The Effect of Weight Gain on Recurrence During Hormonal Therapy in Breast Cancer with Positive Estrogen Receptor and Negative Her2 Subtype

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ABSTRACT

Background. Weight gain is found in patients with positive estrogen subtype breast cancer. The effect of weight gain on breast cancer recurrence is still being debated and associated with a poor prognosis. Being overweight is associated with an increase in estrogen production by adipose tissue.
Methods. A retrospective and prospective cohort study with data collection was conducted from July 2018 - June 2019 at the outpatient unit of Dr. Sardjito Hospital. We reviewed medical records of patients who came from January 2013 - July 2018. Three categories of weight gain: weight loss, increase 0 - 5%, and increase > 5% from baseline will be evaluated.
Statistical Analysis. The relationship between weight gain and some risk factors of recurrence was analyzed with cox regression and multivariate logistic regression tests. The Kaplan Meier method is used to show lifetime data.
Result. Weight gain in breast cancer patients with positive Her2-negative estrogen receptor subtypes was not associated with recurrence (p = 0.264; HR 0.637; 95% CI 0.289 - 1.405). Patients with body mass index ≥ 25 kg / m^2 at diagnosis had a lower risk of relapse than patients with body mass index < 25 kg / m^2 (p = 0.026; HR 0.461; 95% CI, 0.234 - 0.912).
Conclusions Weight gain after diagnosis in breast cancer patients with positive estrogen receptor-negative Her2 subtypes receiving hormonal therapy is not associated with recurrence.

Keyword. Breast cancer, weight gain, estrogen receptor, recurrence

Abstrak

Latar belakang. *Penambahan berat badan banyak ditemukan pada pasien kanker payudara subtipe estrogen positif. Efek penambahan berat badan terhadap kekambuhan kanker payudara masih menjadi perdebatan dan dikaitkan dengan prognosis yang buruk. Berat badan berlebih berkaitan dengan peningkatan produksi estrogen oleh jaringan adiposa.*
Metode Penelitian. *Kohort retrospektif dan prospektif dengan waktu pengambilan data Juli 2018 – Juni 2019 di poli Tulip RSUP Dr. Sardjito. Penelitian dilakukan dengan cara melihat rekam medis pasien yang berobat dari bulan Januari 2013 – Juli 2018. Akan dibandingkan pasien dengan penurunan berat badan, naik 0 – 5%, dan naik > 5% dari berat badan saat terdiagnosis*
Analisis Statistik. *Hubungan penambahan berat badan dan beberapa faktor risiko terhadap kekambuhan dianalisis dengan cox regression dan uji regresi logistik multivariat. Untuk melihat kesintasan digunakan metode Kaplan Meier.*
Hasil Penelitian. *Penambahan berat badan pada pasien kanker payudara subtipe reseptor estrogen positif Her2 negatif tidak berhubungan dengan kekambuhan (p = 0.264; HR 0.637; IK 95% 0.289 – 1.405). Pasien dengan indeks massa tubuh ≥ 25 kg/m2 saat terdiagnosis memiliki risiko lebih rendah untuk kambuh dibandingkan pasien dengan indeks massa tubuh < 25 kg/m^2 (p = 0.026; HR 0.461; IK 95%, 0.234 – 0.912).*
Simpulan. *Penambahan berat badan setelah terdiagnosis pada pasien kanker payudara subtipe reseptor estrogen positif Her2 negatif yang mendapatkan terapi hormonal tidak berhubungan dengan terjadinya kekambuhan.*

Kata Kunci. *Kanker Payudara, estrogen positif, penambahan berat badan, kekambuhan*

Introduction

Weight gain is commonly found in breast cancer patients. Patients experienced weight gain after being diagnosed or while undergoing therapy with a prevalence of 50% - 96%. Goodwin et al. showed that 84% of 535 breast cancer patients gained 1 year after being diagnosed with an average of 1.6 kg.[1] The effect of weight gain on breast cancer recurrence is still being debated. Many researchers claim weight gain after diagnosis has poor prognostic factors, increasing the risk of recurrence and increasing the risk of death.[2] Estrogen has a role in weight management. A study on mice that are blunted with alpha estrogen receptors shows metabolic syndrome profiles such as weight gain, increased visceral fat, and glucose intolerance dysregulation.[3]

