Investigating the impact of polysomy 17 in breast cancer patients with HER2 amplification through meta-analysis

HER2 amplifikasyonu olan meme kanseri hastalarında Polizomi 17’nin etkisinin meta-analiz ile araştırılması

Abstract

Objectives: Since studies regarding the effect of polysomy 17 (P17) in breast cancer cases with some specific clinical findings are few in number and are in small sample sizes, meta-analysis was implemented to exhibit the effects of P17 in patients with Human Epidermal growth factor Receptor 2 (HER2) amplification on lymph node involvement and tumor grade.

Materials and methods: Pubmed literature database was scanned up to June 2017 by using the keywords “polysomy 17 breast cancer” and 141 studies were accessed. Ultimately four of the reviewed papers have been found to be appropriate for examining the effect of P17 on lymph node involvement and tumor grade. Prior to meta-analysis, publication bias and heterogeneity of the studies was examined.

Results: Meta-analysis in the examining the effect of polysomy 17 on lymph node involvement (OR = 1.708, 95% CI: 1.068–2.733), on grade [3]/[3,1] (OR = 3.402, 95% CI: 1.726–6.707), on grade [3]/[3, 2] (OR = 2.581, 95% CI: 0.778–8.559) and on grade [2]/[2,1] (OR = 1.854, 95% CI: 0.531–6.468) was determined in those with HER2 amplification.

Conclusion: It was observed that in terms of lymph node involvement, P17 was a risk factor in patients and with regard to tumor grade, P17 was a risk factor when grade increased in patients with amplification.

Keywords: Meta analysis; Polysomy 17; Breast cancer; HER2-positive; Amplification.

Öz

Amaç: Bazı spesifik klinik bulgulara sahip meme kanseri vakalarında polisomi 17’nin (P17) etkisinin ilişkin çalışmalar az sayıda ve küçük örneklem boyutlarında olması nedeniyle, İnsan Epidermal Büyüme Faktörü Reseptör 2 (HER2) amplifikasyonu olan hastalarda P17’nin lenf nodu tutulumu ve tümör evresi üzerindeki etkilerini ortaya koymak amacıyla meta-analiz uygulanmıştır.


Bulgular: Yapılan meta-analiz sonucunda HER2 amplifikasyonu olan hastalarda, P17’nin lenf nodu tutulumu (OR = 1.708, 95% CI: 1.068–2.733), evre [3]/[3,1] (OR = 3.402, 95% CI: 1.726–6.707), evre [3]/[3, 2] (OR = 2.581, 95% CI: 0.778–8.559) ve evre [2]/[2,1] (OR = 1.854, 95% CI: 0.531–6.468) üzerindeki etkisi belirlendi.

Sonuç: Lenf nodu tutulumu açısından P17’nin amplifikasyonu olan hastalarda risk faktörü olduğu, tümör evresi
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Introduction

Breast cancer is the most frequent type of cancer in
women and the second most common type of cancer in
the worldwide [1]. Targeted treatment for breast cancer
has now become part of primary clinical protocols all
over the world. Trastuzumab is routinely used mono-
clonal antibody to treat patients with breast carcinoma
overexpressing human epidermal growth factor recep-
tor 2 (HER2) that markedly improves response rate
and overall survival when combined to chemotherapy
[2–4]. Approximately 20% of breast cancers overexpress
HER2 which is associated with poor prognosis and
responsiveness to trastuzumab, hence the evaluation of
HER2 status has become an important tool in patient
management [5–7].

