BMI) (weight/height^2) increased (10). It was further noted that the RR of dying from cancer was increased 2-fold when comparing the lightest group with the heaviest group of women (10). In another recent study, Moller *et al.* (11) examined records of hospitalized Danish patients with a diagnosis of obesity and cross-checked these with both cancer and death registries. They found that obesity was associated with an inverse RR of developing breast cancer in subjects under the age of 49, and with a significant positive RR in subjects over the age of 80. This study and others demonstrate that menopausal status and/or age can be an important determining element in relative risk factors in breast cancer. In this review, literature pertinent to this topic has been evaluated to determine the relationship between being overweight/obese, primarily as assessed by BMI, and the risk of developing breast cancer in premenopausal versus postmenopausal women. Although actually measuring body fat would be a better determinant of overweight or obesity, due to technical and practical difficulties this technique is rarely used in large scale studies. Instead indirect measures such as BMI, also known as Quetelet's index (12), are used. Another obesity measure used in some of these investigations is relative weight (body weight divided by height to the 1.5 power). Investigations pertaining to the relationship of BMI and breast cancer have included prospective, cohort, and case-control studies. In the prospective studies, women were followed over a period of years after body weight and height information were obtained. In cohort studies, breast cancer subjects were identified from a group of women, and the characteristics of those individuals who developed breast cancer were compared with those who were cancer free. In case-control studies, subjects diagnosed with breast cancer were compared with selected control subjects matched for age and other factors. In these case-control studies, body weights and heights were usually obtained at or near the time of diagnosis. Importantly, in all these studies body weights and heights were obtained either by self-report or by actual measurement. Although there have been some concerns about the accuracy of self-reported and/or recalled body weight, evaluations of these measures have indicated that the results obtained are reasonably accurate (13–15). Since the purpose of this review was to gain insight into the potential role of being overweight/obese in the risk of developing of premenopausal versus postmenopausal breast cancer, we have focused on articles that have presented data for these groups either individually or separately. In addition, we have focused on studies where ranges of BMI values were presented, thus allowing for an evaluation of a continuous effect rather than an "either/or" comparison.

BMI and Prospective/Cohort Studies of Breast Cancer

A summary of the prospective/cohort studies for both premenopausal and postmenopausal breast cancer is presented in Table I in chronological order of their publication. Number of subjects, menopausal status, BMI ranges, and RR values are included, as well as the dates of the study. There have been fewer prospective/cohort studies on the association of breast cancer and obesity than case-control studies. This is primarily due to the long-term commitment needed by both subjects and researchers to follow up on these investigations.

Seven prospective studies have reported a decreased RR of developing premenopausal breast cancer as BMI levels increased (17, 19, 21, 23, 26, 29). Three studies did not find an association between either BMI or relative weight and premenopausal breast cancer (20, 25, 28). Follow-up in these studies was from as little as 4 years to as many as 21.

Four prospective studies with follow-up periods ranging from 4 to approximately 14 years reported significantly increased RR for developing postmenopausal breast cancer as BMI increased (18, 22, 24, 26). In the Iowa Women's Health Study, the increased RR was even higher in women with a family history of breast cancer (24). Also, with respect to this specific study, no effect of BMI was apparent at 1-year follow-up (30), but was clearly seen after 4 years. Swedish subjects originally followed in Reference 18 have now been followed for 25 years, and in this study it was reported that, for women over 55 years of age, high BMI predicted an increased RR for the development of breast cancer (27). It also was noted that in these women the increased RR associated with increased BMI was most prominent in the first 10 years of the study. In a recent paper using relative weight (28), there was not a significant effect on age-adjusted RR for postmenopausal breast cancer, but the multivariate-adjusted RR of 1.3 was significant. The authors indicated that similar results were obtained for BMI, but the data were not presented. In one early study, no statistics were presented (16). Other studies did not find any significant association of BMI with the development of postmenopausal breast cancer (17, 19, 21, 25). In general, postmenopausal subjects in these four studies were less than 60 years of age at diagnosis. It is likely that body weights of some of these subjects were obtained prior to their reaching menopause, and this may have influenced the outcome of these studies. In fact, this issue was recently addressed by Yong *et al.* (28). These investigators reported that the RR for developing postmenopausal breast cancer was not associated with relative weight calculated from premenopausal height and weight, but that higher relative weight calculated

Table I. Relationship of Obesity with Breast Cancer Relative Risk (RR) in Prospective/Cohort Studies

Author	Dates	Subjects/controls (*n*)	Menopausal status and/or age (years)	BMI range	RR
DeWaard & Baanders–van Halewijn, 1974 (16)	1964–1973	70/7,259	Postmenopausal (55 and up)	<25 to ⩾31 (quintiles)	1.2[a]
Willett *et al.*, 1985 (17)	1976–1980	570/112,540	Premenopausal (30–55)	19.6 to 30.3 (quintiles)	0.66[b]
			Bilateral oopherectomy		1.68[b]
			Hysterectomy—ovaries left		0.62[b]
			Natural menopause		1.02[c]
Tornberg *et al.*, 1988 (18)	1963–1983	1,182/46,570	<50	One BMI unit increase	0.95[b]
			⩾50		1.02[b]
London *et al.*, 1989 (19)	1976–1984	1,078/121,700	Premenopausal	<21 to ⩾29 (quintiles)	0.6[b]
			Postmenopausal		
Tretli, 1989 (20)	1963–1981	12,338/567,333	30–54	Quintiles of BMI	<0.97[c,d]
			55–59		1.10[c]
			60–64		1.18[c]
			65–69		1.22[c]
Vatten & Kvinnsland, 1990 (21)	1974–1988	236/23,826	<51	<22 to ⩾26.8	0.36[b,d]
			⩾51		0.74[c]
den Tonkelaar *et al.*, 1992 (22)	1974–1979	119/16,355	Postmenopausal (49–68)	<23 to >28 (quartiles)	1.65[b,d]
Vatten & Kvinnsland, 1992 (23)	1974–1990	241/25,967	⩽50	<22 to ⩾27 (quartiles)	0.58[b,d]
Sellers *et al.*, 1992 (24)	1986–1989	493/37,105	Postmenopausal (55–69) (no family history of breast cancer)	⩽22.89 to ⩾30.70 (quintiles)	1.50[b]
			Postmenopausal (55–69) (with a family history of breast cancer)		2.21[b]
De Stavola *et al.*, 1993 (25)	1961–1992	168/6,706	Premenopausal[e]	<22 to ⩾26.5 (quartiles)	1.1[d]
			Postmenopausal[e]		1.1[d]
Zang and Wynder, 1994 (26)	1977–1991	148/9,083	Premenopausal (<50)	<21.8 to >27.5 (quartiles)	0.41[b]
		633/9,083	Postmenopausal (⩾50)		1.46[b]
Tornberg & Carsteensen, 1994 (27)	1971–1987	1,466/47,003	<50	<22 to ⩾28	0.41[b,d]
			⩾55		1.13[b,d]
Yong *et al.*, 1996 (28)	1973–1989	226/54,896	Premenopausal	Quintiles of relative wt	0.8[d]
					0.9[e]
		1,198/54,896	Postmenopausal		1.2[d]
					1.3[b,e]

