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EPIDEMIOLOGY

Body mass index and HER-2 overexpression in breast cancer patients over 50 years of age

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Abstract
Purpose In breast cancer, in vitro as well as in vivo experiments have shown an inverse relationship between HER-2 and steroid hormone receptors. It is unknown whether circulating estrogens affect HER-2 expression. We hypothesize that the postmenopausal body mass index (BMI) as a surrogate marker for bio-available estrogens, is inversely associated with HER-2 over-expression.
Patients and methods A total of 535 women over age 50 or with known postmenopausal status, with a unilateral, not previously treated, operable breast cancer were evaluated the evening prior to surgery for body weight, height, abdominal and hip circumference over a 3 years period. Waist-to-hip ratio (WHR) and BMI were calculated. HER-2, estrogen receptor and progesterone receptor staining was done by immunohistochemistry. All tumours with DAKO 2+ staining were submitted for HER-2 detection by FISH analysis. HER-2 was defined as positive if DAKO 3+ or FISH positive. We assessed the frequency of HER-2 positivity in each of 6 quantiles for all parameters of body composition and tested for a trend in HER-2 expression across the 6 quantiles. Furthermore, we investigated whether BMI contributed, together with other known predictors for HER-2, in a standard multivariate logistic regression model that predicts HER-2 over-expression.
Results There is a decrease in HER-2 over-expression per increasing quantile of BMI. In a multivariate model—including both steroid receptors—BMI remains an independent predictor for HER-2 over-expression.
Conclusion In women over age 50 or with known postmenopausal status with an operable breast cancer, there is an inverse association between BMI and HER-2 over-expression.

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Introduction

The proto-oncogene HER-2/neu, also known as c-erb-B2, is located on chromosome 17 q11.2–12 and encodes a transmembrane receptor tyrosine kinase that mediates growth and differentiation of cells [1, 2]. HER-2 is over-expressed in about 10–30% of early [3] and in up to 52% of inflammatory breast cancers [4]. Over-expression of HER-2 is associated with other tumour characteristics such as lower levels of steroid receptors, a high histologic tumour grade, a high cell proliferation rate, lymph-node involvement and relative resistance to certain types of chemo and hormonotherapy [5]. With the introduction of trastuzumab (Herceptin ®), a humanized monoclonal antibody against HER-2, this receptor has become a therapeutic target; large trials recently confirmed a place for trastuzumab in the adjuvant [6, 7] and in the metastatic setting [8].

HER-2 over-expression is inversely associated with the estrogen receptor (ER) and, in women with an ER^+ breast cancer, also with the progesterone receptor (PR) [9–13]. In our population, HER-2 over-expression occurs in 10.9% of all primary operable breast cancers (28.7% in ER^- and 6.8% in ER^+ tumours, respectively).

It is unknown whether circulating estrogens influence the incidence of HER-2 positive breast cancers. However, in vitro and in vivo data might suggest such an association. Indeed, estrogens are able to inhibit c-erbB-2 oncogene expression in human breast cancer cell lines and ER^+ human breast cancer cells transfected with the HER-2 gene express lower levels of steroid receptors than the parental lines [14–16]. Clinical data do also suggest this. Indeed, if the PR, which is an end-product of an estrogen-activated ER, is expressed in ER^+ breast cancers, one supposes the presence of sufficient levels of circulating oestrogens to activate the hormone receptor pathway (Fig. 1); such an ER^+PR^+ breast cancer phenotype is least likely to over-express HER-2. If, on the other hand, the PR is absent in the presence of the ER, it is likely that available estrogens are insufficient to activate the steroid hormone depend tumour growth pathway, which then leads to tumour growth through another growth factor pathway (like the HER-2 pathway). This cross talk between steroid receptors and growth factors like HER-2 therefore suggests a link between circulating estrogens and HER-2 [17].

We recently observed that the association between HER-2 and both hormone receptors is mainly seen in older women [12, 13] where body fat correlates well with serum estrogen levels [18, 19]. We therefore now hypothesise that there will be a lower incidence of HER-2 over-expression in obese than in lean postmenopausal women.