HER2 is a crucial breast cancer oncogene, which is
located on the long arm of chromosome 17 and encodes a
185-KDa cell surface receptor with tyrosine kinase activity
[8]. Abnormalities of chromosome 17 are all important
molecular genetic occasions since it harbors several impor-
tant oncogenes (HER2, TOP2A, TAU), tumor-suppressive
genes (p53, BRCA1, HIC-1), DNA double-strand break repair
and recombination genes that play an essential role in the
development and progression of breast cancer [9]. Two
methods available for clinical use to assess HER2 status
in breast cancer are the fluorescence in situ hybridization
(FISH) for HER2 gene amplification and the immunohisto-
chemistry (IHC) for HER2 protein overexpression [10]. IHC
analysis is usually used as the primary assay and confirma-
tory FISH is performed for a specific subset of IHC results
e.g. 1+ or 2+) [11]. In the most commonly used FISH assay
fluorescently labeled dual-probe is used; one that hybrid-
izes to the target HER2 gene and the other that hybridizes
to the centromeric region of chromosome 17 (CEP17) [12].
Above a certain threshold value of CEP17 signals that are
used as a marker for chromosome 17 number indicates
the presence of polysomy 17 [13]. It is reported that P17 is a
common finding in breast cancer, about 5–50% [6, 14].

Based on the 2013 ASCO/CAP (American Society of
Clinical Oncology/College of American Pathologists)
guideline, tumors containing >10% of cells with complete
and intense membrane staining by IHC are characterized
HER2-positive breast carcinoma. FISH-positive carcinoma
is defined considering the ratio of HER2 to CEP17 signals
for maximum accuracy. When HER2:CEP17 ratio ≥2 or
mean HER2 copy number ≥26, when the HER2:CEP17 ratio
<2 are termed as HER2 gene amplification [15].

In cases of uncommon illnesses and their related
features, meta-analysis applications are frequently-con-
sulted systematic methods of evaluation. Studies regard-
ing the effect of P17 in breast cancer cases in some clinical
findings are few in number and are in small sample sizes.
For this reason it is aimed to study, the effects of P17 in
patients with amplification on lymph node involvement
and grade have been examined.

Materials and methods

With the aim of researching the effects of P17 on lymph
node involvement and tumor grade the Pubmed literature
database was scanned up by using the keywords “poly-
somy 17 breast cancer”, until June 2017 and 141 studies
were accessed. For research the impact of P17 on lymph
node involvement and tumor grade in breast cancer
patients through meta-analysis, 4 of the publications
examined were found to be suitable for the purpose of our
research. Among these studies, the lymph node involve-
ment and grade having findings with HER2 amplification
were included in the study.

In the analysis, while the impact of P17 was being
researched, lymph node involvement and lacking were
determined as “+” and “−”, respectively. When the
impact of P17 on grade was being researched, meta-analy-
sis was conducted by separation of cases into three catego-
ries; grade1–grade2, grade1–grade3 and grade2–grade3.

Prior to meta-analysis, publication bias of the studies
was examined with Begg and Egger tests. In cases of pub-
lication bias, the trim and fill method was applied. Heter-
ogeneity of the studies was evaluated according to the
Cochran Q test, while to determine degree of heterogene-
ity, the $F$ statistic was employed. In the meta-analyses,
the lowest number of studies taken for analysis was 3. In the
studies, the value of $\alpha$ was taken as 0.10 for the homoge-
neity and publication bias tests.

In cases where heterogeneity was determined in the
publications following Cochran’s Q test, the DerSimonian-
Laird method was carried out using the random effects
model, while when there was homogeneity in the pub-
cations, the Mantel Haenszel method was applied using
the fixed effects model [16]. In the statistical analyses, the
MedCalc version 16.4 and Stata/SE 14.0 programs were
used.
Results

Examination of impact of polysomy 17 on lymph node involvement in patients with amplification

With the aim of examining the impact of P17 on lymph node involvement, following the literature review of studies on patients with polysomy 17 and amplification, three studies were found. As a result of the Egger test ($p = 0.790$) and Begg’s test ($p = 0.602$), it was determined that there was no publication bias. Cochran’s Q test revealed that there was no heterogeneity ($p = 0.688$; $I^2 = 0\%$). The results of the meta-analysis carried out to examine the impact of P17 on lymph node involvement are given in Table 1 and the forest graph is presented in Figure 1.