[a] No statistics presented.
[b] Significant trend over designated groups by chi-square analyses.
[c] Not significant.
[d] Age-adjusted.
[e] Multivariate-adjusted.

from height and weight obtained after menopause was a positive risk factor (28).

BMI and Case-Control Studies of Premenopausal Breast Cancer

A summary of the results for the premenopausal case-control studies with respect to numbers of subjects, BMI ranges, and RR is presented in Table II. Ten investigators reported a significantly inverse relationship of BMI on the RR for developing breast cancer in premenopausal women (34, 35, 42–44, 47, 50, 51, 53, 54). Data from one of these studies (43) was recently reanalyzed for stage of diagnosis, and it was found that the inverse relationship was present for in situ and local tumors but not for regional or distant cancers (58). In an additional study, a RR of 0.69 for largest BMI compared with the smallest was reported, but no statistics were presented (59). Sixteen studies reported no significant relationship between BMI and the RR of developing premenopausal breast cancer (31–33, 36–39, 41, 45, 46, 48, 51, 52, 55, 56, 60). Several of these studies had relatively small sample sizes, which may have affected the results (36, 51, 55, 56). Two studies reported a significantly increased RR for the development of premenopausal breast cancer with increasing BMI (40, 49). When data from one of these studies (40) were combined with data from a study where no effect was found (37), no statistical differences were found for these Italian women (61). Using relative

Table II. Summary of Relative Risk (RR) of Breast Cancer in Relation to Body Mass Index (BMI) in Case-Control Studies—Premenopausal Women

Author	Subjects/controls (*n*)	Age range	BMI ranges	RR
Mirra *et al.*, 1971 (31)	237/~775(h)[a]	20–49	<22 to ≥27 (quintiles)	1.2[b]
Staszewski, 1977 (32)	900/581(h)[c]	25–49	<24 to ≥30 (quintiles)	0.99[b]
Wynder *et al.*, 1978 (33)	301/982	>30	8 levels of BM1	No effect
Paffenberger *et al.*, 1980 (34)	374/724(h)	$\bar{X}$ ~ 43	< 21.5 to ≥24.5 (tertiles)	0.65[d]
Helmrich *et al.*, 1983 (35)	465/1,313(h+c[e])	Not specified	<20.7 to ≥27 (quartiles)	0.5[d]
Talamini *et al.*, 1984 (36)	89/127(h)	Not specified	<25 to ≥30 (tertiles)	0.8[b]
Toti *et al.*, 1986 (37)	446/661(h)	Not specified	<22 to ≥27 (quartiles)	1.20[b]
Hislop *et al.*, 1986 (38)	306/324(c)	Not specified	≤21 to ≥27 (quartiles)	0.84[b,f]
Schatzkin *et al.*, 1987 (39)	221/334(h)	Not specified	≤24 vs ≥30 (tertiles)	1.2[b]
LaVecchia *et al.*, 1987 (40)	456/406(h)	Not specified	<20 to ≥30 (quartiles)	2.08[d]
Ewertz, 1988 (41)	639/539(c)	Not specified	<20 to ≥32 (quartiles)	1.25[b]
Kampert *et al.*, 1988 (42)	~762/~1,400(h)	>25	20 to 28 (quintiles)	0.62[d,g]
Swanson *et al.*, 1989 (43)	702/788(c)	≥26–49	20 to 30 (quartile)	0.80[b]
	751/733(c)	Premenopausal	20 to 30 (quartile)	0.95[b]
Pryor *et al.*, 1989 (44)	99/101(c)	20–54	≤20.5 to >24.7 (quartile)	0.4[d]
Rosenberg *et al.*, 1990 (45)	270/537(h+c)	Not specified	<21 to ≥26 (tertiles)	0.8[b]
Hsieh *et al.*, 1990 (46)	3,993/11,783(h)[3]	Not specified	+4 kg/m^2	1.04[b]
Bouchardy *et al.*, 1990 (47)	154/302(h)	25–44	<23 to ≥27 (tertiles)	0.4[d]
	272/525(h)	45–54		0.6[d]
Lund *et al.*, 1990 (48)	422/527(c)	<45	<20 to >23 (quartiles)	1.2[b]
Chu *et al.*, 1991 (49)	2,053/1,759(c)	Not specified	<23 to >32.3 (sextiles)	1.3[d]
Harris *et al.*, 1992 (50)	192/184(h)	<59	<22 to >27 (tertiles)	0.5[d]
Lee *et al.*, 1992 (51)	104/195(h)	Not specified	<21.5 to ≥25 (tertiles)	1.1[b]
Radimer *et al.*, 1993 (52)	135/321(c)	Not specified	<25 to 35.9 (quintiles) Rel wt (kg/m$^{1.5}$)	0.9[b]
Taioli *et al.*, 1995 (53)	196/191(h)	>24	<21 to ≥27 (quartiles)	0.4[d]
Swanson *et al.*, 1996 (43)	1,588/1,394(c)	20–44	<22 to >28.8 (quartiles)	0.65[d]
Franceschi *et al.*, 1996 (54)	988/840(h)	>23	<21.7 to >28.8 (quintiles)	0.7[d]
Mannisto *et al.*, 1996 (55)	132/184(c)	>25	<21.1 to ≥28.0 (quintiles)	0.9[b]
Chie *et al.*, 1996 (56)	37/37(c)	Not specified	≤21 to ≥25 (tertiles)	1.00[b]
Hu *et al.*, 1997 (57)	84/198(c)	≥25	≤20.9 to ≥23 (tertiles)	0.45[d]

