Chromosome-specific Aneusomy in Carcinoma of the Breast

Diane L. Persons,2 Robert A. Robinson, Ping H. Hsu, Steven A. Seelig, Thomas J. Borell, Lynn C. Hartmann, and Robert B. Jenkins3

Departments of Laboratory Medicine and Pathology [D. L. P., T. J. B., R. B. J.] and Medical Oncology [L. C. H.], Mayo Clinic/Foundation, Rochester, Minnesota 55905; Department of Pathology, University of Iowa Hospital, Iowa City, Iowa 52242 [R. A. R.]; and Vysis, Inc., Downers Grove, Illinois 60515 [P. H. H., S. A. S.]

ABSTRACT

Fluorescence in situ hybridization was performed on touch preparations from 55 primary infiltrating ductal carcinomas of the breast to determine numeric chromosome abnormalities. The frequency of aneusomy, measured by both nondisomy and chromosomal gain, was determined for chromosomes X, 4, 6–12, 17, and 18 with the use of chromosome-specific, α-satellite DNA probes. The presence of chromosome-specific numeric abnormalities was correlated with established clinicopathological parameters, including tumor size, lymph node involvement, tumor grade, estrogen receptor level, and menopause status. In addition, a case-control study was performed to explore a possible association between chromosome-specific aneusomy and recurrence in lymph-node-negative patients.

Although chromosomes 8 and 6 were most frequently aneusomic, numeric abnormalities of chromosomes 4 and 11 were most strongly associated with established prognostic factors. For chromosomes 4 and 11, strong associations were found with tumor involvement of lymph nodes and increased tumor size, along with a weaker association with tumor grade. In addition, numeric abnormalities of the following chromosomes were associated with the corresponding prognostic factors: chromosomes X, 7, and 12 with lymph node status; chromosomes 10, 17, and 6 with tumor size; and chromosomes 7, 12, 17, and X with tumor grade. No correlations were observed with estrogen receptor level or menopause status. In the case-control study performed on isolated nuclei of paraffin-embedded tissue from lymph node-negative breast cancer patients (19 cases and 19 controls), the gain of chromosome 4 was correlated with disease progression. These findings suggest that chromosome-specific aneusomy is associated with certain established prognostic factors and may be associated with disease progression.

INTRODUCTION

Breast cancer is the most common life-threatening malignant neoplasm in women. An estimated 182,000 new cases will be identified, and 46,000 deaths will occur in U.S. women in 1994 (1). As with other solid tumors, technical difficulties have resulted in limited cytogenetic information on cultured breast tumors (2). Efforts to avoid culturing by performing direct cytogenetic analysis on breast tumors have been hampered by low mitotic rates and poor chromosome morphology. Chromosomes that have thus far been found to be relatively frequently involved in structural alterations in breast cancer include chromosomes 1, 3, 6, and 11, whereas numeric abnormalities reportedly often involve chromosomes 7, 8, 18, and 20 (3–7).

FISH4 using chromosome-specific, α-satellite DNA probes can be used to evaluate aneusomy in interphase and/or metaphase cells (8). Large numbers of uncultured interphase cells can be evaluated rapidly. Several studies have used FISH for analysis of aneuploidy in solid tumors (9–12). In situ hybridization studies in breast cancer have been limited to evaluation of aneuploidy in the breast cancer cell line MCF-7 (13, 14) and the study of seven primary tumors for abnormalities of chromosomes 1 and 18 (13).

Using FISH, touch preparations of 55 primary infiltrating ductal breast carcinomas were analyzed for numeric abnormalities of chromosomes X, 4, 6–12, 17, and 18 (for which directly labeled α-satellite probes were available) at two collaborating institutions. In addition, a case-control study using isolated nuclei from paraffin-embedded tissue was performed to examine possible associations between chromosome-specific aneusomy and disease progression in node-negative breast carcinoma. In this report, we present the chromosome aneusomy results detected by FISH and correlate the findings with clinicopathological data.

