Frequency of Driver Mutations in Lung Adenocarcinoma from Female Never-Smokers Varies with Histologic Subtypes and Age at Diagnosis

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Abstract

Purpose: Our previous study revealed that 90% [47 of 52; 95% confidence interval (CI), 0.79–0.96] of Chinese never-smokers with lung adenocarcinoma harbor known oncogenic driver mutations in just four genes EGFR, ALK, HER2, and KRAS. Here, we examined the status of known driver mutations specifically in female never-smokers with lung adenocarcinoma.

Experimental Design: Tumors were genotyped for mutations in EGFR, KRAS, ALK, HER2, and BRAF. Data on age, stage, tumor differentiation, histologic subtypes, and molecular alterations were recorded from 349 resected lung adenocarcinomas from female never-smokers. We further compared the clinicopathologic parameters according to mutational status of these genes.

Results: Two hundred and sixty-six (76.2%) tumors harbored EGFR mutations, 16 (4.6%) HER2 mutations, 15 (4.3%) EML4-ALK fusions, seven (2.0%) KRAS mutations, and two (0.6%) BRAF mutations. In univariate analysis, patients harboring EGFR mutations were significantly older (P < 0.001), whereas patients harboring HER2 mutations were significantly younger (P = 0.036). Higher prevalence of KRAS (P = 0.028) and HER2 (P = 0.021) mutations was found in invasive mucinous adenocarcinoma (IMA). The frequency of EGFR mutations was positively correlated with acinar predominant tumors (P = 0.002). Multivariate analysis revealed that older age at diagnosis (P = 0.013) and acinar predominant subtype (P = 0.005) were independent predictors of EGFR mutations. Independent predictors of HER2 mutations included younger age (P = 0.030) and IMA (P = 0.017). IMA (P = 0.006) and poor differentiation (P = 0.028) were independently associated with KRAS mutations.

Conclusions: The frequency of driver mutations in never-smoking female lung adenocarcinoma varies with histologic subtypes and age at diagnosis. These data have implications for both clinical trial design and therapeutic strategies.

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Translational Relevance

We carried out comprehensive mutational analyses of EGFR, KRAS, ALK, HER2, and BRAF on lung adenocarcinomas from 349 Chinese never-smoking women and examined correlations between molecular alterations and clinicopathologic features. In logistic regression analyses, older age at diagnosis (P = 0.013) and acinar predominant subtype (P = 0.005) were independent predictors of EGFR mutations. Independent predictors of HER2 mutations consisted of younger age at diagnosis (P = 0.030) and invasive mucinous adenocarcinoma (IMA) subtype (P = 0.017). IMA subtype (P = 0.006) and poor differentiation (P = 0.028) were independently associated with KRAS mutations. HER2 mutations are present in a small proportion of patients with non–small cell lung carcinoma. However, in our study, when limited to the youngest one third of patients, the frequency of HER2 mutations was 9.1% in all the patients, and 27.5% in EGFR wild-type patients. These data may help inform both clinical trial design and therapeutic strategies for the treatment of never-smoking women with lung adenocarcinoma.

involved genes such as KRAS, HER2, ALK, and BRAF. Tumors harboring HER2 mutations, ALK fusions, and BRAF mutations are sensitive to BIBW 2992 (10), crizotinib (11), and PLX4032 (12), respectively.

In 2011, a new multidisciplinary classification of lung adenocarcinoma was proposed by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS). In the new classification, the term bronchioloalveolar adenocarcinoma (BAC) was no longer used, and invasive adenocarcinomas were classified according to the predominant subtype (13). It is appealing to know the association between adenocarcinoma histologic subtypes and prevalence of driver mutations.

Mutations in the tyrosine kinase domains of EGFR and HER2 are both more frequent in adenocarcinomas, never-smokers, females, and Asian patients (14–16). We previously showed that up to 90% [47 of 52; 95% confidence interval (CI), 0.79–0.96] of lung adenocarcinoma from Chinese never-smokers harbor known oncogenic driver mutations in just 4 genes EGFR, HER2, and KRAS (17). Here, we extended our comprehensive mutational analyses of EGFR, KRAS, ALK, HER2, and BRAF to 349 never-smoking women with lung adenocarcinoma and examined correlations between molecular alterations and clinicopathologic features.

Materials and Methods

Patients and samples

From October 2007 to July 2011, we consecutively procured lung tumors resected with curative intent at the Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China. Subjects eligible for this study had to meet the following criteria: pathologically confirmed lung adenocarcinoma and sufficient tissue for comprehensive mutational analyses. Patients who received neoadjuvant chemotherapy were excluded. This research was approved by the Institutional Review Board of the Fudan University Shanghai Cancer Center. Written informed consent was obtained from all patients.