[a] h = Hospital controls.
[b] Not significant.
[c] Numbers are for total pre- and postmenopausal subjects, unable to separate due to presentation.
[d] Significant trend over designated groups by chi-square analysis.
[e] c = community controls.
[f] Age-adjusted for subjects <45 and ≥45 years of age.
[g] Recalculated RR because authors used 24 kg/m^2 as reference value.

weight calculations, Radimer *et al.* (52) reported no differences in RR between premenopausal breast cancer and control subjects. This study also had a relatively small sample size.

Several recent reports have attempted to clarify the relationship of BMI with the development of premenopausal breast cancer. In a meta-analysis, using results from some of the papers cited above, Ursin *et al.* (62) reached the general conclusion that there was a significant trend for decreased RR for premenopausal breast cancer in association with increasing BMI. Using a different approach, Pathak and Whittemore evaluated seven populations representing subjects considered to be at high, medium, or low risk for the development of breast cancer (63). They concluded that the inverse relation of BMI with the RR for development of premenopausal breast cancer was only characteristic of populations that were reported to be at high risk for this type of cancer.

BMI and Case-Control Studies of Postmenopausal Breast Cancer

For postmenopausal women a significant positive trend for RR of development of breast cancer in association with increasing BMI has been reported in 13 case-control studies (Table III) (31, 32, 34, 36, 37, 46, 49, 50, 53, 54, 60, 65, 67). Several additional investigators reported RR similar to that found in the studies cited above, but these values did not reach statistical significance (35, 40–42, 56, 57). When results from one of these studies (40) were combined with data from another study (37), a significant RR of 1.57 for development of postmenopausal breast cancer in association with increasing BMI was obtained (61). However, other studies have reported no significant relationship between BMI (or relative weight) with the RR for the development of postmenopausal breast cancer (38, 44, 45, 47, 51, 52, 55, 59, 65, 66). A number of these studies, as well as two

Table III. Summary of Relative Risk (RR) of Breast Cancer in Relation to Body Mass Index (BMI) in Case-Control Studies—Postmenopausal Women

Author	Subjects/controls (*n*)	Age ranges	BMI ranges	RR
Mirra *et al.*, 1971 (31)	299/755(h)[a]	≥50	<22 to ≥27 (quartiles)	1.6[b]
Staszewski, 1977 (32)	900/581(h)[c]	>50–69	<24 to >30 (quartiles)	2.08[b]
Wynder *et al.*, 1978 (33)	206/513(h)	Perimenopausal	8 levels of BMI	No effect
	256/514(h)	Postmenopausal		No effect
Paffenberger *et al.*, 1980 (34)	1,029/1,778(h)	$\bar{X}$ ~ 63	<21.5 to ≥24.5 (tertiles)	1.39[b]
Helmrich *et al.*, 1983 (35)	693/1,803(h+c[d])	<70	<20.7 to >27 (quartiles)	1.3[e]
Talamini *et al.*, 1984 (36)	275/240(h)	≤79	<25 to ≥30 (tertiles)	2.1[b]
Lubin *et al.*, 1985 (64)	1,065/964(h)	≥60	≤19 to ≥27.1 (quartiles)	2.38[b]
	1,065/981(c)			2.53[b]
Kolonel *et al.*, 1986 (65)	138/154(c)(Japanese)	45–74	Undefined quartiles	1.1[e]
	134/142(c)(Caucasian)			1.2[e]
Toti *et al.*, 1986 (37)	1,107/838(h)	Not specified	<22 to ≥27 (quartiles)	1.50[b]
Hislop *et al.*, 1986 (38)	517/528(c)	<70	≤21 to ≥27 (quartiles)	0.88[e]
Schatzkin *et al.*, 1987 (39)	310/233(h)	<70	≤24 vs ≥30 (tertiles)	2.5[f]
LaVecchia *et al.*, 1987 (40)	646/871(h)	<75	<20 to ≥30 (quartiles)	1.37[e]
Ewertz, 1988 (41)	106/125(c)	Perimenopausal (w/i 5 years)	<20 to ≥32 (quintiles)	1.38[e]
	489/458(c)	Postmenopausal (>5 years)	<20 to ≥32 (quintiles)	1.28[e]
Kampert *et al.*, 1988 (42)	~886/~1,400(h)	50 years old[g]	20 to 28 (quartiles)	1.1[e]
		65 years old[g]	20 to 28 (quartiles)	1.29[b,h]
Swanson *et al.*, 1989 (43)	1,858/1,891	≥50–93	20 to 30 (quartiles)	1.26[b]
	1,017/1,111(c)	Postmenopausal	20 to 30 (quartiles)	1.34[b]
Pryor *et al.*, 1989 (44)	70/88(c)	≤54	≤20.5 to >24.7 (quartile)	0.7[e]
Kyogoku *et al.*, 1990 (66)	213/213(h)/213(c)	Postmenopausal	Undefined quartiles	1.1[e]
Rosenberg *et al.*, 1990 (45)	329/660(h+c)	<70	<21 to ≥26 (tertiles)	1.2[e]
Hsieh *et al.*, 1990 (46)	3,993/11,783(h)	Not specified	+4 kg/m^2	1.11[b]
Bouchardy *et al.*, 1990 (47)	223/429(h)	55–64	<23 to >27 (tertiles)	0.9[e]
	361/694(h)	65–92		1.0[e]
	773/816(c)	Perimenopausal		0.7[e]
Chu *et al.*, 1991 (49)	547/643(c)	<54 natural menopause	<23 to >32.3 (sextiles)	2.7[b]
	625/712(c)	<54 hysterectomy (ovaries remain)		1.0[e]
	325/428(c)	<54 hysterectomy (ovaries removed)		0.5[b]
Graham *et al.*, 1991 (67)	439/494(c)	41–85	≤22 to ≥29 (quartiles)	1.80[b]
Harris *et al.*, 1992 (50)	412/336(h)	>40	<22 to >27 (tertiles)	1.6[b]
Radimer *et al.*, 1993 (52)	185/471(c)	<80	<25 to >35.9 (quintiles) Rel wt (kg/m$^{1.5}$)	0.9
Lee *et al.*, 1992 (51)	82/195(h)	Not specified	<21.5 to ≥25 (tertiles)	0.7[e]
Taioli *et al.*, 1995 (53)	421/340(h)	Not specified	<21 to ≥27 (quartiles)	1.5[b]
Franceschi *et al.*, 1996 (54)	1,574/1,727(h)	50–59	<21.7 to >28.8 (quintiles)	1.1[e]
		60–69		1.5[b]
		≥70		2.9[b]
Mannisto *et al.*, 1996 (55)	195/232(c)	≤75 ($\bar{X}$ ~ 60)	<21.1 to ≥28.0 (quintiles)	0.9[e]
Chie *et al.*, 1996 (56)	50/50(c)	Not specified	≤21 to ≥=25 (tertiles)	2.4[e]
Hu *et al.*, 1997 (57)	63/120	≤75	≤20.9 to ≥23 (tertiles)	1.98[e]