Examination of impact of polysomy 17 on grade in patients with amplification

With the aim of examining the impact of P17 for grade 3 cases compared to grade 1 cases, following the literature review of studies on patients with P17 and amplification, three studies were found. As a result of the Egger test ($p = 0.847$) and Begg’s test ($p = 0.602$), it was determined that there was no publication bias. Cochran’s Q test revealed that there was no heterogeneity ($p = 0.440$; $I^2 = 0\%$). The results of the meta-analysis carried out to examine the impact of P17 on grade are given in Table 2 and the forest graph is presented in Figure 2.

With the aim of examining the impact of P17 for grade 2 cases compared to grade 1 cases, following the literature review of studies on patients with P17 and amplification, four studies were found. As a result of the Egger test ($p = 0.347$) and Begg’s test ($p = 0.174$), it was determined that there was no publication bias. Cochran’s Q test revealed that there was heterogeneity ($p = 0.003$; $I^2 = 78.35\%$). The results of the meta-analysis carried out to examine the impact of polysomy 17 on grade are given in Table 3 and the forest graph is presented in Figure 3.

Discussion

Breast cancer is one of the cancer types seen in women worldwide and is the leading cause of cancer deaths [17]. Since it is a heterogeneous disease, it is characterized by multiple subtypes due to different gene expression profiles. This leads to the emergence of multiple prognostic and predictive tumor markers [18]. Accurate detection of human epidermal growth factor receptor 2 (HER2/neu) changes in tumors is crucial in assessing patient prognosis, predicting standard chemotherapy response, and determining compliance to HER2-tailored treatments [19].

Table 1: Relevant statistics for meta-analysis in examining the effect of polysomy 17 on lymph node involvement in those with amplification.

<table>
<thead>
<tr>
<th>Study</th>
<th>Polysomy 17a/n</th>
<th>Her 2 Neg a/n</th>
<th>Odds ratio</th>
<th>95% C.I.</th>
<th>z</th>
<th>p-Value</th>
<th>Weights (%)</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watters et al. 2003</td>
<td>51/89</td>
<td>40/84</td>
<td>1.476</td>
<td>0.810–2.690</td>
<td>61.71</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakopoulou et al. 2002</td>
<td>9/16</td>
<td>4/9</td>
<td>1.607</td>
<td>0.310–8.322</td>
<td>8.21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsukamoto et al. 2000</td>
<td>27/42</td>
<td>20/46</td>
<td>2.340</td>
<td>0.991–5.525</td>
<td>30.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed effects</td>
<td>87/147</td>
<td>64/139</td>
<td>1.708</td>
<td>1.068–2.733</td>
<td>2.234</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a/n, (number of lymph node involvement positive)/(total number of cases).
Several related studies usually guide most clinical decisions and these studies often differ in terms of their design; methodological quality; population studied; and the intervention, test, or condition considered. Clinical decision-making necessitates ongoing compromise of studies that ensures different answers to the same question so that combining available information to generate an integrated result seems more coherent. Meta-analysis is an application which enables a more general and representative value with regard to population parameter to be achieved in a particular topic [20, 21]. There are studies in the literature investigating the various effects of P17 and variable HER2 amplification status in breast cancer patients, but no meta-analysis study is available based on our criteria [22–24]. In this study, too, due to these that in the literature there are few studies related with P17 and that the studies were made with a small number of cases in terms of the subgroups, impact of amplification on prognosis for breast cancer was examined through meta-analysis. In this study, the aim was to examine the impact of P17 on the lymph node involvement and grade factors namely for cases with HER2 amplification.

**Table 2:** Relevant statistics for meta-analysis in examining the effect of polysomy 17 on grade (grade [3]/grade [3, 1]) in those with amplification.