Patients and methods

During a 3-year period (January 2002–December 2004), all patients admitted to the University Hospitals

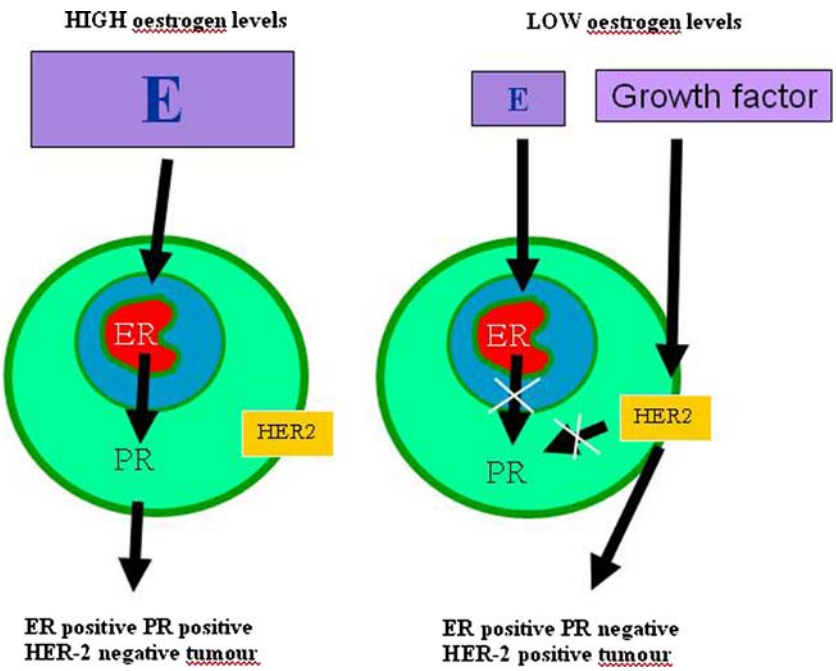

Fig. 1 Cross-talk between oestrogen en growth factor signaling pathway [17]. Legend: E, Oestrogen; ER, Oestrogen receptor; PR, Progesterone receptor

Leuven for surgical breast cancer treatment, were prospectively assessed for body weight, length, abdominal (AC) and hip circumference (HC). Measurements were done in a standardised way the evening before surgery by the ward nurse: the abdominal circumference was measured at the level of the minimal waist circumference in a standing position. When this place was not easily observed, several measurements were taken at probable sites and the minimal circumference was recorded. The hip circumference was measured at the level of the greatest protrusion of the gluteus muscle. Both measurements were done with attention to measure in a plane horizontal to the floor and to have direct contact between the skin and the measuring tape, without compressing the soft tissues. BMI [Weight in kg/(Length in m)^2] and waist-to-hip ratio (WHR = AC in cm/HC in cm) were calculated.

After surgery, histological tumour size, grade en lymph node status as well as ER, PR and HER-2 status were noted in a central computer based pathology file system. In our hospital, immunohistochemical (IHC) staining for ER, PR and HER-2 is semi-quantitatively done on a routine basis for clinical purposes. This was carried out for ER, PR and HER-2 according to the Envision method using respectively the NCL-ER-6F11/2, NCL-PgR-312 and CB11 antibodies. Using the H- or Allred-score for both hormone receptors, a positive result was defined as a score higher than 50/300 or 2/8, respectively. The DAKO scoring system was used to evaluate HER-2 staining. Tumours with a DAKO 0 or 1+ score were categorised as HER-2 negative. Tumours with a DAKO 2+ score were submitted for fluorescence in situ hybridisation (FISH) to determine HER-2 gene expression. HER-2 over-expression was defined as a DAKO 3+ score (this is complete membrane staining in over 10% of tumour cells) or HER-2 positivity on FISH analysis. All ER and PR readings were done by 1 pathologist (RD). HER-2 readings were validated by 2 independent readers (RD and IVB).

For this study, we reviewed the records of all patients above age 50, or with known postmenopausal status defined as a history of amenorrea for more than 1 year or elevated plasma levels of luteinizing and follicle stimulating hormone. Patients with in situ breast cancer only, bilateral breast cancer, previous breast cancer therapy of any kind or those with insufficient data were excluded.