[a] h = Hospital controls.
[b] Significant trend over designated groups by chi-square analysis.
[c] Numbers are for total pre- and postmenopausal subjects, unable to separate due to presentation.
[d] c = community control.
[e] Not significant.
[f] Highest versus lowest significant difference.
[g] Menopause at age 50 years.
[h] Recalculated RR because 24 kg/m^2 used as reference value, no statistics available.

studies with high RR that was not significant, had small sample sizes and/or represented populations with low obesity rates (44, 56, 57, 65, 66). Age of the subjects may also play an important role in the interaction of body weight and postmenopausal breast cancer risk. An example of this is the results of a recent reanalysis of combined data from three Italian studies (37, 40, 68) that included more than 3000 postmenopausal breast cancer subjects over 50 years of age

(69). When all women were combined, a significant increase in risk of 1.40 was found for BMI quintiles ranging from <21.8 to >28.4 kg/m^2. However, when the subjects were divided into three age categories (i.e., 50–59, 60–69, and ⩾70 years of age), a significant increase in the RR for development of breast cancer was found for only the youngest and oldest groups. The results of this study highlight the fact that age, time from menopause, and weight gain may all be important factors in postmenopausal breast cancer risk.

Body Fat Distribution and Breast Cancer

The location of body fat (i.e., body fat distribution) has been shown to have a role in the negative association of excess body fat with a variety of diseases. In particular, upper body obesity (or central or abdominal obesity) has been shown, in women, to be associated with an overall increase in the risk of dying (70), as well as with increased incidence of specific conditions such as cardiovascular disease and diabetes (71–75). Recent interest has also focused on the distribution of body fat to clarify the role of obesity in relationship to breast cancer risk. In 1990, three separate studies indicated an increased RR for breast cancer development in association with abdominal obesity. In a prospective cohort study, height and weight were determined in subjects ~50 years of age of whom approximately one-half were premenopausal, although by the time of breast cancer diagnosis the majority of subjects were postmenopausal (76). For all subjects, there was an RR of 1.7 for breast cancer development associated with the highest quartile for central body obesity (sum of trunkal skinfolds divided by the sum of extremity skinfolds). When only postmenopausal breast cancer subjects were evaluated, the RR was 2.0. In the second study, Schapira *et al.* (77) reported that breast cancer subjects with no designated menopausal status have a higher waist-to-hip ratio, as well as higher abdomen-to-thigh skinfold ratio, than do control subjects. Using subjects from the Iowa Women's Health Study, Folsom *et al.* (30) reported that women with postmenopausal breast cancer had significantly greater waist-to-hip ratios compared with subjects that did not develop breast cancer.

Several additional publications from the Iowa Women's Health Study further support a role for upper body obesity in the development of postmenopausal breast cancer. For example, Sellers *et al.* (24) found that a family history of breast cancer was associated with a higher RR for postmenopausal breast cancer development in association with increased waist-to-hip ratio. Sellers *et al.* (78) later reported that the RR for postmenopausal breast cancer was further increased when a family history of both breast and ovarian cancer was present in association with greater waist-to-hip ratio (i.e., 2.10 for breast cancer alone and 4.83 for both breast and ovarian cancer).

An increased RR for breast cancer development in association with central obesity has also been reported by Bruning *et al.* (79) for postmenopausal breast cancer subjects, but not for premenopausal individuals. Mannisto *et al.* (55) found the RR for breast cancer increased in both premenopausal and postmenopausal Finnish women in association with a greater waist-to-hip ratio. Kodama *et al.* (80) reported that for Japanese breast cancer subjects of all ages the waist-to-hip ratios were higher in comparison with both urban and rural control subjects. Results presented by other investigators, however, have not confirmed this association either for specified postmenopausal and/or premenopausal breast cancer subjects (22, 43, 54) or for breast cancer subjects with no specified menopausal status (81, 82). Schapira *et al.* (83) recently reported that breast cancer subjects who were matched for age, weight, height, BMI, and percent body fat with control subjects had higher visceral fat as assessed by computed tomography. This supports a role for specific locations of body fat in breast cancer development, and that the determination of the relationship of body fat distribution to breast cancer may necessitate the actual determination of body fat at various sites.

Adolescent or Young Adult Body Weight/BMI as a Predicator of Breast Cancer Risk

Another approach employed to determine the potential relationship between body weight/BMI and the development of breast cancer has been to evaluate body weight status of subjects at an earlier age point(s). Prospective studies do this to some extent, since body weight is measured or reported at the initiation of the study and the subjects are followed until cancer has been diagnosed. But, subjects' ages when body weights were obtained, and the lengths of time from body weight measurement/report until breast cancer diagnosis, vary in these studies. Thus, some investigators have attempted to use more consistent age designations. In particular, body weights or BMI's that date from the mid to late teens or early 20s have been the most popular choice.