Mutational analyses

RNA was extracted as per standard protocol after frozen tumor specimens were dissected into TRIzol (Invitrogen). Total RNA samples were reverse transcribed into cDNA. EGFR (exons 18–22), HER2 (exons 18–21), KRAS (exons 2–3), and BRAF (exons 11–15) were amplified by PCR using cDNA. Amplified products were analyzed by direct dideoxynucleotide sequencing. To identify EML4-ALK fusions, multiple 5’ primers were used along with a fixed 3’ primer localizing to ALK exon 20 to detect all known EML4 fusion variants as previously described (17). Note, in our previous study (17), we screened for more mutations; based upon results from the first 52 cases analyzed, subsequent tumors were analyzed for a more restricted set of mutations.

Clinicopathologic variables

Clinicopathologic data collected for analyses included age at diagnosis, pathologic tumor–node–metastasis (TNM) stage, tumor differentiation, and histologic subtypes of adenocarcinoma according to the new IASLC/ATS/ERS multidisciplinary classification of lung adenocarcinoma (13). TNM stages were evaluated in accordance with the seventh edition of the lung cancer staging classification system (18).

Statistical methods

The Pearson χ² test (when no cell of a contingency table has expected count less than 5) or the Fisher exact test (when any cell of a contingency table has expected count less than 5) was used to assess the association between 2 categorical variables. Independent sample t test was applied to investigate correlation between a categorical variable and a continuous variable. For multivariate analyses, binary logistic regression model was used. All the statistical analyses were conducted in the SPSS for Windows (version 16.0). P values were 2 tailed for all the tests. Statistical significance was set as P < 0.05.

Results

Patient characteristics

A total of 349 never-smoking female lung adenocarcinoma cases met eligibility for this study. All patients were Chinese. A summary of patient characteristics was listed in Table 1. The median age at diagnosis was 58 years (range, 23–80). The number of patients in stages I–IV was 206, 33, 99, and 11 respectively. Seventy-seven (22.1%), 175 (50.1%), and 97 (27.8%) tumors were poorly, moderately,
Table 1. Demographics and clinicopathologic features of 349 never-smoking female patients with lung adenocarcinoma

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>31–40</td>
<td>13 (3.7)</td>
</tr>
<tr>
<td>41–50</td>
<td>60 (17.2)</td>
</tr>
<tr>
<td>51–60</td>
<td>147 (42.1)</td>
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<tr>
<td>61–70</td>
<td>82 (23.5)</td>
</tr>
<tr>
<td>71–80</td>
<td>44 (12.6)</td>
</tr>
<tr>
<td><strong>Mean ± SD (range)</strong></td>
<td>57.9 ± 10.3 (23–80)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>125 (35.8)</td>
</tr>
<tr>
<td>IB</td>
<td>81 (23.2)</td>
</tr>
<tr>
<td>IIA</td>
<td>26 (7.4)</td>
</tr>
<tr>
<td>IIB</td>
<td>7 (2.0)</td>
</tr>
<tr>
<td>IIIA</td>
<td>91 (26.1)</td>
</tr>
<tr>
<td>IIIB</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td>IV</td>
<td>11 (3.2)</td>
</tr>
<tr>
<td><strong>Differentiation</strong></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>77 (22.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>175 (50.1)</td>
</tr>
<tr>
<td>Well</td>
<td>97 (27.8)</td>
</tr>
<tr>
<td><strong>Histologic subtype</strong></td>
<td></td>
</tr>
<tr>
<td>AIS</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>MIA</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td>Lepidic predominant</td>
<td>34 (9.7)</td>
</tr>
<tr>
<td>Acinar predominant</td>
<td>183 (52.4)</td>
</tr>
<tr>
<td>Papillary predominant</td>
<td>54 (15.5)</td>
</tr>
<tr>
<td>Micropapillary predominant</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Solid predominant</td>
<td>46 (13.2)</td>
</tr>
<tr>
<td>IMA</td>
<td>14 (4.0)</td>
</tr>
<tr>
<td>Enteric predominant</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>349</td>
</tr>
</tbody>
</table>

and well differentiated, respectively. The most common histologic subtype was acinar predominant (52.4%), followed by papillary predominant (15.5%), solid predominant (13.2%), and lepidic predominant (9.7%). Other invasive types of adenocarcinoma included 14 (4.0%) invasive mucinous adenocarcinoma (IMA), 6 (1.7%) micropapillary predominant, and 2 (0.6%) enteric predominant. There were 2 (0.6%) adenocarcinoma in situ (AIS) and 8 (2.3%) minimally invasive adenocarcinoma (MIA), all were nonmucinous. Detailed clinicopathologic data for each patient were listed in Supplementary Table S1.