Univariate and multivariate analyses were performed using the SAS software package (Release 9.1.3). Mean values and standard deviations (SD) were calculated for all parameters of body composition and compared between HER-2 negative and HER-2 positive patients. We used the *t* test (for continuous data) to calculate *p*-values that reflect whether there is a significant difference for a certain variable between HER-2 negative and HER-2 positive patients. The pooled *t* test was used in case of equal variances in both groups of patients, while the Satterthwaite *t* test was used in case of unequal variances. Patients were then divided in 6 quantiles from the lowest (Q1) to the highest (Q6) for each parameter of body composition and the frequency of HER-2 over-expression per quantile was calculated. The Cochran–Armitage test was used to test for a trend in HER-2 expression across the 6 quantiles for each parameter of body composition. Next, we used the Fisher's exact test to identify significant differences in clinicopathological features between HER-2 negative and HER-2 positive patients. Odds ratios and their 95% confidence intervals were calculated. Finally, with multivariate logistic regression analysis we aimed to investigate whether the parameters of body composition (based on the actual numeric values) that were found to be statistically significant for the prediction of HER-2 over-expression in univariate analyses also significantly contributed in a standard logistic regression model. The standard logistic regression model was fitted with the LOGISTIC procedure from SAS. The Wald Chi-Square statistic was used to assess the significance of the coefficient of the different variables (p-value < 0.05).

Results

Sufficient data were obtained in 535 patients. Their clinicopathological tumour characteristics are presented in Table 1 .The overall incidence of HER-2 positivity was 11.8%. Median age did not differ significantly between HER-2 positive and HER-2 negative patients (61 years (range 47–86) vs. 63 years (range 40–91) respectively; $p = 0.43$). Table 2 compares mean values of parameters of body composition between HER-2 negative and HER-2 positive patients. Mean length and weight did not differ significantly between both groups. The mean BMI however was significantly lower when comparing HER-2 positive to HER-2 negative cases (25.4 kg/m^2 vs. 26.9 kg/m^2 respectively; $p = 0.04$). Other parameters of body fat distribution (AC, HC and WHR) did not show statistically significant different values between HER-2 negative and HER-2 positive cases.

The distribution of HER-2 positive tumours per quantile of the total population is set out in Table 3 for all parameters of body composition separately. More than a fifth of the HER-2 positive tumours occurred

Table 1 Clinicopathological patient and tumour characteristics

	N	%
HER-2 status		
negative	472	88.2
positive	63	11.8
ER expression		
negative	81	15.2
positive	453	84.8
PR expression		
negative	166	31.3
positive	365	68.7
Tumour grade		
grade 1–2	330	62.1
grade 3	201	37.9
Tumour size		
≤20 mm	262	49.0
>20 mm	273	51.0
Lymph node		
negative	360	67.3
positive	175	32.7
BMI (kg/m^2)		
<20	37	6.9
20–25	230	43.0
26–30	170	31.8
31–35	70	13.1
>35	28	5.2
Total	535	100.0%

in the lean (Q1) patients, whereas only 10% of the tumours was seen in the obese patients (Q6). Moreover, when considering all quantiles, we see a decrease in HER-2 positivity with increasing BMI. This trend proved to be statistically significant ($p = 0.05$). When using BMI classes in stead of the quantiles, we could see that in the patient population with a BMI < 20 kg/m^2 21.6% of the tumours were HER-2 positive. In the categories of 20–25 kg/m^2, 26–30 kg/m^2 and > 30 kg/m^2 respectively, only 12.6%, 11.2% and 7% of the tumours were HER-2 positive. Table 4a shows the univariate model including histopathological tumour characteristics. ER (OR: 0.17; CI: 0.09–0.32) and PR positive tumours (OR: 0.23; CI: 0.10–0.34) had a lower chance of being HER-2 positive whereas tumours that were greater in size (OR: 1.93; CI: 1.08–3.51) or of higher grade (OR: 5.82; CI: 3.11–11.35) were more often associated with HER-2 positivity.

When generating a multivariate logistic regression model, taking in account BMI and the other know predictors for HER-2 status (ER, PR, tumour size, tumour grade and lymph node status), the inverse relation between BMI and HER-2 over-expression persisted ($p = 0.04$) (Table 4b).