Several investigators have reported that increased body weight at 18 years of age is associated with a decreased RR for the development of premenopausal breast cancer (17, 38). In an extensive evaluation, Choi *et al.* (84) examined body weights at 15, 20, and 25 years of age, and found, for premenopausal breast cancer subjects, that mean body weight at 15 years of age was significantly lower than the mean body weight of control subjects. Several additional studies have found a significantly lower RR for premenopausal breast cancer in association with elevated BMI at or near 18 years of age (19, 34, 85). Recently, Ursin *et al.* (86) reported that women with premenopausal bilateral breast cancer had reduced BMI at either 18 years of age or at menarche in comparison to their sisters who had not developed breast cancer. LeMarchand *et al.* (87) studied cohorts of Hawaiian women whose body weights were initially obtained as part of the 1942 U.S. Census and were then reobtained in 1972 from state drivers' license records. For one of the five designated cohorts, there was an inverse relation of BMI between 10 and 14 years of age with premenopausal

breast cancer risk. However, for the other four cohorts, no significant effects were reported, and several other studies did not report an association between teenage body weights (or BMIs) and premenopausal breast cancer risk (41, 48, 52). In an additional study, Pryor *et al.* (44) reported an RR of 2.9 for higher versus lower BMI at 12 years of age for developing premenopausal breast cancer, but at 18 years of age the RR was 0.8 for this association. Thus, a number of studies suggest that being heavier as a teenager or young adult may reduce the risk of developing premenopausal breast cancer; but, again, results from all studies have not been consistent.

The relationship between adolescent body weight and the subsequent development of postmenopausal breast cancer also has been investigated. Choi *et al.* (84) found there was no relationship between mean body weight at either 15, 20, or 25 years of age for women who developed postmenopausal breast cancer either between 50 and 69 or after 70 years of age. One study found both higher body weight and relative weight at 25 years of age to be associated with an increased RR of developing postmenopausal breast cancer (52). In a number of other studies, a lower risk for the development of postmenopausal breast cancer in association with elevated BMI as a teenager has been reported (49, 66, 85, 87, 88). In one case, however, this observation was found for only one of five cohorts (87). In an additional study (49), a RR similar to that in the other studies was reported, but it was not statistically significant. In young (less than 54 years of age) women, no association of BMIs from either 12 or 18 years of age was found with the development of postmenopausal breast cancer (44).

Weight Changes from Adolescence in Association with Premenopausal Breast Cancer

Weight changes from adolescence until breast cancer diagnosis have also been investigated as a potential risk factor in the development of both pre- and postmenopausal breast cancer. In one report that did not specify menopausal status, women whose average age was 48 years who had an increase of 8 kg/m^2 BMI units were found to be at increased RR for breast cancer development (89). For Swedish and Norwegian women, Lund *et al.* (48) found no significant effect of change in BMI status from the age of 20 until 18 months prior to diagnosis of premenopausal breast cancer. In an additional study of Finnish women, no significant effect of either weight loss or gain from age 20 was found with respect to the development of premenopausal breast cancer (55). However, Taioli *et al.* (53) and London *et al.* (19) have reported that weight changes of greater than 20 kg are associated with a decreased RR of developing premenopausal breast cancer, and LeMarchand *et al.* (87) have reported that women who had been classified at greater or equal to the median BMI at 10–14 years of age, and who remained in this classification as an adult, had an RR of 0.31 for developing premenopausal breast cancer. In contrast, Chu *et al.* (49) have found that women reported to be of normal weight based on BMI at 18 years of age, but who were overweight as adults, were at increased risk for premenopausal (as well as postmenopausal) breast cancer development compared with women who reported being overweight at 18 and either remained overweight as adults or were no longer overweight. In fact, being overweight at both time points resulted in a slightly lower risk. Brinton and London (85) have reported that the RR for breast cancer development before 50 years of age was significantly lower with weight gain from the age of 20 as reflected by an increased BMI. In a recent study, Ursin *et al.* (86) found that the risk of developing premenopausal bilateral breast cancer was greater with a BMI increase from either the age of menarche or from 18 years of age, although these results did not reach statistical significance. In this case-control study, the control subjects were the sisters of the breast cancer subjects who had not developed breast cancer by the age of diagnosis in the affected sister. Paffenberger *et al.* (34) reported no difference in mean change in BMI from age 20 until interview for premenopausal breast cancer compared with control subjects.

Weight Changes from Adolescence in Association with Postmenopausal Breast Cancer

The association of weight gain since adolescence with development of postmenopausal breast cancer also has been investigated. Lubin *et al.* (64) reported that breast cancer patients had a greater change in BMI status than did surgical control subjects from 18 years of age. Several studies have indicated that increases in either body weight or BMI status from the teenage years until near the time of diagnosis were associated with increased RR for development of postmenopausal breast cancer (19, 30, 34, 50, 64, 90). For example, weight gains greater than 17.3 and 20kg were reported, respectively, by Folsom *et al.* (30) and London *et al.* (19), to result in a 40% and 60% increased RR. Brinton and London (85) reported a significant increased risk of breast cancer development in women over 50 years of age was associated with a greater change in highest adult BMI compared with BMI at 20 years of age but not with weight change until diagnosis. As mentioned earlier, Chu *et al.* (49) have found that women reported to be of normal weight based on BMI at 18 years of age, but who were overweight as adults, were at increased risk for both pre- and postmenopausal breast cancer development compared with women who reported being overweight at 18 and either remained overweight as adults, or were no longer overweight. Similar results for postmenopausal breast cancer were recently published by Barnes-Josiah *et al.* (91), using subjects from the Iowa Women's Health Study. Regardless of BMI reported for 18 years of age, high weight gain from then until diagnosis resulted in an RR of 1.59 for subjects with high BMIs at 18, and an RR of 1.92 for those subjects with low BMIs at 18. However, other reports using relative weights obtained at late teenage years and at diagnosis have indicated no effect of weight change on the development of post-

menopausal breast cancer (52, 55, 65). In an additional study, Kyoguku *et al.* (66) found no effect of weight change from the age of 20 until diagnosis on the development of postmenopausal breast cancer in Japanese subjects, but there was little overall weight change in these women compared with the relative weight changes seen in other populations.

