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Original Article

The Relationship of REG1A and Ki67 Expression with Prognostic Parameters in Breast Carcinomas

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ABSTRACT

Objective: Invasive breast carcinoma is the most common cancer in women. Literature data on REG1A expression in breast carcinoma was limited. Our study aimed to investigate the relationship between REG1A and Ki67 expressions with prognostic factors that might affect clinical behaviour and disease-free survival in invasive breast carcinomas.

Methods: Patients diagnosed with invasive breast carcinoma at the Dr. Lütfi Kirdar Kartal Training and Research Hospital Pathology Clinic and followed up in the Oncology Clinic between 2007–2011 were included in our study. Patient records, oncology files, all pathological slides, paraffin blocks were examined are and evaluated. The most appropriate blocks were then selected for immunohistochemical analysis.

Results: Our study included 104 cases of primary invasive breast carcinoma. The age of patients ranged between 24–95, and the mean age was 53.9±14.8. All cases were female. There was a statistically significant correlation between vascular invasion, histological grade, metastasis, ER, PR, c-erbB2 and REG1A exspression in breast carcinoma. In addition, there was a statistically significant correlation between tumor size, vascular invasion, metastasis, ER, PR, c-erbB2 and Ki67 exspression in breast carcinoma.

Conclusion: In conclusion, identifying new prognostic parameters, one of which is REG1A, might have a role in the prediction of prognosis and development of new treatment strategies.

INTRODUCTION

Invasive breast carcinoma is the most common cancer in women and accounts almost for 30% of all cancers.[1] Approximately 1 out of 8 women has an invasive breast carcinoma risk.[1] Since breast carcinoma is frequently seen in women, an intensive study is underway to obtain etiological clues for prevention strategies, to identify modifiable risk factors, and to determine risk factors that stimulate breast cancer development.[2] Regeneration gene 1A (REG1A) is a growth factor that affects pancreatic islet B cells. This gene was identified during an investigation of pancreatic islets of a mouse which had been regenerated after 90% of which had been retracted.[3] 17 REG gene families have been identified so far. The REG1 gene, which has two forms, namely REG1A and REG1B, belongs to this family. REG1 mRNA is mainly found in the pancreas, but it also found in the stomach and kidneys in lesser amounts.[4] Though the effect of its expression on inflammatory diseases[5] and carcinogenesis of gastroenteric tissue has been investigated, the biological function of REG1A has not yet been fully understood.[6] REG1A gene is uncovered to have an effect on the Wnt/B-cathenin pathway in liver tumorigenesis.[7] In the lung,[8] stomach,[9,10] colon[11] and bile ducts[12] cancers, survival was longer in patients with REG1A-negative tumors. In esophageal cancer, if the patient received neoadjuvant chemoradiotherapy followed by an esophagectomy, the prognosis was better in REG1A gene expression positive cases.[13] In breast carcinoma, literature data on REG1A expression was limited.

Ki67 is a monoclonal antibody developed against a nuclear antigen found in the nucleus in all phases of the cell cycle

except G0. Since cells at any cyclic phase completely enter the G0 phase regardless of DNA content, determination of the Ki67 fraction might give rational data on the proliferated cell component of a tumor.[14] Ki67 gene which is composed of two molecules, 345 and 395 kd, respectively, is placed on the 10th chromosome. Immunohistochemically, the percentage of cells with Ki67-positive nuclear staining shows proliferative fraction and is detected to be high in aggressive tumors.[15,16] In many tumors (breast, lung, esophagus, kidney, prostate cancers, malignant melanoma, Non-Hodgkin- lymphoma, glial tumors) a high Ki67 rate is recognized as a poor prognostic factor.[17]

We, in our study, aimed to investigate the relationship between REG1A and Ki67 expressions with prognostic factors that might affect clinical behaviour and disease-free survival in invasive breast carcinomas.