MATERIALS AND METHODS

Tissue Samples and Slide Preparation. Tissue samples for FISH analysis of touch preparations were obtained from patients with primary breast carcinoma at the time of diagnosis. None of the patients had received prior therapy. Samples were collected at the two study sites (Mayo Clinic, site 1; and University of Iowa, site 2) between January 1992 and December 1993. The study was limited to infiltrating ductal carcinomas. Intraductal carcinoma was present in a minority of cases; however, the infiltrating component was the major component in all cases. Fresh tissue from 10 normal breasts was used as control specimens. Touch preparations were made from tissue samples obtained adjacent to areas where histological frozen sections verified the presence of tumor cells. Touch preparations made from each tissue sample were fixed in cold methanol for 20 min, air dried, and stored at −20°C until in situ hybridization was performed.

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1 This work was supported in part by a grant from Vysis, Inc.
2 Present address: Department of Pathology and Laboratory Medicine, the University of Kansas Medical Center, Kansas City, KS 66160.
3 To whom requests for reprints should be addressed, at Laboratory Genetics, 970 Hilton, Mayo Clinic, 200 1st Street S.W., Rochester, MN 55905. Phone: (507) 284-4696; Fax: (507) 284-0043.
4 The abbreviations used are: FISH, fluorescence in situ hybridization; DAPI, 4’,-6-diamidino-2-phenylindole dihydrochloride.

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In the retrospective case-control study, isolated nuclei were obtained from paraffin-embedded breast carcinoma from lymph node-negative cases. Nineteen cases of node-negative breast carcinoma were matched by tumor size (within 0.5 cm) and surgical date. Cases were defined by evidence of disease progression within the first 3 years following surgery, whereas control patients, who had been followed for a minimum of 6.5 years, showed no evidence of progression.

**In Situ Hybridization with Centromere Enumeration Probes.** Detailed FISH methods for touch preparations have been described previously (15). Briefly, frozen slides of touch preparations were thawed, fixed for 20 min in 3:1 methanol:acetic acid, dehydrated in an ethanol series, and air dried. For paraffin-embedded tissue, isolated nuclei were prepared by the method of Hedley et al. (16) from two to four 40-µm sections of tissue. The sections were deparaffinized in Histo-Clear (National Diagnostics, Atlanta, GA) for 10 min (three times), dehydrated for 5 min in 100% ethanol (twice), and rinsed in distilled water for 5 minutes (twice). Two ml of an 8.5-mg/ml pepsin solution [P-7012; Sigma Chemical Co., St. Louis, MO; 8.5 mg/ml in 0.9% NaCl (pH 1.5)] were added, and the sections were incubated at 37°C for 2–2.5 h with vortexing every 30 min. The digested material was filtered through 40-µm nylon mesh (Tetko, Briarcliff Manor, NY) and centrifuged at 2400 rpm for 5 min. The material was washed twice in PBS, resuspended in 200–500 µl PBS, and dropped onto Superfrost/Plus slides (Fischer Scientific, Pittsburgh, PA). The cell suspension was spread over an approximately 22 × 22-mm area and oven dried at 60°C for 10 min.

Fluorescent, directly labeled α-satellite DNA probes for chromosomes X, 4, 6–12, 17, and 18 and the hybridization solution were provided by Vysis, Inc. Probes were used in either single-color or in two-color combinations. A total of 10 µl probe and hybridization mix was placed on the slide, which was coverslipped and sealed with rubber cement. Following simultaneous denaturing of the probe and target DNA in a 90°C oven for 1 min for touch preparations, the slides were incubated overnight at 41°C in a moist chamber. For isolated nuclei from paraffin-embedded tissue, slides were denatured at 80°C for 10 min and incubated at 50°C for approximately 1 h. Posthybridization washes (10 min each) for touch preparations included three 50% formamide washes in 2× SSC (300 mM/μL sodium chloride and 30 mM/μL sodium citrate) at 45°C and single washes in 2× SSC at 45°C, 2× SSC-0.1% NP40 at 45°C, and 2× SSC-0.1% NP40 at room temperature. Times for posthybridization washes for isolated nuclei were reduced to 1–5 s in one 50% formamide wash and 5–10 s in 2× SSC at 45°C, 2× SSC-0.1% NP40 at 45°C, and 2× SSC-0.1% NP40 at room temperature. Nuclei were counterstained with 1 µg/ml DAPI in the antifade p-phenylenediaminedihydrochloride.