Weight Change during Adulthood on the Development of Breast Cancer

Several recent papers have assessed the role of weight change during adulthood on the development of breast cancer. Taioli *et al.* (53) reported that weight gain of 20 kg during adulthood led to a slightly although not significantly increased RR for the development of postmenopausal breast cancer. In another study (92), recalled body weight at 16, 25, 30, and 40 years of age and at diagnosis was greater at all time points for breast cancer subjects compared with both hospitalized and community control subjects. In particular, more breast cancer than control subjects had substantial weight gain from 16–30 years of age, as well as from 30 years of age until diagnosis. The age range of the women was from 25 to 75 years, and although the results were not presented separately for menopausal status, 80% were reported to be postmenopausal. An additional study has been reported on the effects of adult weight gain on breast cancer development in Asian-American women 20–55 years of age (93). There was a significant increase in the RR for development of breast cancer in women who were in their 50s at diagnosis and who had gained seven or more kilograms during their adult life, but there was not a significant effect of weight gain in women who were in their 30s or 40s at diagnosis. A similar relationship was found for recent weight gain in this population. Furthermore, the RR for breast cancer development for women in their 50s who were above the median for relative weight and had a recent weight gain of more than 5 kg was three times the risk as that for women who were below the median for relative weight and had no recent weight gain. In a study of Italian women, weight gain from age 30 until diagnoses resulted in an RR of 0.8 over quartiles from loss or no gain to a gain of 12 kg for premenopausal breast cancer development and RR of 1.2 for postmenopausal breast cancer, but neither trend reached statistical significance ($P = 0.13$ and 0.16, respectively, for premenopausal and postmenopausal subjects (54).

Few studies have evaluated the role of weight loss on the RR of breast cancer development. One recent study found no effect of self-reports of weight loss either from 22 to 44 or from 45 years of age on the development of postmenopausal breast cancer (55). However, in premenopausal women the RR for breast cancer was significantly reduced in association with weight loss from 45 years of age (55). Shapira *et al.* (94) reported that in 64% of women, ranging from 21–75 years of age, who were evaluated in a weight loss program and who lost 4.5 kg or more had changes in their upper body fat localization. Using these results they calculated that the RR for development of breast cancer in these subjects was reduced by 45%. Menopausal status did not appear to be taken into consideration in this estimate. In an additional study using subjects with and without family histories for breast cancer and the risk factor calculations from the study cited above, Schapira *et al.* (95) concluded that a weight loss of more than 7 kg decreased breast cancer risk by 25.7% in women with a history of familial breast cancer and by 42.8% in women without a history of familial breast cancer. It should be noted that these subjects were not followed to determine the actual rates of breast cancer development.

Obesity and Prognosis following Breast Cancer Diagnosis

Body weight status has also been evaluated with respect to prognosis following diagnosis of breast cancer. A number of studies have shown that obesity/overweight reflected by either body weight or BMI at the time of diagnosis for either premenopausal or postmenopausal breast cancer is associated with earlier recurrence and/or shortened survival (96–115). There are, however, several studies that do not support this observation (116–119). Two additional studies evaluated the effects of premorbid body weight/BMI that were obtained prior to breast cancer diagnosis on the patients' outcome from the disease (120, 121). One study found a negative effect of obesity (120), while the second did not (121). It is interesting to speculate that poorer prognosis reported for African-American women with breast cancer might be related to their higher body weights at cancer diagnosis (122–124). A potential explanation for the impact of obesity on breast cancer prognosis may be due to lower chemotherapy doses implemented to prevent toxicity (125).

Whether body fat distribution plays a role in breast cancer prognosis remains to be determined, since few publications have addressed this issue. Zhang *et al.* (100) found that waist-to-hip ratio upon entry into the Iowa Women's Health Study was not associated with mortality in women who developed postmenopausal breast cancer. In addition, den Tonkelaar *et al.* (118) found that central fat distribution as assessed by skinfold measurements obtained at entry into the DOM project in the Netherlands was not associated with prognosis in women who developed postmenopausal breast cancer. It should be noted that in both these studies the anthropometric measurements were not made at diagnosis but at some earlier time point.

Another factor that is used in the determining of the prognosis of a breast cancer patient is the estrogen receptor status of the tumor. In several studies using subjects with both pre- and postmenopausal breast cancer, it has been found that the percentage of women with estrogen receptor–positive tumors increases as BMI increases (99, 126, 127). However, in an additional study, no differences in BMI status were found between subjects with estrogen receptor–positive or –negative tumors, although both groups with

ages ranging from 20 to 54 years had increased RR for breast cancer as BMI increased (128). As body weight increased so did lymph node involvement. In an additional study, Schapira *et al.,* (129) found in both premenopausal and postmenopausal breast cancer patients that although body weight and BMI were not associated with estrogen receptors in the tumors, women with upper body fat distribution assessed by skinfold measurements had higher levels of estrogen receptors.

In studies where subjects have been separated by menopausal status the association of estrogen receptor–positive tumors with increasing BMI appears to be primarily associated with postmenopausal breast cancer (55, 130–133). In one case (134), however, there was no effect of BMI on estrogen receptor status in women aged 35–64, but the time to recurrence was reduced in obese women with small tumors and estrogen or progesterone receptor–positive tumors. A recently published study has integrated the tumor estrogen and progesterone receptor status with BMI (obtained on average 12.5 years prior to diagnosis, but with a range from 0 to 26 years) and breast cancer prognosis (114). Overall mortality for both pre- and postmenopausal breast cancer subjects was greater beginning 6 years after diagnosis for those classified as obese. When subjects were evaluated separately by estrogen and progesterone receptor status, those who were classified as obese and who were both estrogen and progesterone receptor-positive had an RR of dying of 4.3 compared with an RR of 0.28 for obese women who were negative for both receptors. In contrast, for lean subjects positive receptor status provided a more favorable outcome.