MATERIALS AND METHODS

Cases diagnosed in the pathology clinic of our hospital and followed up in the oncology clinic were included in this study. Patient records, oncology files, all pathological slides, paraffin blocks were examined and evaluated, and the most appropriate blocks are selected for immunohistochemical analysis.

Immunohistochemical investigation and evaluation

Three micron slices from paraffin blocks are taken onto poly-L-lysin covered slides, deparaffinized in 60°C autoclave and tissue microarray (TMA) technique (Leica Bond Max, Germany) is applied. To block endogenous peroxidase, slides are placed into 0.5% hydrogen peroxide for 15 minutes, incubated with rabbit polyclonal Anti-REG1 alfa antibody (Abcam, Code ab47099, 1/400 dilution, UK); liquid mouse monoclonal antibody Ki67 antigen (Leica, Code NCL-L-Ki67-MM1, 1/100 dilution, UK); liquid mouse monoclonal antibody estrogen receptor (ER) (Novocastra, Code NCL-L-ER-6F11/2, 1/50 dilution, UK); liquid mouse monoclonal antibody progesterone receptor (PR) (Novocastra, Code NCL-L-PGR-312, 1/100 dilution, UK); and liquid mouse monoclonal antibody c-erbB2 oncoprotein (Novocastra, Code NCL-L-CB11, 1/40 dilution, UK) for 30 minutes. Post-primary antibody and polymer (Leica; LOT 11776) are used for 10 minutes, respectively. Contrast staining is done with Mayer haematoxylin and the slides are covered with closing material. As positive tissue control, positively stained urothelial carcinoma for REG1A and tonsil slides for Ki67 are used. For the REG1A protein, cytoplasmic staining in tumor cells is considered positive and the absence of staining in the cytoplasm is considered negative. In positive cases, if cytoplasmic staining is seen in more than 10% of the tumor cells, it is considered strongly positive, and if seen in less than 10%; it is considered weakly positive. Staining rates of Ki67 in tumor cells are scored between 0 and 2. If less than 5% of tumor cells are stained; the staining score is 0; if it is between 5–20%; score 1; if more than 20%; score 2. If the score is 0 or 1, the staining is considered negative; and 2, it is considered positive. For ER and PR, if there is nuclear staining in tumor cells, the staining is considered positive, and if there is no nuclear staining, negative. Positive cases are scored as 1 and negative cases as 0. For c-erbB2, if there is no immune staining in cells, the score is 0 (negative); if it is hardly detected, incomplete membranous staining, the score is 1 (negative); if there is moderate complete membranous staining in a minimum of 10% of invasive carcinoma cells, the score is 2 (positive) and if there is uniform strong membranous staining in invasive carcinoma cells, the score is 3 (positive).

Statistical analysis

Continuous variables are given as (±) standard deviation and categorical variables as percentages (%). Mann-Whitney U test is used for the difference between continuous variables, Chi-square test, for the difference between categorical variables, and Pearson & Spearman Correlation Test for correlation analysis. All statistical analysis were done by SPSS 16.0 (SPSS INC Chicago, IL, USA) for which $p<0.05$ was considered significant.

RESULTS

Our study included 104 cases of primary invasive breast carcinoma. The age of patients ranged between 24–95, and the mean age was 53.9±14.8. All cases were female. Besides 82 cases of invasive ductal carcinoma, there were other tumor types such as mixt carcinoma, invasive lobular carcinoma, mucinous carcinoma, invasive papillary carcinoma, metaplastic carcinoma, and apocrine carcinoma. Invasive ductal carcinomas were histological grade 2 or grade 3. The characteristics of the cases including tumor histological subtypes, tumor sizes, histological grades are presented in Table 1. The characteristics of the cases such

Table 1. Distribution of histological subtypes, grade and tumor size of the cases