In Indonesia, 52.1% of breast cancer patients express estrogen receptors and hormonal therapy with estrogen blockers as standard therapy.[4] Tamoxifen is a selective estrogen receptor modulator. Tamoxifen administration for 5 years is a standard therapy in patients with pre-menopausal breast cancer positive hormone receptor subtypes, while patients who have experienced menopause can be given aromatase inhibitors as an alternative to tamoxifen or sequentially after tamoxifen.[5] Tamoxifen is known to have side effects such as menopause symptoms, thromboembolism, endometrial cancer, and weight gain. A study showed that tamoxifen was associated with an increased incidence of diabetes in elderly breast cancer patients.[6]

The effect of weight gain after diagnosis on recurrence is not yet understood. Some of the hypotheses proposed include hormonal disorders, increased estrogen production, changes in the endocrine system, changes in the immune system, changes in activity levels, and psychological factors. Adipose tissue is an endocrine organ that can convert androgens into estrogens. In addition, adipose tissue also produces compounds that cause the progression of breast cancer such as leptin, adiponectin, and inflammatory cytokines.[7] The study that shows the relationship between weight gain after diagnosis to recurrence and the study that evaluates the effect of hormonal therapy on weight gain is still controversial. In addition, it is important to know the independent risk factors that influence weight gain after being diagnosed. If weight gain after diagnosis, especially in breast cancer-positive estrogen receptor subtypes, is an indicator of a poor prognosis interventions as early as possible should be given to maintain weight.

Methods

This is a retrospective and prospective cohort study in the outpatient clinic of RSUP Dr. Sardjito. Data retrieval time is July 2018 - June 2019. The subjects were female breast cancer patients of pre-menopausal, postmenopausal age, age ≥ 18 years, positive estrogen receptor status, after undergoing surgery and receiving adjuvant chemotherapy or immediately given hormonal therapy for at least 12 months. Exclusion criteria: had chemotherapy and hormonal therapy outside RSUP Dr. Sardjito and double tumor.

Based on the calculation of the sample size formula for cohort studies, the minimum sample size is 154 subjects. Basic characteristics will be analyzed descriptively and 3 variations of weight gain using Chi-Square. To examine the relationship between several risk factors and recurrence, a univariate cox regression and multivariate cox regression analysis will be performed. Statistically, significant risk factors will be continued to a multivariate logistic regression test. Lifetime or survival can be obtained from the Kaplan Meier method.

Table 1. Baseline characteristic

Baseline characteristic		Weight gain						P
		gain 0-5%		gain >5%		loss		
		N	%	N	%	N	%	
Age		52.7 ± 9.3		49.2 ± 9.6		51.4 ± 8.1		0.243
Education	No school	0	0.0%	2	5.4%	0	0.0%	0.574
	SD	11	28.9%	7	18.9%	8	19.0%	
	SMP	2	5.3%	4	10.8%	4	9.5%	
	SMA	9	23.7%	10	27.0%	8	19.0%	
	Bachelor	3	7.9%	2	5.4%	2	4.8%	
	Undergraduate	4	10.5%	6	16.2%	11	26.2%	
	N.A	9	23.7%	6	16.2%	9	21.4%	
Occupation	Housewife	12	31.6%	13	35.1%	11	26.2%	0.995
	Retired	7	18.4%	6	16.2%	7	16.7%	
	Employees	4	10.5%	5	13.5%	5	11.9%	
	Entrepreneur	6	15.8%	6	16.2%	10	23.8%	
	Labor	5	13.2%	4	10.8%	4	9.5%	
	N.A	4	10.5%	3	8.1%	5	11.9%	
Insurance	JKN PBI	13	34.2%	13	35.1%	14	33.3%	0.690
	JKN non PBI	25	65.8%	23	62.2%	28	66.7%	
	N.A	0	0.0%	1	2.7%	0	0.0%	
Marital status	Married	34	89.5%	31	83.8%	35	83.3%	0.733
	Single	0	0.0%	1	2.7%	2	4.8%	
	Divorced	4	10.5%	5	13.5%	5	11.9%	
Menopause	Pre menopause	18	47.4%	11	29.7%	14	33.3%	0.242
	Post menopause	20	52.6%	26	70.3%	28	66.7%	
BMI baseline	Underweight	4	10.5%	5	13.5%	1	2.4%	0.590
	Overweight	9	23.7%	10	27.0%	12	28.6%	
	Obese	5	13.2%	2	5.4%	5	11.9%	
	Ideal	20	52.6%	20	54.1%	24	57.1%	
PR (%)	Positive	28	73.7%	27	73.0%	30	71.4%	0.771
	Negative	10	26.3%	10	27.0%	11	26.2%	
	N.A	0	0.0%	0	0.0%	1	2.4%	
Tumor size	T1	5	13.2%	6	16.2%	7	16.7%	0.537
	T2	13	34.2%	16	43.2%	13	31.0%	
	T3	9	23.7%	10	27.0%	15	35.7%	
	T4	11	28.9%	5	13.5%	6	14.3%	
	N.A	0	0.0%	0	0.0%	1	2.4%	
Nodes	Positive	15	39.5%	14	37.8%	18	42.9%	0.939
	Negative	22	57.9%	21	56.8%	23	54.8%	
	N.A	1	2.6%	2	5.4%	1	2.4%	
Stage	I	5	13.2%	4	10.8%	6	14.3%	0.905
	II	19	50.0%	20	54.1%	20	47.6%	
	III	14	36.8%	13	35.1%	15	35.7%	
	N.A	0	0.0%	0	0.0%	1	2.4%	