Weight Gain following Cancer Diagnosis

It has been reported that weight gain occurs in many individuals following diagnosis and initial surgery for breast cancer (135, 136). This has been observed in individuals following diagnosis and treatment of the primary tumor (137–144) with and without node-positive classification (139, 140), as well as in subjects with recurrence of cancer (145–148). Although adjuvant therapy appears to result in larger weight gains, even subjects not receiving treatment have been reported to gain weight. However, several recent studies (149, 150) have reported that, in women with advanced breast cancer, treatment with the aromatase inhibitor, anastrozole, resulted in lower weight gains than when treatment was with megestrol acetate. Interestingly, when postmenopausal women were treated with tamoxifen in a study of cardiovascular risk factors, there were no effects on body weight or BMI (151). This supports the weight gain following breast cancer diagnosis is not due to chemotherapy treatment alone. Other psychosocial factors associated with coping with the diagnosis of breast cancer have also been implicated. Some studies have suggested that premenopausal women may be at greater risk for large weight gains in comparison with postmenopausal women (138, 139, 141, 144).

There have been few attempts to evaluate the consequences of this weight gain during treatment on long-term prognosis. Camoriano *et al.* (139) reported an increased relapse rate associated with weight gain in one study where both premenopausal and postmenopausal subjects were followed for a median of 6.6 years (139). In another study (147), all subjects with a weight gain of over 10 kg were reported to have died after a 10-year follow-up. A number of factors, such as increased food intake, decreased physical activity or resting metabolic rate, and serum hormones such as estradiol (137, 140, 152, 153), have been evaluated to determine their potential role in this weight gain, but no definitive causal factor has been identified.

Several studies have implemented interventions to prevent weight gain associated with treatment. In one study, premenopausal women receiving adjuvant chemotherapy were either provided with nutrition counseling from a dietitian or were given standard counseling from either physicians or nurses (154). In the dietitian-counseled group, 28% of the subjects gained 2–5 kg and 19% gained more than 6 kg, while in the control group 32% gained 2–5 kg and 24% gained more than 6 kg. These differences were not significantly different. In another study (143), the interactions of a low-fat (20%) diet and tamoxifen treatment were determined at 6, 12, and 18 months following initiation of treatment. Tamoxifen treatment appeared to prevent the weight loss observed when subjects were in the low-fat diet group.

Animal Studies of Obesity and Breast Cancer

Surprisingly, the use of animal models where many variables can be controlled has been limited in the breast cancer epidemiology field. In one study using dogs, obesity (reported by the pets' owners) 1 year prior to breast cancer diagnosis was not a risk factor (155). Dogs with breast cancer were compared with both cancer control and noncancer control dogs and were matched for age of diagnosis, spay status, and size. It was found that spayed dogs that were thin at 9–12 months of age had a significantly decreased risk of developing breast cancer. There was also a lower risk in intact dogs that were reported to be thin at this age; however, the results did not reach statistical significance.

There are several pertinent studies, however, that have been reported using various rodent models. In one series of experiments, spontaneously developing mammary cancer appeared at 242 days of age in mice made obese by administration of gold-thioglucose, compared with 303 days of age in mice that did not become obese (156). Interestingly, food restriction delayed the appearance of tumors in these obese mice (157, 158). In general, the incidence of spontaneous mammary tumors has been found to correlate with body weight in both mice and rats (159, 160). However, it was reported in obese (ob/ob) mice that were the F_2 offspring of C3H and Vob cross that there was a lower incidence of spontaneous tumors in these mice, though tumors generally appeared at a much earlier age in these obese mice

(161). In an additional study, using genetically obese (A^{vy}/A) mice treated with the chemical carcinogen dimethylbenz[a]anthracene (DMBA), mammary tumors developed more frequently than in comparably treated lean mice (162). In the one study reporting on the use of genetically obese rats, Klurfeld *et al.* (163) found that DMBA-treated (LA/N) corpulent rats had a 100% incidence of mammary tumors in comparison with either a 27% or a 21% incidence in DMBA-treated food-restricted corpulent or DMBA-treated lean rats, respectively. Thus, although limited in number, these studies in rodents further support a role for elevated body weight and/or body fat in the development of breast cancer.

In addition to the studies cited above, it has been widely reported that food restriction decreases both the incidence and latency of breast tumors in rodents (164–169). These results have been interpreted to be due to the lower energy intake of food-restricted animals. However, two recent publications (170, 171) suggest an alternative explanation. Harris *et al.* (171) have reported that rats treated with DMBA and subjected to periods of intermittent energy restriction followed by ad libitum feeding, and consequently to periods of weight loss and regain, had a similar incidence of mammary tumors as ad libitum fed rats, while chronically food-restricted rats had a much lower incidence of mammary tumors. Weight gain, energy intake, and feed efficiency were all highly correlated with tumor incidence. In the second study, methyl-*N*-nitrosourea–treated rats were subjected to either chronic or cyclic food restriction or were ad libitum fed (170). Although both intervention groups had similar body weights, caloric intakes, and fat-pad weights, the incidence of mammary tumors was significantly higher in the weight-cycled compared with the ad libitum fed rats. Together, these animal model studies using dietary intervention suggest that weight gain may be the key dietary factor in the development of breast cancer.

Potential Mechanisms for the Role of Body Weight in Breast Cancer Development

The information presented suggests that under some circumstances, which remain to be clearly delineated, body weight, body fat and/or its distribution, and/or weight gain may separately or in combination play a role in the development of breast cancer and also in its prognosis. It is clear that this subject needs to be more carefully investigated to identify the specific factors involved, and to determine those stages in the life cycle when they may be of particular importance. This is a challenge given the fact that, as recently pointed out by Ballard-Barbash (172), body weight does not have to remain constant. In addition, body weight and changes in body weight can be affected by genetic, as well as environmental factors—that is, there are multiple regulatory mechanisms governing body fatness.