Characteristics	Patient number
Histological subtype	
Invasive ductal carcinoma	82
Mixt carcinoma	13
Invasive lobular carcinoma	3
Mucinous carcinoma	2
Invasive papillary carcinoma	2
Metaplastic carcinoma	1
Apocrine carcinoma	1
Histological grade	
Grade 2	68
Grade 3	27
Tumor size	
T1 (<2 cm)	22
T2 (2–5 cm)	62
T3 (>5 cm)	20

Table 2. Characteristics of cases regarding certain established prognostic parameters

Characteristics	Positive	Negative
	n (%)	n (%)
Lymphovascular invasion	59 (56.7)	45 (43.3)
Perineural invasion	56 (53.8)	48 (46.2)
Lymph node metastasis	70 (67.3)	34 (32.7)
Estrogen receptor	70 (67.3)	34 (32.7)
Progesterone receptor	70 (67.3)	34 (32.7)
c-erbB2	42 (40.4)	62 (59.6)
Distant organ metastasis	88 (84.6)	16 (15.4)

as lymphovascular invasion, perineural invasion, lymph node positivity, ER, PR, c-erbB2, metastasis are presented in Table 2.

REG1AThe mean ages for the patients with a strong, weak and negative REG1A expression were 54.5±14.4, 51.3±16.9, and 56.1±12.5, respectively, with no statistically significant relationship among the three groups (p=0.06).

The relationship between REG1A expression in breast carcinoma and tumor size, vascular invasion, perineural invasion, histological grade, lymph node positivity, metastasis, ER, PR, c-erbB2 is presented in Table 3. There was a statistically significant relationship between vascular invasion, histological grade, metastasis, ER, PR, c-erbB2 and REG1A expression in breast carcinoma Ki67.

The mean age of the patients with Ki67 positivity and negativity was, 54.0±14.6 and 53.8±15.2, respectively, with no statistically significant difference between the groups (p=0.69).

The relationship between Ki67 expression in breast carcinoma and tumor size, vascular invasion, perineural invasion, histological grade, lymph node positivity, metastasis, ER, PR, c-erbB2 is presented in Table 4.

There was a statistically significant relationship between tumor size, vascular invasion, metastasis, ER, PR, c-erbB2 and Ki67 expression in breast carcinoma.

DISCUSSION

In our study; there was a statistically significant correlation between vascular invasion, histological grade, metastasis, ER, PR, c-erbB2 and REG1A expression in breast carcinoma. In addition, there was a statistically significant correlation between tumor size, vascular invasion, metastasis, ER, PR, c-erbB2 and Ki67 expression in breast carcinoma.

Recently, novel approaches such as molecular status and gene analysis, apart from pathological grade and stage,

Table 3. Comparison of REG1A expression with certain parameters in breast carcinoma

		REG1A			p-value
		Strong (n=52)	Weak (n=30)	Negative (n=22)	
Age, mean±SD	24–95	54.5±14.4	51.3±16.9	56.1±12.5	0.47
Tumor size, n (%)	T1	3 (13.6)	5 (16.7)	14 (26.9)	0.06
	T2	14 (63.6)	16 (53.3)	32 (61.5)	
	T3	5 (22.7)	9 (30)	6 (11.5)	
Vascular invasion, n (%)	Yes	23 (44.2)	22 (73.3)	14 (63.6)	0.04
	No	29 (55.8)	8 (26.7)	8 (36.4)	
Perineural invasion, n (%)	Yes	28 (53.8)	19 (63.3)	9 (40.9)	0.48
	No	24 (46.2)	11 (36.7)	13 (59.1)	
Histological Grade, n (%)	Others	4 (44.4)	3 (33.3)	2 (22.3)	<0.05
	2	41 (60.3)	18 (26.5)	9 (13.2)	
	3	7 (25.9)	9 (33.3)	11 (40.7)	
Lymph node, n (%)	Negative	8 (36.4)	5 (16.7)	21 (40.4)	0.40
	Positive	14 (63.6)	25 (83.3)	31 (59.6)	
Metastasis, n (%)	Negative	10 (45.5)	27 (90)	51 (98.1)	<0.001
	Positive	12 (54.5)	3 (10)	1 (1.9)	
ER, n (%)	Negative	13 (59.1)	13 (43.3)	8 (15.4)	<0.001
	Positive	9 (40.9)	17 (56.7)	44 (84.6)	
PR, n (%)	Negative	15 (68.2)	14 (46.7)	13 (25)	<0.001
	Positive	7 (31.8)	16 (53.3)	39 (75)	
c-erbB2, n (%)	(-)	3 (13.6)	6 (20)	29 (55.8)	<0.001
	(+)	1 (4.5)	6 (20)	17 (32.7)	
	(++)	6 (27.3)	6 (20)	4 (7.7)	
	(+++)	12 (54.5)	12 (40)	2 (3.8)	