**Analysis of Interphase in Situ Hybridization.** Hybridization signals were enumerated within 500 interphase nuclei per specimen. Criteria for analysis of nuclei have been described previously (15). Overlapping nuclei and nuclei lacking any hybridization signals were excluded from analysis. All specimens had more than approximately 85% of nuclei with hybridization signals. Analysis and photography were performed on fluorescence microscopes equipped with a triple-pass filter (DAPI/Green/Orange; Vysis) for simultaneous detection of SpectrumGreen, SpectrumOrange, and DAPI, or a dual-pass filter (DAPI/Orange) for detection of SpectrumOrange and DAPI.

Two methods of analysis were used to evaluate the significance of numerical chromosome abnormalities. In method 1, the presence of significant aneusomy was determined by using a cutoff value of 40% nondisomy (any signal pattern other than two signals) for each chromosome. In method 2, the presence of 25% of the nuclei with more than two signals was considered abnormal for any given chromosome. The associations between chromosome-specific aneusomy by either method and clinicopathological variables were determined by χ² analysis (lymph node status, estrogen receptor status, and menopause status) and ANOVA (tumor size and tumor grade). A one-tailed, paired t test was performed for analysis of cases and their corresponding controls in the case-control study.

**RESULTS**

**Touch Preparation Studies.** The use of dual-color FISH for chromosome centromere enumeration is illustrated in Fig. 1. The numbers of centromeric signals (one, two, three, four, etc.) for the 11 chromosomes were counted in each of 55 breast carcinoma touch preparations. It should be emphasized that the use of centromere probes identifies the copy numbers of individual chromosomes but does not determine whether the chromosomes are structurally normal or abnormal.

Because a standard approach for analysis of chromosome-specific aneusomy has not been developed, the chromosome copy number data were analyzed by two methods. In the first method, the frequency of chromosome-specific aneusomy within the 55 cases was determined by using a cutoff value based on normal controls. The mean nondisomy (patterns other than two signals) among the 11 chromosomes in the 10 normal breast touch preparations varied between 9 and 14%. The mean nondisomy values plus 3 SD varied between 26 and 37% (data not shown). Therefore, to assure identification of only significant aneusomic populations, a 40% cutoff value was chosen. Significant aneusomy (>40% nondisomy) for at least one of the chromosomes examined was observed in 44 of 55 cases. Fig. 2 is an example of the pattern of the percentage of nondisomic cells observed in one case for the 11 chromosomes. In this case, chromosomes 6, 7–12, and 18 were classified as aneusomic.

The second method of analysis of numeric chromosome abnormalities focused on specific chromosome gains (more than two signals). In control specimens, the mean gain for individual chromosomes varied between 1.5 and 7.2%. The mean values plus 3 SD varied between 1.9 and 10.4%. Observing more than two signals for a specific chromosome reflects either endoreduplication of the specific chromosome or a tetraploidization event resulting in doubling of the number of all chromosomes. This method was chosen because cytogenetic evidence has suggested that trisomies may be relevant as early changes in breast cancer (7). In addition, it was thought that analyzing the chromosomal gain would be a sensitive measurement of aneusomy that would avoid certain technical artifacts, such as decreased hybridization efficiency and random chromosomal loss.

The frequency of aneusomy by both methods for each chromosome in the cohort of 55 cases is illustrated in Fig. 3. The most commonly aneusomic chromosome was chromosome 8.
which had an abnormal copy number (nondisomy) in 53% of cases and was gained in 58% of the cases. Likewise, chromosome 6 was aneusomic in a higher proportion of cases (47% nondisomic and 50% gain) than were the remaining chromosomes. Nondisomy and/or gain of the remaining nine chromosomes was observed in 24–44% of the cases.