Discussion

These findings in 535 patients show that BMI is an independent predictor of HER-2 in a multivariate model with tumour grade, size and both hormone receptors as suggested in our hypothesis. The inverse relation between BMI and HER-2 could be mediated by a hormonal pathway. Indeed, postmenopausal obesity is associated with higher levels of bio-available

Table 2 Mean values for body composition by HER-2 status in all patients

	HER-2 negative		HER-2 over-expression		*p*-value
	N	mean ± SD	*N*	mean ± SD	
Length (cm)	472	161.1 ± 8.3	63	161.7 ± 6.3	0.55
Weight (kg)	472	69.0 ± 13.1	63	66.3 ± 11.6	0.11
Abdominal circumference (cm)	471	94.0 ± 14.2	63	91.2 ± 13.4	0.14
Hip circumference (cm)	472	103.9 ± 12.2	63	101.4 ± 9.6	0.06
BMI (kg/m^2)	472	26.9 ± 9.2	63	25.4 ± 4.5	0.04
WHR	471	0.9 ± 0.1	63	0.9 ± 0.1	0.53

Table 3 Trend analysis showing the distribution of HER-2 positive tumours amongst the 6 quantiles for each parameter of body composition separately

	HER-2 distribution amongst quartiles in absolute numbers (%)							
	Q1	Q2	Q3	Q4	Q5	Q6	Total	*p*-value
Length	12 (19%)	7 (11%)	11 (17%)	15 (24%)	7 (11%)	11 (17%)	63 (100%)	0.96
Weight	13 (21%)	13 (21%)	11 (17%)	11 (17%)	7 (11%)	8 (13%)	63 (100%)	0.08
AC	15 (24%)	7(11%)	9 (14%)	18 (29%)	7 (11%)	7 (11%)	63 (100%)	0.21
HC	10 (16%)	17 (27%)	9 (14%)	9 (14%)	13 (21%)	5 (8%)	63 (100%)	0.13
BMI	14 (22%)	13 (21%)	10 (16%)	10 (16%)	10 (16%)	6 (10%)	63 (100%)	0.05
WHR	13 (21%)	6 (10%)	10 (16%)	12 (19%)	13 (21%)	9 (14%)	63 (100%)	0.91

AC: Abdominal circumference, HC: Hip circumference

Table 4 Tumour characteristics and parameters of body composition predicting HER-2/neu over-expression in all patients

	HER-2		Odd ratio (95% CI)	*p*-value
	Positive	Negative		
(a) Univariate analysis				
ER status				
positive	8.0%	92.0%	0.17 (0.09–0.32)	<0.001
negative	33.3%	66.7%		
PR status				
positive	6.6%	93.4%	0.23 (0.10–0.34)	<0.001
negative	23.5%	76.5%		
Tumor grade				
grade 3	22.9%	77.1%	5.82 (3.11–11.35)	<0.001
grade 1–2	4.9%	95.1%		
Tumor size				
>20 mm	15.0%	85.0%	1.93 (1.08–3.51)	0.02
≤20 mm	8.4%	91.6%		
Lymph node				
positive	14.9%	85.1%	1.52 (0.85–2.69)	0.15
negative	10.3%	89.7%		
(b) Multivariate analysis				
ER status (negative versus positive)			0.377 (0.167–0.852)	0.02
PR status (negative versus positive)			0.500 (0.238–1.051)	0.07
Tumor grade (grade 3 versus grade 1–2)			3.181 (1.633–6.198)	<0.01
Tumor size (≤20 mm versus >20 mm)			2.021 (1.077–3.791)	0.03
Lymph node status (negative versus positive)			1.419 (0.775–2.600)	0.26
BMI			0.933 (0.874–0.995)	0.04

estrogen due to aromatisation of androstenedione to estrogen in the adipose tissue and due to decreased levels of sex hormone binding globulin (SHBG) [18, 19]. This estrogen has already been show to downregulate HER-2 in human breast cancer cell lines [14, 16]. Definitive conclusions on this pathway however cannot be drawn from our study as we did not determine estrogen and SHBG levels.

A few case-control studies already addressed the effect of body composition on HER-2 expression in postmenopausal breast cancer. Most of them found a positive correlation between BMI and the risk of postmenopausal breast cancer in general, but not between BMI and HER-2 positive cancers specifically [20–22]. Only a small study including 250 postmenopausal patients mentioned a 2 times higher incidence of HER-2 positive than HER-2 negative cancers in obese (BMI > 29 kg/m2) postmenopausal patients [23]. However, when stratifying for ER, this difference lost statistical significance.