ER: Estrogen receptor; PR: Progesterone receptor; SD: Standard deviation.

Table 4. Comparison of Ki67 expression with certain parameters in breast carcinoma

		Ki67		p-value
		Negative	Positive	
Age, mean±SD	24–95	54.0±14.6	53.8±15.2	0.69
Tumor size, n (%)	T1	19 (30.2)	3 (7.3)	0.001
	T2	37 (58.7)	25 (61)	
	T3	7 (11.1)	13 (31.7)	
Vascular invasion, n (%)	Yes	29 (46)	30 (73.2)	0.005
	No	34 (54)	11 (26.8)	
Perineural invasion, n (%)	Yes	37 (58.7)	19 (46.3)	0.15
	No	26 (41.3)	22 (53.7)	
Lymph node, n (%)	Negative	24 (38.1)	10 (24.4)	0.10
	Positive	39 (61.9)	31 (75.6)	
Metastasis, n (%)	Negative	58 (92.1)	30 (73.2)	0.01
	Positive	5 (7.9)	11 (26.8)	
ER, n (%)	Negative	15 (23.8)	19 (46.3)	0.01
	Positive	48 (76.2)	22 (53.7)	
PR, n (%)	Negative	19 (30.2)	23 (56.1)	0.008
	Positive	44 (69.8)	18 (43.9)	
c-erbB2, n (%)	(-)	28 (44.4)	10 (24.4)	0.007
	(+)	17 (27)	7 (17.1)	
	(++)	6 (9.5)	10 (24.4)	
	(+++)	12 (19)	14 (34.1)	

ER: Estrogen receptor; PR: Progesterone receptor; SD: Standard deviation.

have been used in breast carcinomas. Consequently, more effective adjuvant therapies such as antimolecular drugs are being developed and introduced. Since following adjuvant therapy or surgery, it is still hard to determine the probability of recurrence, additional prognostic markers are required.[19]

Though there are many studies on various prognostic factors in breast carcinomas, REG1A has been under investigation recently and studies are limited. Sasaki et al.,[18] in a study performed on breast carcinomas, found a significant correlation between REG1A expression and age and showed an increase in REG1A expression in young patients below 50. In our study, in a wide age range (24–95 yrs), we could not find a significant association between REG1A expression and age.

The same investigators in a study including 150 cases, 143 of which were invasive ductal carcinoma, could not observe a statistically significant correlation between histological subtypes and REG1A staining intensities in breast carcinomas,[18] and our results are consistent with theirs. Still, caution should be exercised as this may be due to a small sample group and a limited number of cases, especially in certain histological subtypes (metaplastic carcinoma, apocrine carcinoma, mucinous carcinoma, invasive papillary carcinoma etc.), and thus, should be confirmed in larger series.

There are some studies analysing REG1A staining and tumor size correlation. In one of them conducted by YSasaki et al.,[18] in breast carcinomas, no statistically significant correlation was established between tumor size and REG1A staining intensities. Another study on pulmonary non-small cell carcinomas was performed by Minamiya and Kawai.[8] In 86 patients, the authors showed that REG1A expression was an independent poor prognostic factor, but did not find a correlation between tumor size and REG1A staining intensity. In our study, similarly, we didn't observe a significant correlation between tumor size and REG1A staining intensities.