Clinicopathological data, including lymph node status, tumor size, tumor grade, estrogen receptor status, and menopausal status for the 55 cases, are summarized in Table 1. Significant statistical correlations ($P < 0.05$) between the clinicopathological variables and the frequency of aneusomy (40% nondisomy) and gain (more than two signals in 25% cells) for each chromosome are shown in Table 2. Aneusomy for chromosomes 4 ($P = 0.007$, nondisomy; $P = 0.009$, gain), 11 ($P = 0.05$, nondisomy; $P = 0.001$, gain), and X ($P = 0.006$, nondisomy; $P = 0.01$, gain) was found to be significantly associated with tumor involvement of lymph nodes. An association with lymph node status was also observed with the gain of chromosomes 7 ($P = 0.005$) and 12 ($P = 0.03$).
Table 1  Clinicopathological patient data (n = 55)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>4</td>
</tr>
<tr>
<td>40-49</td>
<td>5</td>
</tr>
<tr>
<td>50-59</td>
<td>12</td>
</tr>
<tr>
<td>60-69</td>
<td>16</td>
</tr>
<tr>
<td>&gt;69</td>
<td>18</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>21</td>
</tr>
<tr>
<td>Negative</td>
<td>34</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
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</tr>
<tr>
<td>&lt;2</td>
<td>12</td>
</tr>
<tr>
<td>2-5</td>
<td>39</td>
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<tr>
<td>&gt;5</td>
<td>4</td>
</tr>
<tr>
<td>Tumor grade</td>
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</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Estrogen receptor</td>
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</tr>
<tr>
<td>Positive</td>
<td>45</td>
</tr>
<tr>
<td>Negative</td>
<td>10</td>
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<tr>
<td>Menopause</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>45</td>
</tr>
<tr>
<td>After</td>
<td>10</td>
</tr>
</tbody>
</table>

Increasing tumor size was found to be associated with numeric chromosome abnormalities determined by both methods involving chromosomes 4 (P = 0.04, nondisomy; P = 0.0005, gain), 10 (P = 0.0002, nondisomy; P = 0.001, gain), 11 (P = 0.01, nondisomy; P = 0.0003, gain), and 17 (P = 0.03, nondisomy; P = 0.002, gain). In addition, chromosome 6 (P = 0.01) was associated with tumor size.

Tumor grade was associated with abnormal chromosomes 7 (P = 0.03, nondisomy; P = 0.004, gain) and 12 (P = 0.009, nondisomy; P = 0.02, gain), as determined by both methods. Nondisomy of chromosome X (P = 0.02) was also associated with tumor grade, as was the gain of chromosomes 4 (P = 0.05), 11 (P = 0.02), and 17 (P = 0.03).

Table 2  Chromosome-specific aneusomy: associations with clinicopathological variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Method 1</th>
<th>Method 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node status</td>
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<tr>
<td>4</td>
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</tr>
<tr>
<td>7</td>
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<td>0.005</td>
</tr>
<tr>
<td>11</td>
<td>0.05</td>
<td>0.001</td>
</tr>
<tr>
<td>12</td>
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<td>0.03</td>
</tr>
<tr>
<td>X</td>
<td>0.006</td>
<td>0.01</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.04</td>
<td>0.0005</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>10</td>
<td>0.0002</td>
<td>0.001</td>
</tr>
<tr>
<td>11</td>
<td>0.01</td>
<td>0.0003</td>
</tr>
<tr>
<td>17</td>
<td>0.03</td>
<td>0.002</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>7</td>
<td>0.03</td>
<td>0.004</td>
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<tr>
<td>11</td>
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<tr>
<td>12</td>
<td>0.009</td>
<td>0.02</td>
</tr>
<tr>
<td>17</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>0.02</td>
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</tr>
</tbody>
</table>

No associations were observed between aneusomy by either method for any of the 11 chromosomes and estrogen receptor or menopause status.