HER-2 over-expression is considered as an important prognostic factor for poor breast cancer outcome [5]. A lower likelihood for obese women to be HER-2 positive does not fit with the generally accepted belief that women with a greater BMI have less favourable outcomes from breast cancer than lean women [24]. However, the small lower likelihood of HER-2 positivy in obese women may easily be counteracted by other poor prognostic factors more frequently seen in obese patients such as larger tumours and a greater number of involved lymph nodes at first breast cancer diagnosis [25]. Also, not all reports agree with the fact that obesity remains a negative predictor when stratified for these other variables and some suggest that the poorer overall survival in obese breast cancer patients may be due rather to non-breast cancer than to breast cancer related death [26, 27].

HER-2 is considered as a predictor for a lower response to anti-estrogens like tamoxifen in postmenopausal women [28]. A higher likelihood of HER-2 positivity in lean women suggests that tamoxifen may be less effective in these patients. However, recent data from the NSABP-14 trial do not show a BMI-dependent effect of tamoxifen on reducing breast cancer recurrence and mortality [26]. An interesting finding from this trial however was that underweight women had lower ER and PR levels than obese patients. As this phenotype with lower hormone receptor levels is

related to a higher prevalence of HER-2 positivity, this empowers our findings on the inverse relation between BMI and HER-2.

Other parameters of body fat distribution like AC, HC and WHR did not predict HER-2 status in our study. However, mean values for all parameters, except for length, were lower in the HER-2 positive cases (table 2).

A weakness in our study is that we defined HER-2 over-expression as an IHC 3+ result or a DAKO 2+ result combined with FISH positivity. However, this should not show major differences with FISH-only determination of HER-2 status as the concordance rate between FISH and IHC 3+ is 96,1% and the negative predictive value of an IHC 0 or 1+ score is 97.2% [29]. On the other hand, IHC testing with selective FISH confirmation of IHC 2+ results has the advantage of being less time consuming and cheaper [29].

The overall HER-2 incidence in our population (11.8%) may seem lower than published in other reports, but seems acceptable when compared with the recently reported data for HER-2 over-expression in postmenopausal women in the BIG/Femta trial [30].

Another restriction of our study is that we did not dispose of direct fat volume measurements such as those that could be obtained by under water weighing, CT-scan, ultrasound or skin fold thickness measurements. BMI gives nevertheless a good estimate of the total body fat and is a widely used and clinically relevant method for obesity assessment, whereas WHR is used to evaluate the body fat distribution (central versus peripheral) [31]. Moreover, our anthropometric data are very robust as they were collected in a standardised prospective way.

In conclusion, we demonstrated for the first time that BMI, as a surrogate marker for estrogens, is inversely related with HER-2 over-expression in women over age 50—or with known postmenopausal status—with a unilateral operable invasive breast cancer. These results should of course be confirmed in larger series and further research must be aimed at documenting the exact pathway leading from BMI to HER-2. Bio-available estrogens might be a possible mediator.