In the literature, we didn't find a study investigating the correlation between perineural invasion and REG1A staining in the breast. In ours, there wasn't any relation between perineural invasion and REG1A staining. As well, we didn't find any literature on the correlation between REG1A staining intensity and vascular invasion or histological grade in the breast. However; Astrosini et al.,[20] who showed that in colorectal carcinoma and related peritoneal carcinomatosis REG1A expression had a prognostic significance, did not find a significant correlation between vascular invasion or histological grade and REG1A staining intensity. On the contrary, in our study of breast carcinomas, there was a statistically significant correlation between vascular invasion, histological grade, and REG1A staining intensity. We observed that in patients with vascular invasion and poor histological grade, REG1A expression was higher.

In the studies of Minamiya et al.[8] on breast cancers and Minamia and Kawai on lung cancers, there was no correlation was found between REG1A staining and lymph node pos-

itivity.[18,19,21] y No correlation was found between REG1A expression and lymph node positivity in our study either.

Our literature search didn't reveal any study investigating the relationship between REG1A and metastasis in breast cancers. In a study on colorectal carcinomas, REG1A staining intensity did not show a significant relationship with lung or liver metastasis.[20] However, in our study, there was a significant relationship between REG1A staining intensity and metastasis, and in cases with metastasis, the REG1A staining intensity was detected to be higher.

Sasaki et al.[18] showed that high REG1A expression in breast carcinomas was a poor prognostic factor and in healthy breast tissue, REG1A expression was not common. In REG1A positive patients, c-erbB2 positivity was higher than REG1A negative patients. Besides, patients with c-erbB2 positive breast cancer had a higher REG1A expression than c-erbB2 negative ones. We also observed that as REG1A staining intensity increased, c-erbB2 staining also increased.

Sasaki et al.[18] showed that in <50 years-old patients with breast carcinoma, REG1A expression rate was higher probably due to hormones such as estrogen and progesterone. However, they did not find a relationship between ER, PR and REG1A. However, in our study, there was a significant inverse relationship between REG1A expression and ER or PR expression. In patients with high ER or PR levels, REG1A staining intensity was lower. Sasaki et al.[18] showed that 10-year disease-free survival was better in breast carcinoma patients expressing low levels of REG1A than those with high levels. Astrosini et al.[20] found that disease-free survival was shorter in REG1A-expressing colorectal cancers In a study on non-small cell carcinoma of the lung, 5-year overall survival and disease-free survival were obviously better in tumors expressing low levels of REG1A.[8] We also found, in 4 years follow-up, that disease-free survival was better in breast cancers expressing low levels of REG1A (Fig. 1).

Our analysis on REG1A showed that there was a significant relationship between REG1A staining intensity and vascular invasion, histological grade, metastasis, ER, PR and c-erbB2 status. REG1A positive patients had shorter disease-free survival (Fig. 1) supporting the value of REG1A as a prognostic marker in breast tumors. We observed no relationship between REG1A staining intensity and histological subtypes, age, perineural invasion, tumor size and lymph node positivity. Other factors (sample size, immunohistochemical assay techniques, interpretation biases) that may have contributed to these results should be evaluated.

In a study investigating the effect of the Ki67 proliferation index in tamoxifen resistance in 70 post-menopausal breast cancer patients, Elzawahry et al.[22] found no significant correlation between Ki67 proliferation index and patient age, tumor differentiation, tumor size, lymph node positivity and distant metastasis. They stated that Ki67 proliferation index might be related to tumor biology and aggressivity rather than the stage of breast cancer. However, there are also studies reporting a correlation between the Ki67 proliferation index and the stage of breast cancer.[23,24]