<table>
<thead>
<tr>
<th>Study</th>
<th>Polysomy 17</th>
<th>Her 2 Neg</th>
<th>Odds ratio</th>
<th>%95 C.I.</th>
<th>z</th>
<th>p-Value</th>
<th>Weights (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watters et al. 2003</td>
<td>50/56</td>
<td>38/62</td>
<td>5.263</td>
<td>1.957–14.151</td>
<td>1.921</td>
<td>0.164</td>
<td>100</td>
</tr>
<tr>
<td>Nakopoulou et al. 2002</td>
<td>5/11</td>
<td>1/4</td>
<td>2.500</td>
<td>0.194–32.195</td>
<td>1.175</td>
<td>0.241</td>
<td>100</td>
</tr>
<tr>
<td>Tsukamoto et al. 2000</td>
<td>20/29</td>
<td>17/33</td>
<td>2.092</td>
<td>0.738–5.927</td>
<td>1.081</td>
<td>0.280</td>
<td>100</td>
</tr>
<tr>
<td>Fixed effects</td>
<td>75/96</td>
<td>56/99</td>
<td>3.402</td>
<td>1.726–6.707</td>
<td>3.536</td>
<td>&lt;0.001</td>
<td>100</td>
</tr>
</tbody>
</table>

*a/n, (number of grade 3)/(total number of cases grade 3 and grade 1).

**Table 3:** Relevant statistics for meta-analysis in examining the effect of polysomy 17 on grade (grade [3]/grade [3, 2]) in those with amplification.

<table>
<thead>
<tr>
<th>Study</th>
<th>Polysomy 17</th>
<th>Her 2 Neg</th>
<th>Odds ratio</th>
<th>%95 C.I.</th>
<th>z</th>
<th>p-Value</th>
<th>Weights (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watters et al. 2003</td>
<td>50/91</td>
<td>38/71</td>
<td>1.059</td>
<td>0.568–1.974</td>
<td>0.523</td>
<td>0.600</td>
<td>100</td>
</tr>
<tr>
<td>Nakopoulou et al. 2002</td>
<td>5/10</td>
<td>1/7</td>
<td>6.000</td>
<td>0.516–69.757</td>
<td>2.251</td>
<td>0.025</td>
<td>100</td>
</tr>
<tr>
<td>Tsukamoto et al. 2000</td>
<td>20/33</td>
<td>17/30</td>
<td>1.176</td>
<td>0.431–3.212</td>
<td>0.708</td>
<td>0.480</td>
<td>100</td>
</tr>
<tr>
<td>Visscher et al. 2000</td>
<td>43/66</td>
<td>4/28</td>
<td>11.217</td>
<td>3.470–36.265</td>
<td>2.749</td>
<td>0.007</td>
<td>100</td>
</tr>
<tr>
<td>Random effects</td>
<td>118/200</td>
<td>60/136</td>
<td>2.581</td>
<td>0.778–8.559</td>
<td>1.550</td>
<td>0.121</td>
<td>100</td>
</tr>
</tbody>
</table>

*a/n, (number of grade 3)/(total number of cases grade 3 and grade 2).
For cases with amplification, the literature review carried out with regard to the impact of P17 on lymph node involvement revealed three studies [25–27]. Although P17 was not found to be an important risk factor for lymph node involvement in each of these studies, it was determined that P17 had a risk factor 1.7 times more significant in cases with positive lymph node involvement, than cases with negative lymph node involvement.

When studies investigating the effect of P17 on tumor grade in patients with amplification were screened, three studies comparing grade 1 and grade 3 were found in the literature. Whilst the two of studies revealed that P17 was not a significant risk factor [25, 26], the other stated that it was a significant risk factor [27]. As a result of the meta-analysis, it was revealed that P17 was not a significant risk factor for grade 3 cases compared to grade 2 cases in patients with amplification.

When studies investigating the effect of P17 on tumor grade in patients with amplification were screened, three studies comparing grade 2 and grade 1 were found in the literature. Whilst the two of studies revealed that P17 was not a significant risk factor [25, 26], the other stated that it was a significant risk factor [27]. As a result of the meta-analysis, it was revealed that P17 was not a significant risk factor for grade 2 cases compared to grade 1 cases in patients with amplification.

In conclusion, when meta-analysis results are evaluated generally, it was observed that in terms of lymph node involvement, P17 was a risk factor in patients with HER2 amplification. With regard to grade, P17 was a risk factor when grade increased in patients with amplification.

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References