**Lymph Node-negative Case-Control Study.** Table 3 summarizes the results of aneusomy of specific chromosomes in breast carcinomas from node-negative patients whose disease progressed in the first 3 years following diagnosis (cases) compared with matched control patients (controls), in whom no evidence of disease progression was observed within at least 6.5 years following diagnosis. The difference in the mean percentage of aneusomic (other than two signals) cells and the difference in the mean percentage of gain (more than two signals) between matched cases and controls are illustrated for each chromosome. The most significant difference in the mean values for both aneusomy and gain was observed with chromosome 4 (P = 0.09 and 0.05, respectively).

**DISCUSSION**

In this study, we have described chromosome-specific, numeric abnormalities in a group of 55 primary infiltrating ductal carcinomas of the breast. Most previous cytogenetic studies of breast cancer have suggested that most breast tumors have clonal chromosomal abnormalities (17-22). In contrast, other authors have reported that a substantial proportion of primary tumors has a normal diploid karyotype (23, 24). The difference in these results could be due to a number of factors, including case selection and various culture artifacts. The use of FISH on uncultured tumor nuclei provides the advantage of accurately reflecting the in vivo chromosome complement. In addition, culture artifacts, such as overgrowth of normal diploid cells or selection of subclones possessing in vitro growth advantages, are avoided. The observation of significant aneusomy for at least one of the chromosomes examined in 44 of 55 of the tumors in this study supports the previous reports of the presence of clonal abnormalities in a large fraction of primary breast tumors. Because our method detected only numeric abnormalities and examined only one-half of the chromosomes, it is likely that an even higher proportion of primary tumors contains either structural and/or numeric clonal abnormalities.

In this study, chromosomes 8 and 6 were found to be the most frequently aneusomic chromosomes in the 55 breast carcinomas. Both the gain and loss of chromosome 8 have been described as frequent aneusomy in breast cancer cytogenetic studies (25-27). Rohan et al. (7) recently described trisomy 8 as a clonal aberration in 10 of 39 clonally abnormal breast carcinomas. In addition, they reported trisomy 8 as the most frequent nonclonal aberration. The investigators performed FISH in two cases in which nonclonal trisomy 8 was observed. Three signals for the centromere of chromosome 8 were present in 11 and 14% of the nuclei of the two cases. The authors suggested that their findings indicated that trisomy 8 was present in microclones. The present study confirms previous reports and shows that an abnormal copy number of chromosome 8 was present in more than 50% of the cases.

Chromosome 6 is one of the most frequently structurally abnormal chromosomes present in breast cancer (21). However, the gain or loss of the entire chromosome has not been reported as a frequent finding by conventional cytogenetic studies. In addition, 6q is a frequent site of loss of heterozygosity in breast tumors (28). Numeric abnormalities of chromosome 6, includ-
ing those that were possibly structurally abnormal, were detected in approximately 50% of the cases in this study.

Aneusomy, as evaluated by either specific chromosome nondisomy or chromosomal gain, was found to be associated with select prognostic factors. Evaluation of chromosome-specific gain seemed to be a more sensitive measurement than nondisomy for correlating aneusomy with prognostic variables. It is of interest that the chromosomes that most commonly had numeric abnormalities, chromosomes 8 and 6, were not found to be associated with prognostic factors, with the exception of a weak association of chromosome 6 with tumor size. In contrast, some of the other less commonly aneusomic chromosomes showed strong associations with recognized prognostic factors in this disease, namely, lymph node status (chromosomes 4, 7, 11, 12, and X), tumor size (chromosomes 4, 10, 11, and 17), and tumor grade (chromosomes 4, 7, 11, 12, 17, and X).

Numeric abnormalities of chromosome 4 were strongly associated with lymph node status. A statistically significant association with tumor size and a weak association with tumor grade were also found. Lu et al. (5) reported the loss of chromosome 4 to be a relatively common finding (5 of 22 cases) by direct cytogenetic analysis of primary breast tumors. In this study, however, a significant association with the prognostic factors was seen with the gain of the chromosome, along with nondisomy. In the retrospective case-control study comparing disease progression and chromosome-specific aneusomy in lymph node-negative cases, disease progression was found to be most closely associated with abnormalities of chromosome 4. Although significant with small sample size the finding was not statistically significant with nondisomy (P = 0.09), marginally significant associations were observed with the gain of chromosome 4 and disease progression (P = 0.05).