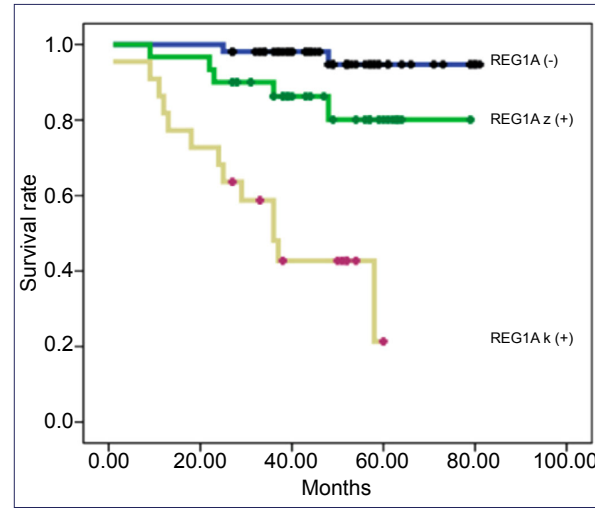

Figure 1. The relationship between REG1A and disease free survival.

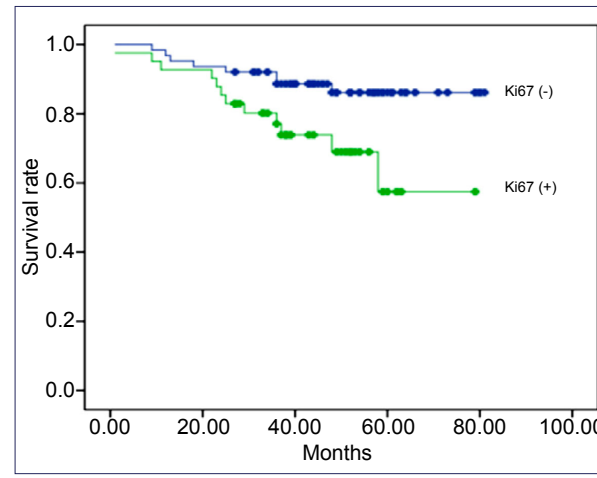

Figure 2. The relationship between Ki67 and disease free survival.

In our study, similarly to other studies, tumor size and metastasis status were significantly associated with the Ki67 proliferation index[23,24] while there was no significant association of age and lymph node positivity with Ki67 proliferation index[22] Elzawahry et al.[22] found a significant association between the Ki67 proliferation index and c-erbB2 overexpression, but no significant relationship between Ki67 index and ER or PR staining. In another study, there was an inverse correlationship between Ki67 expression and ER positivity.[25] Todorovic-Rakovic et. al. found that activation of the c-erbB2 signalling pathway hyperstimulated the MAPK/Erk pathway and led to the activation of the non-genomic pathway of estrogen and to the occurrence of estrogen negative phenotypes by downregulation of the ER.[26] The significant relationship found between the Ki67 index and c-erbB2 overex-

pression in our study is consistent with the literature.[22] In c-erbB2 positive patients, the Ki67 proliferation index was high. As a result, in breast cancer patients with a high Ki67 proliferation index, increased c-erbB2 expression might have a prognostic role in breast cancer, as in other studies.

Similar to the study by Lee et al.,[25] but unlike the study of Elzawahry et al.[22] there was an inverse correlation between ER positivity, one of the most important biological markers in breast cancers, and the Ki67 proliferation index, in our study, Ki67 proliferation index was significantly associated with c-erbB2 and ER. In cases with a high Ki67 proliferation index, ER positivity decreased in line with the literature.[22–25] Elzawahry et al.[22] studied their cases regarding disease-free survival (time between curative surgery and first local/distant recurrence or death) and overall survival (time between initial diagnosis and death or loss during follow-up). They reported that patients with a higher Ki67 proliferation index had shorter overall survival and disease-free survival. In a study conducted by Sun et al.[27] on non-luminal breast cancers, it was shown that a high Ki67 proliferation index was associated with shorter disease-free survival. In our 4-year follow-up, similarly, disease-free survival was shorter in patients with high Ki67 proliferation index (Fig. 2).