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References

1. Akiyama T, Sudo C, Ogawara H et al (1986) The product of the human c-erB-2 gene: a 185-kilodalton glycoprotein with tyrosine kinase activity. Science 232:1644–1646
2. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL (1987) Human breast cancer: correlation of relapse and survival with amplification on HER-2/neu oncogene. Science 235:177–182
3. Thor AD, Schwartz LH, Koerner FC et al (1989) Analysis of c-erbB-2 expression in breast carcinomas with clinical follow-up. Cancer Res 49:7147–7152
4. Parton M, Dowsett M, Ashley S, Hills M, Lowe F, Smith IE (2004) High incidence of HER-2 positivity in inflammatory breast cancer. Breast 13:97–103
5. Ross JS, Fletcher JA, Linette GP et al (2003) The HER-2/neu gene and protein in breast cancer 2003: Biomarker and target of therapy. The Oncologist 8:307–325
6. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353:1659–1672
7. Romond EH, Perez EA, Bryant J et al (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2 positive breast cancer. N Engl J Med 353:1673–1684
8. Slamon DJ, Leyland-Jones B, Shak S et al (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783–792
9. Ciocca DR, Fujimura FK, Tandon AK et al (1992) Correlation of HER-2 amplification with expression and with other prognostic factors in 1103 breast cancers. J Natl Cancer Inst 84:1279–1282
10. Konecny G, Pauletti G, Pegram M et al (2003) Quantitative association between HER-2/neu and steroid hormone receptors in hormone receptor-positive primary breast cancer. J Natl Cancer Inst 95:142–153
11. Huang HJ, Neven P, Drijkoningen M et al (2005) Association between tumour characteristics and HER-2/neu by immunohistochemistry in 1362 women with primary operable breast cancer. J Clin Pathol 58:611–616
12. Huang HJ, Neven P, Drijkoningen M et al (2005) Association between HER-2/neu and the progesterone receptor in oestrogen-dependent breast cancer is age-related. Breast Cancer Res Treat 91:81–87
13. Huang HJ, Neven P, Drijkoningen M et al (2005) Hormone receptors do not predict the HER2/neu status in all age groups of women with an operable breast cancer. Ann Oncol 16:1755–1761
14. Russell KS, Hung MC (1992) Transcriptional repression of the neu proto-oncogene by estrogen stimulated estrogen receptor. Cancer Res 52:6624–6629
15. Dati C, Antoniotti S, Taverna D, Perroteau I, De Bortoli M (1990) Inhibition of c-erbB-2 oncogene expression by estrogens in human breast cancer cells. Oncogene 5:1001–1006
16. Pietras RJ, Arboleda J, Reese DM et al (1995) HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. Oncogene 10:2435–2446
17. Osborne CK, Schiff R, Arpino G, Lee AS, Hilsenbeck VG (2005) Endocrine responsiveness: understanding how progesterone receptor can be used to select endocrine therapy. Breast 14:458–465
18. Siiteri PK (1987) Adipose tissue as a source of hormones. Am J Clin Nutr 45:277–282
19. Schapira DV, Kumar NB, Lyman GH (1991) Obesity, body fat distribution, and sex hormones in breast cancer patients. Cancer 67:2215–2218
20. Treurniet HF, Rookus MA, Peterse HL, Hart AA, Van Leeuwen FE (1992) Differences in breast cancer risk factors to neu (c-erbB2) protein overexpression of the breast tumor. Cancer Res 52:2344–2345

21. Gammon MD, Hibshoosh H, Terry MB et al (1999) Oral contraceptive use and other risk factors in relation to HER-2/neu overexpression in breast cancer among young woman. Cancer Epidemiol Biomarkers Prev 8:413–419
22. Huang WY, Newman B, Millikan RC et al (2000) Risk of breast cancer according to the status of HER-2/neu oncogene amplification. Cancer Epidemiol Biomarkers Prev 9:65–71
23. Tsakountakis N, Sanidas E, Stathopoulos E et al (2005) Correlation of breast cancer risk factors with HER-2/neu protein overexpression according to menopausal and estrogen receptor status. BMC Women's Health 5:1
24. Berclaz G, Li S, Price KN et al (2004) Body mass index as a prognostic feature in operable breast cancer: the international breast cancer study group experience. Ann Oncol 15:875–884
25. Chlebowski RT, Aiello E, McTiernan A (2002) Weight loss in breast cancer patient management. J Clin Oncol 20:1128–1143
26. Dignam JJ, Wienand K, Johnson KA, Fisher B, Xu L, Mamounas E (2003) Obesity, tamoxifen use and outcomes in women with estrogen receptor-positive early stage breast cancer. J Natl Cancer Inst 95:1467–1476
27. Kroenke CH, Chen WY, Rosner B, Holmes MD (2005) Weight, weight gain and survival after breast cancer diagnosis. J Clin Oncol 23:1370–1378
28. Dowsett M, Harper-Wynne C, Boeddinghaus I et al (2001) HER-2 amplification impedes the antiproliferative effects of hormone therapy in estrogen receptor-positive primary breast cancer. Cancer Res 61:8452–8458
29. Yaziji H, Goldstein LC, Barry TS et al (2004) HER-2 testing in breast cancer using parallel tissue-based methods. JAMA 291:1972–1977
30. Viale G, Regan M, Dell'Orto P et al (2005) Central review of ER, PgR and HER-2 in BIG 1–98 evaluating letrozole vs. tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. San Antonio Breast Cancer Symposium, Abstract 44
31. NHLBI expert panel on the identification, evaluation and treatment of overweight and obesity in adults (1998) Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults: the evidence reports. Obes Res 6 (suppl 2):51S–209S