Result

We reviewed the medical records of patients from January 2013 - July 2018. Based on the medical records, we obtained basic patient data, laboratory results, histopathological results, and imaging. Observation of the medical record found that patients with positive estrogen receptor subtypes and negative Her2 were 221 patients. We excluded 1 male sex patient, 9

patients who came in with stage 4, and 11 patients with incomplete data. Patients who enter the inclusion criteria are patients who have received hormonal therapy for at least 12 months. There were 83 patients who had not completed hormonal therapy for 12 months. The final sample is 117 patients (n = 117). Body measurements were carried out with a standard scale that had been calibrated. Patients also assessed progress status based on the results of examinations in the medical record.

This study divides weight gain into 3 groups, patients with decreased body weight, a gain of 0 - 5%, and a gain of > 5%. Patients who experienced weight loss were 42 patients (35.9%), a gain of 0 - 5% were 38 patients (32.5%), and a gain of > 5% were 37 patients (31.6%). Table 1 shows the baseline characteristics of patients based on weight gain. According to the table, we obtained homogeneous characteristic data from the three weight gain groups (p> 0.05).

The relationship between BMI to recurrence is shown in table 2. There are significant differences in overweight patients when compared with ideal BMI. Patients with a higher BMI at the time of diagnosis were a protective factor for recurrence compared to an Ideal BMI (p = 0.013; HR 0.352; 95% CI, 0.155 - 0.801). A total of 7 patients (22.6%) with overweight had a recurrence while 24 patients (77.4%) did not experience a recurrence.

Table 2. Cox regression analysis BMI to recurrence

BMI	Recurrence status				p	HR	IK 95%
	Yes		No				
	n	%	n	%			
Underweight	3	30.0%	7	70.0%	0.266	0.510	0.156 - 1.671
Overweight	7	22.6%	24	77.4%	0.013	0.352	0.155 - 0.801
Obese	4	33.3%	8	66.7%	0.443	0.665	0.235 - 1.885
Ideal	31	48.4%	33	51.6%			

Table 3. Cox regression analysis BMI ≥ 25 kg/m^2 compared to BMI < 25 kg/m^2

BMI	Recurrence status				p	HR	IK 95%
	Yes		No				
	n	%	N	%			
≥ 25 kg/m^2	11	25.6%	32	74.4%	0.026	0.461	0.234 - 0.912
< 25 kg/m^2	34	45.9%	40	54.1%			

Patients with BMI ≥ 25 kg / m^2 were 43 patients (36%) and patients with BMI <25 kg / m^2 were 74 patients (64%). BMI ≥ 25 kg / m^2 which relapsed 11 patients (25.6%) and 32 patients (74.4%) did not relapse. BMI < 25 kg / m^2 that had recurred were 34 patients (45.9%) and 40 patients (54.1%) had no recurrence. After cox regression analysis, patients with BMI ≥ 25 kg / m^2 became a protective factor against recurrence compared to patients with a normal BMI (p = 0.026; HR 0.461; 95% CI, 0.234 - 0.912).