In this study, we found a significant correlation between Ki67 proliferation index and tumor size, vascular invasion, metastasis, ER, PR, and c-erbB2 stainings. Accordingly, Ki67 can be used as a supportive marker to differentiate high-grade tumors from low-grade tumors. However, we didn't find any correlation between Ki67 and age, and lymph node positivity. Ki67 was not associated with lymph node positivity, possibly due to other factors (eg, sample size, immunohistochemical assay techniques, interpretation biases etc.). The results showed that patients with a high Ki67 proliferation index had shorter disease-free survival (Fig. 2). This supports the role of the Ki67 proliferation index as a prognostic marker in breast tumors.

We did not find any study on the relationship between REG1A expression and Ki67 proliferation index in breast cancer. Yonemura et al.[10] found that in gastric carcinomas, the patients with REG1A expression had a higher proliferation index. In our study, we investigated the relationship between REG1A and Ki67 proliferation index in breast carcinomas, and similar to gastric carcinomas, tumors expressing REG1A had a higher Ki67 proliferative index. This suggests that, as Ki67, REG1A expression might be a poor prognostic factor in breast carcinomas.

As a conclusion, identifying new prognostic parameters, one of which is REG1A, might have a role in predicting prognosis, and developing new treatment strategies.

Ethics Committee Approval

This study approved by the Dr. Lutfi Kirdar Kartal Training and Research Hospital Clinical Research Ethics Committee (Date: 24.04.2012, Decision No: 2).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: G.G.G.; Design: S.H.K.; Supervision: D.İ.E.; Fundings: A.S.; Materials: A.E.G.; Data: A.N.K.; Analysis: G.G.G.; Literature search: S.Ş.; Writing: G.G.G.; Critical revision: N.Ö.B.

Conflict of Interest

None declared.

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Meme Karsinomlarinda Reg1A ve Ki67 Ekspresyonunun Prognostik Parametreler ile İlişkisi

Amaç: Meme kanseri kadınlarda görülen en sık kanserdir. Meme kanserlerinde REG1A ek-spresyonuna ilişkin literatürler sınırlı sayıdadır. Bizim çalışmamız meme kanserlerinde klinik davranış ve hastalıksız sağkalımı etkileyebilecek prognostik faktörler ile Ki67 ve REG1A ekspresyonunun ilişkisini belirlemeyi amaçlamıştır.

Gereç ve Yöntem: Çalışmamıza 2007–2011 yılları arasında Kartal Eğitim ve Araştırma Hastanesi patoloji bölümünde meme kanseri tanısı almış ve onkoloji kliniğinde takip edilen hastalar dahil edilmiştir. Hasta kayıtları, onkoloji dosyaları, patoloji lamları ve parafin bloklar gözden geçirilmiş ve değerlendirilmiştir. Daha sonra en uygun bloklar immünhistokimyasal çalışma için seçilmiştir.

Bulgular: Çalışmamızda 104 primer meme kanseri içemektedir. Hastaların yası 24–95 arasında değişmekte olup ortalama yaş 53.9±14.8 saptanmıştır. Tüm hastalar kadındır. Meme kanserinde REG1A ekspresyonu ile; vasküler invazyon, histolojik grede, metastaz, ER, PR, c-erbB2 arasında anlamlı bir ilişiki vardı. Aynı zamanda; meme kanserinde Ki67 ekspresyonu ile; tümör boyutu, vasküler invazyon, metastaz, ER, PR, c-erbB2 arasında anlamlı bir ilişki vardı.

Sonuç: Sonuç olarak yeni prognostik parametrelere karar verilirken REG1A ekspresyonu prognozu belirlemede yeni tedavi stratejilerinin geliştirilmesinde rol oynayabilir.

Anahtar Sözcükler: Ki67; meme kanseri; REG1A.