Despite the complex nature of this problem, some conclusions can be drawn concerning the relationship between body weight and breast cancer risk. In younger subjects, higher body weight, primarily reflected as elevated BMI, appears to offer a protective effect with respect to the development of premenopausal breast cancer. It is not clear how this is mediated. It has been speculated that obese women have more anovulatory menstrual cycles, which in turn result in lower circulating progesterone and estradiol levels (173–175). This consequently results in decreased exposure of breast tissues to these hormones, resulting in lower rates of breast epithelial cell proliferation (62). In partial support of this hypothesis, a recent study (176) found that in premenopausal women decreasing total serum estradiol levels correlated with increasing BMI levels, although this difference was not statistically significant ($P = 0.11$), and no differences were observed in free estradiol levels. In addition, serum hormone binding globulin (SHBG) levels were significantly decreased with increasing BMI. In the same study, postmenopausal women also had decreasing SHBG with increasing BMI, but total and free estradiol values were significantly increased. These changes suggest that a different relationship may exist between these factors in pre- and postmenopausal women. Others have hypothesized that breast cancer risk is related to the cumulative number of ovalutory cycles (177). How or whether the associated changes in hormonal milieu might protect premenopausal women from breast cancer remains to be determined.

In the mid-1970s, elevated levels of estrone and several androgens were implicated as risk factors in the development of postmenopausal breast cancer, and elevated SHBG was found to be protective (178). Additional studies reported that there appeared to be an inverse relationship between the risk of postmenopausal breast cancer and serum SHBG levels (179–182) and/or high estrone/estradiol levels (179–181). Obesity in both pre- and postmenopausal women has been characterized by low levels of SHBG (183–185). This suggests that this metabolic disturbance may be a consequence of the obesity.

A recent publication by Lipworth *et al.* (186) has integrated some of these findings. These investigators reported that the inverse correlation of SHBG and postmenopausal breast cancer was accentuated when measured hormome levels and BMI were controlled. Although this would support a role for free estrogen (resulting from low SHBG levels) in the increased risk of breast cancer in obese women, an alternative explanation proposed by Lipworth *et al.* (186) is that SHBG concentrations are controlled by the high serum insulin and/or insulin-like growth factor–I (IGF-I) levels that are characteristic of obese women.

In addition, direct effects of insulin and insulin-like growth factors on the development of breast cancer have been proposed (187–190). Both insulin and IGF-I have been shown to have growth stimulatory effects on breast cancer cell lines (191–198). Effects on proliferation mediated through IGF receptors have also been reported (199). Defects in insulin and insulin-like growth factors have been identified in human breast cancer cell lines to result in increased cell proliferation (200). In addition, studies in rats

have shown that experimentally induced diabetes can result in the cessation of chemically induced mammary tumor growth; but, when these rats are treated with insulin, tumor growth resumes (201, 202). Finally, food restriction in rats has also been shown to result in lower serum insulin and/or IGF-I levels in conjunction with a lower incidence of DMBA-induced mammary tumorigenesis (203).

Results from human studies have also supported a potential role for insulin and IGF-I in the development of breast cancer. In a case-control study designed to evaluate lifestyle factors in relation to the risk of breast cancer, Bruning *et al.* (204) have found that women with early breast cancer development had higher serum levels of C-peptide than did control subjects who had other types of malignancies (melanoma, lymphoma, or cervical cancer). SHBG was found to be inversely related to C-peptide, while estradiol and triacylglycerol were positively related. The authors indicated that insulin resistance, independent of either BMI or waist-to-hip ratios, was a significant risk factor for breast cancer. Others have also speculated that elevated insulin levels, insulin resistance, and/or IGF-I may be involved in the development of breast cancer (189, 204–206). In one recent report, serum IGF-I levels were found to be increased in subjects with premenopausal breast cancer while IGFBP-3 was found to be decreasing resulting in a significant elevation of the ratio of IGF-I to IGFBP-3 compared with control subjects (207). This was not found, however, in postmenopausal breast cancer subjects. In an additional study, Rocha *et al.* (208) reported that IGFBP-3 mRNA and protein levels in human breast tumor samples were 3-fold higher in subjects with poor prognosis. Webster *et al.* (209) recently reported that levels of insulin and IGF-I receptors were positively correlated with p53 overexpression in primary human breast tumors. Increased insulin receptor numbers have also been associated with human breast cancers (210). Interestingly, tamoxifen treatment has been shown to result in lowered IGF-I levels, potentially playing a role in its therapeutic action (211).

Conclusions

As described in this review, weight gain may have an effect on the development of breast cancer regardless of age and independent of obesity itself. French *et al.* (212) have reported that 47% of women from a sample in the Iowa Women's Health Study reported continuous weight gain during their adult life, and another 17% reported a one-time weight gain of over 20 pounds in adulthood that was then maintained. Although it has not been easy to evaluate the effects of weight cycling in humans, there is the perception that individuals who lose weight usually regain it, and that even normal-weight women lose and regain weight (213). Several recent studies have indicated that approximately 40% of women contacted were trying to lose weight (13, 214, 215). This once again included women considered to be in normal weight ranges. Given the fact that most individuals do not maintain their lost weight, the impact of weight gain may be substantial. Furthermore, although one could argue that the RR of developing breast cancer in relation to higher BMI or weight gain is not very great particularly in comparison with a family history of breast cancer, when one consideres the recent reports of increasing numbers of overweight and obese women in the United States and other countries (1–3) the number of individuals potentially affected by this risk factor is quite high.

Overall it seems clear that body weight, weight gain, and/or body fat and body fat distribution probably have significant clinical implications for the development of human breast cancer and its prognosis. However, sorting out all the factors potentially involved has been and will continue to be an arduous task in humans. For example, it remains to be determined if other growth factors and oncogene products are affected by obesity and weight gain, and whether they hold the key to this perplexing interrelationship of body weight and breast cancer risk. The development of more relevant animal models in which molecular correlation between obesity and breast cancer can be studied in detail, as well as continued efforts to understand the growth regulatory pathways governing breast carcinoma cell growth, should provide new insights into this complex problem.

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