Correlation between driver mutations and clinicopathologic features

Two hundred and sixty-six (76.2%) tumors harbored EGFR mutations, 16 (4.6%) HER2 mutations, 15 (4.3%) EML4-ALK fusions, 7 (2.0%) KRAS mutations, and 2 (0.6%) BRAF mutations (Fig. 1). All were mutually exclusive. Only 43 (12.3%) cases did not have any of these mutations.

Among EGFR tyrosine kinase domain mutations, 124 were exon 19 deletions, 111 were L858R, 8 were G719X mutations in exon 18, and 10 were insertions in exon 20. Five T790M were detected in chemotherapy-naive patients (4 concurrent with L858R, one with G719S). Other aberrations were composed of 709EF=Del, E709K, F723I, L692V, and V689L in exon 18; K757M, 746 ELREAT ins L, 745–746 ins IPYAM, and 746–747 ins GVV in exon 19; S784Y, 1768S, V774M, P776L, and S766I in exon 20; and L861Q, L833V, and V834L in exon 21.

All the 16 HER2 mutations were exon 20 insertions. EML4-ALK fusions involved 6 V1, 4 V2, 2 V3a/b, and 3 other fusion variants. KRAS mutations included 3 G12C, 2 G12D, 1 G12V, and 1 G12A. The 2 BRAF alterations were both V600E mutations.

As shown in Table 2, patients with EGFR mutations were significantly younger than those who did not (mean age, 52.6 vs. 58.1 years; P = 0.003). HER2 mutations were significantly younger than those who did not (mean age, 52.6 vs. 58.1 years; P = 0.036). There were no significant differences in the distributions of disease stage or tumor differentiation. Clinicopathologic characteristics among EGFR mutation subtypes were not statistically different (Supplementary Table S2). Because the number of cases with KRAS or BRAF mutations was low, we only listed individual patient characteristics for these patients in Supplementary Table S1.

On the basis of the findings of correlation between age and the presence of driver mutations, we further equally stratified patients into 3 categories according to age at diagnosis: ≤54, >54 and ≤61, and >61 years old. The 3 age groups contained 121 (34.7%), 111 (31.8%), and 117 (33.5%) patients, respectively. Figure 2 showed the distribution of molecular drivers among various age groups. Although more than half of the patients harbored EGFR mutations in each category, the frequency of EGFR mutation increased significantly from 66.9% in patients with ≤54 years to 76.6% in patients with >54 and ≤61 years, and 85.5% in those >61 years (P = 0.004). The mutation rate of HER2 was 9.1% in patients with ≤54 years, whereas only 3.6% of patients with >54 and ≤61 years, and one patient (0.9%) in the oldest category harbored HER2 mutations (P = 0.008). The incidences of KRAS mutation, EML4-ALK fusion, and BRAF mutation, respectively, were low and comparable among the age categories.

The distribution of driver mutations according to adenocarcinoma histologic subtypes was shown in Fig. 3. We compared frequency of driver mutations in each individual subtype to all other subtypes (Supplementary Table S3). All the AIS and MIA harbored EGFR mutations. The frequency of EGFR mutations was positively correlated with acinar predominant tumors (83.1% vs. 68.7%; P = 0.002) and negatively with IMA (28.6% vs. 78.2%; P < 0.001) and solid predominant tumors (60.9% versus 78.5%; P = 0.009). Significantly higher prevalence of KRAS (14.3% vs. 1.5%; P = 0.028) and HER2 (21.4% vs. 3.9%; P = 0.021) mutations was found in IMA.
Multivariate analyses of predictors of driver mutations

Correlations among EGFR, HER2, and KRAS mutations with clinicopathologic features were further evaluated by logistic regression analysis incorporating patient age, TNM stage, tumor differentiation, and histologic subtypes. We used median age (58 years) as cutoff value. ORs, 95% CI, and \( P \) values were listed in Table 3. Older age at diagnosis (OR, 1.93; 95% CI, 1.15–3.24; \( P = 0.013 \)) and acinar predominant subtype (OR, 2.10; 95% CI, 1.25–3.52; \( P = 0.005 \)) were independent predictors of EGFR mutations. Independent predictors of HER2 mutations included younger age at diagnosis (OR, 4.17; 95% CI, 1.15–15.11; \( P = 0.030 \)) and IMA subtype (OR, 5.81; 95% CI, 1.37–24.72; \( P = 0.017 \)). IMA subtype (OR, 14.30; 95% CI, 2.15–95.10; \( P = 0.006 \)) and poor differentiation (OR, 6.91; 95% CI, 1.24–38.60; \( P = 0.028 \)) were independently associated with KRAS mutations.