Chromosome 11 had a similar pattern of association with the same prognostic factors as chromosome 4. Structural abnormalities of chromosome 11, including loss of chromosomal material and amplification of sequences, have been reported in breast cancer. Mackay et al. (29) correlated the loss of sequences at 11p13-15 to the lack of estrogen receptors and increased tumor size. Another study (30) reported associations between the loss of sequences on 11p and grade III tumors, distal metastases, and the lack of estrogen and progesterone receptors. Amplification of sequences harboring the genes inte-2, bcl-1, and hst, located at 11q13, has been reported in 4–17% of breast tumors (31, 32).

Strong associations between tumor size and abnormal copy numbers of chromosomes 10 and 17 were observed. Although not a frequent finding, clonal numeric abnormalities of chromosome 17 have occasionally been reported in conventional cytogenetic studies of breast tumors (21, 33). Abnormalities of chromosome 17 are of great interest for several reasons. A region on the short arm of chromosome 17, including the TP53 gene, has the highest frequency of allele loss (deleted in >50% of informative cases) in primary breast carcinomas (28, 34–36). Furthermore, approximately 40% of breast carcinomas have loss of heterozygosity on the long arm of chromosome 17 (34, 36). Several candidate tumor suppressor genes reside on 17q, including BRCA-1 (37), the prohibitin gene (38), nm23 (39), and Wnt-3 (40).

Numeric abnormalities, especially gains, of chromosome 7 were found to be associated with lymph node status and tumor grade. Trisomy 7 has been described as a frequent clonal and nonclonal abnormality in primary breast carcinomas (7). It has also been noted as the sole cytogenetic abnormality in some breast tumors (21, 41).

This study demonstrated a high frequency of chromosome copy number aberrations in breast carcinoma. Although chromosomes 8 and 6 were the most frequently abnormal chromosomes, chromosomes 4 and 11 showed the strongest associations with established prognostic factors. For both chromosomes 4 and 11, strong associations were noted with lymph node status and tumor size. In addition, aneusomy of chromosome 4 was most closely associated with disease progression in node-negative breast cancer patients.

REFERENCES


\begin{table}
\begin{tabular}{lllll}
\hline
Chromosome & Cases (n = 19) & Controls (n = 19) & Difference (mean ± SE) & t test one-tailed P \\
\hline
4 & 21.3 ± 15.1 & 15.9 ± 8.6 & 5.4 ± 3.7 & 0.09 \\
6 & 27.1 ± 19.9 & 20.4 ± 16.8 & 6.7 ± 6.3 & 0.15 \\
7 & 22.4 ± 16.1 & 21.2 ± 20.9 & 1.1 ± 5.8 & 0.43 \\
8 & 26.7 ± 18.7 & 22.3 ± 17.1 & 4.4 ± 7.0 & 0.27 \\
9 & 18.3 ± 15.3 & 22.1 ± 21.6 & -3.8 ± 6.4 & 0.72 \\
10 & 19.0 ± 15.2 & 18.8 ± 11.4 & 0.1 ± 4.6 & 0.49 \\
11 & 21.9 ± 16.5 & 19.3 ± 16.2 & 2.6 ± 6.0 & 0.34 \\
12 & 18.0 ± 13.8 & 19.3 ± 18.0 & -1.3 ± 5.7 & 0.59 \\
17 & 21.5 ± 16.3 & 20.7 ± 13.5 & 0.8 ± 5.2 & 0.45 \\
18 & 21.8 ± 15.7 & 17.1 ± 6.1 & 4.7 ± 4.2 & 0.14 \\
X & 24.0 ± 16.2 & 23.3 ± 16.8 & 0.7 ± 6.2 & 0.46 \\
\hline
\end{tabular}
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