The relationship between weight gain during hormonal therapy is shown in Table 4. Weight gain is divided into 3 categories, weight loss, a gain of 0 - 5%, and a gain of > 5%. In this study, 42 patients (36%) experienced weight loss, weight gain 0 - 5% were 38 patients (32%), and

weight gain > 5% were 37 patients (32%). Patients who experienced recurrence were 45 patients (38%) and patients who did not experience recurrence were 72 patients (62%).

After Cox regression analysis, patients who gained 0 - 5% were not related to recurrence when compared to patients who experienced weight loss (p = 0.331; HR 1.39; IK 95 % 0.715 - 2,706). Patients with weight gain > 5% were also not associated with recurrence compared with patients who experienced weight loss (p = 0.264; HR 0.637; 95% CI 0.289 - 1.405).

Table 4. Cox regression analysis of weight gain to recurrence

	Recurrence status						
	Yes		No		P	HR	IK 95%
Weight gain	N	%	n	%			
Gain 0 - 5%	19	50.0%	19	50.0%	0.331	1.391	0.715 - 2.706
Gain > 5%	10	27.0%	27	73.0%	0.264	0.637	0.289 - 1.405
Weight loss	16	38.1%	26	61.9%			

Based on weight gain, patients with weight gain> 5% have the longest free progression time of 5 years which is 50.7 months. Furthermore, patients who experienced weight loss had a 5 years progression-free survival for 38.2 months and patients with weight gain 0 - 5% had the shortest progression-free survival time for 43.5 months. But after the log-rank test, the result was statistically not significant with p = 0.118.

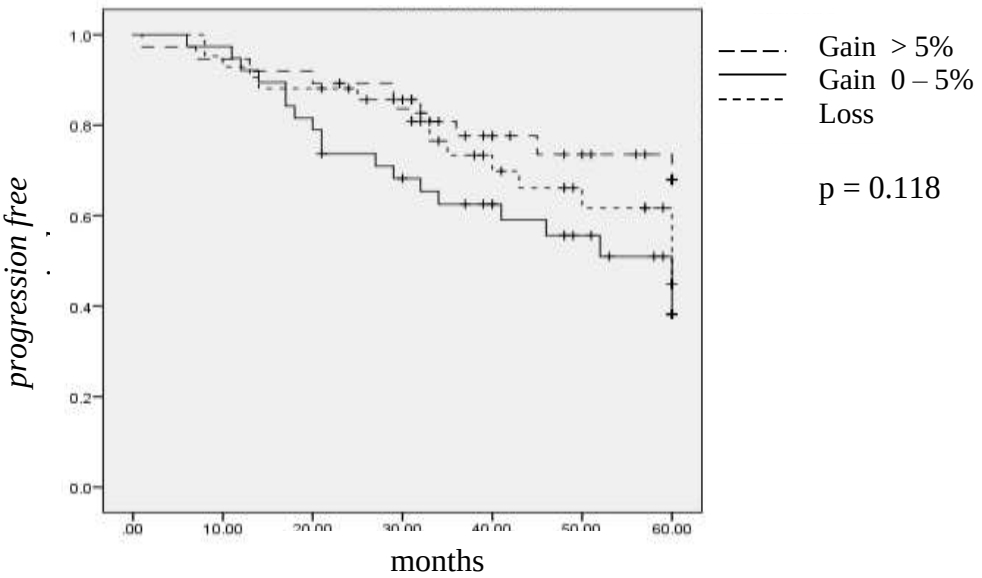

Figure 1. 5-year progression-free survival based on weight gain

There are confounding factors that can affect recurrence. These factors include menopause, tumor size, involvement of lymph nodes, and cancer stage. Surgery and radiotherapy are factors that affect recurrence. However, in this study, all research samples had been surgically removed and radiotherapy. Table 5 explains the factors that influence recurrence in this study. Variables that can be continued to multivariate analysis are variables with a value of p <0.25.

Table 5. Cox regression analysis variables that correlated to recurrences

Variable	p	HR	IK 95%
Menopause	0.312	1.361	0.749 – 2.474
Tumor size	0.736	0.991	0.939 – 1.046
Nodes	0.542	0.994	0.973 – 1.014
Stages	0.676	0.985	0.915 – 1.095
BMI ≥ 25 kg/m^2	0.026	0.461	0.234 - 0.912
Weight gain	0.331	1.391	0.715 – 2.706

On Table 5, only BMI ≥ 25 kg / m^2 with a value of p <0.25 (p = 0.026). In conclusion, BMI ≥ 25 kg / m^2 is an independent factor with a lower risk of recurrence compared to patients with BMI < 25 kg / m^2 in this study.

Discussion

A total of 117 subjects in this study had baseline characteristics that were not significantly different. Including several confounding factors that affect recurrences such as lymph node involvement, tumor size, or tumor stage. So, it can be concluded that the subjects of this study are homogeneous. Breast cancer-positive estrogen receptor subtypes with Her2 negative (luminal A and luminal B / Her2 negative) have the best 5-year progression-free survival time of 92.2% (95% CI, 90.5 - 93.9). This type of breast cancer has the best prognosis compared to the Her2 and basal (triple negative) subtypes. In the ATLAS study the administration of tamoxifen hormonal therapy > 10 years had a low risk of recurrence of 21.4% (RR 0.75; 95% CI, 0.62 - 0.9) and 25.1% (RR 0.90; 95% IK, 0.79 - 1.02; p = 0.002) at patients who received tamoxifen for 5 - 9 years.[8]

In this study, overweight patients (p = 0.013; HR 0.352; 95% CI, 0.155 - 0.801) and BMI ≥ 25 kg / m^2 became a protective factor against recurrence compared to BMI < 25 kg / m^2 at first times diagnosed (p = 0.026; HR 0.461; 95% CI, 0.234 - 0.912). Overweight patients had better progressive free survival time for 5 years than those with thin, normal, or obese but were not significant (p = 0.053). However, there was a significant difference in 5-year progression-free survival time in patients with BMI ≥ 25 kg / m^2 compared with patients with BMI < 25 kg / m^2. Patients with BMI ≥ 25 kg / m^2 had longer progression-free survival (51.4 months) compared with patients with BMI < 25 kg / m^2 (45.1 months) (p = 0.021). The results of this study differ from previous studies which stated overweight, or obesity had lower survival. Obese breast cancer patients have a large tumor size with lymphatic vessel invasion and have significantly lower progression-free survival. But this happens in the triple-negative subtype. Whereas in the positive estrogen receptor subtype, there was no significant difference in progression-free survival based on BMI. In addition, this can be due to differences in the efficacy of hormonal therapy, especially in postmenopausal patients.[9]

In this study, weight gain did not affect recurrence. Both patients with weight gain 0 - 5% (p = 0.331; HR 1.39; 95% CI 0.715 - 2.706) or gained weight > 5% (p = 0.264; HR 0.637; 95% CI 0.289 - 1,405). 5 years of progression-free survival there was no significant difference in the three categories of weight gain (p = 0.118). Studies about the effect of body weight, weight gain, and BMI on breast cancer patients with

positive estrogen receptor subtypes on recurrence are still limited. One of them is research by Dignam. According to Dignam, recurrence in breast cancer patients receiving tamoxifen therapy is not affected by body weight or BMI. The results of Dignam's study show there was no statistical difference between obese or thin/normal patients who received tamoxifen for the recurrence of breast cancer (p = 0.96; HR 1.52; 95% CI, 0.77 - 2.03). Besides, weight / BMI does not affect the efficacy of tamoxifen. Statistically reduced relapse rates in patients receiving tamoxifen therapy were also not affected by body weight or BMI (p = 0.34).[10]

Conclusion

Weight gain after diagnosis in breast cancer patients with Her2 negative estrogen receptor-positive subtypes receiving hormonal therapy is not associated with recurrence.

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