Discussion

While the incidence of lung cancer in men seems to have reached a plateau, lung cancer rates in women are still rising (1). In parallel, translational research has progressed to the point where we can define the disease at a clinically relevant molecular level. Previous studies have shown distinct molecular features in Asian female never-smokers with lung adenocarcinoma (14–16). However, our study is the first to clarify the spectrum of well-identified oncogenic driver mutations specifically in a large set of lung adenocarcinoma from East Asian never-smoking women, and to analyze correlations between driver mutations and clinicopathologic characteristics, especially histologic subtypes of adenocarcinoma in line with the new IASLC/ATS/ERS classification of lung adenocarcinoma.

There have been few studies examining the relationship between age at diagnosis and the status of multiple driver mutations concurrently in lung cancer. In those that studied associations with just EGFR mutations, the data are conflicting (19–21). Two studies, retrospectively, genotyped lung cancer specimens for EGFR from large clinical trials and revealed that EGFR mutations were associated with younger age of onset (20, 21). However, these trials mainly

![Figure 1. Frequency of driver mutations in lung adenocarcinoma from female never-smokers. The majority (87.7%) of patients harbored a known mutation (mut) in EGFR, HER2, ALK, KRAS, or BRAF.](image)

<table>
<thead>
<tr>
<th>Clinicopathologic variables</th>
<th>EGFR Mut</th>
<th>Wild</th>
<th>( P )</th>
<th>HER2 Mut</th>
<th>Wild</th>
<th>( P )</th>
<th>EML4-ALK Mut</th>
<th>Wild</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.9</td>
<td>54.5</td>
<td>&lt;0.001</td>
<td>52.6</td>
<td>58.1</td>
<td>0.036</td>
<td>54.5</td>
<td>58.0</td>
<td>0.190</td>
</tr>
<tr>
<td>Mean</td>
<td>9.7</td>
<td>11.4</td>
<td></td>
<td>6.6</td>
<td>10.4</td>
<td>0.036</td>
<td>8.8</td>
<td>10.3</td>
<td>0.190</td>
</tr>
<tr>
<td>Differentiation</td>
<td>77</td>
<td>20</td>
<td>0.066</td>
<td>4</td>
<td>93</td>
<td>0.634</td>
<td>3</td>
<td>94</td>
<td>0.786</td>
</tr>
<tr>
<td>Poor</td>
<td>51</td>
<td>26</td>
<td></td>
<td>5</td>
<td>72</td>
<td></td>
<td>4</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>138</td>
<td>37</td>
<td></td>
<td>7</td>
<td>168</td>
<td></td>
<td>8</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>22</td>
<td>20</td>
<td></td>
<td>4</td>
<td>93</td>
<td></td>
<td>3</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>166</td>
<td>40</td>
<td>0.116</td>
<td>8</td>
<td>198</td>
<td></td>
<td>6</td>
<td>200</td>
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<td>Stage II</td>
<td>24</td>
<td>9</td>
<td></td>
<td>1</td>
<td>32</td>
<td></td>
<td>3</td>
<td>30</td>
<td></td>
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<tr>
<td>Stage III</td>
<td>68</td>
<td>31</td>
<td></td>
<td>7</td>
<td>92</td>
<td></td>
<td>5</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>8</td>
<td>3</td>
<td>0.533</td>
<td>0</td>
<td>11</td>
<td>0.653</td>
<td>1</td>
<td>10</td>
<td>0.150</td>
</tr>
<tr>
<td>Stage I A</td>
<td>99</td>
<td>26</td>
<td></td>
<td>5</td>
<td>120</td>
<td></td>
<td>5</td>
<td>120</td>
<td></td>
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<tr>
<td>Stage I B</td>
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<td>14</td>
<td></td>
<td>3</td>
<td>78</td>
<td>1.000</td>
<td>1</td>
<td>80</td>
<td>0.407</td>
</tr>
</tbody>
</table>

Abbreviations: Mut, mutant type; Wild, wild-type.
enrolled Caucasian patients. Moreover, a considerable percentage of patients in both studies were males, smokers, or diagnosed with nonadenocarcinoma histology (20, 21). This age discrepancy could be partly due to the fact that female patients with lung cancer, who are enriched for \( \text{EGFR} \) mutations, tend to be younger at diagnosis than male patients (22). More recently, a study on 98 Korean females with NSCLC-stratified patients into 5-year age groups showed that \( \text{EGFR} \) mutation rate significantly increased with age (19), which is consistent with our results. Never-smokers and adenocarcinomas comprised, respectively, 84% and 83% of this population (19). Collectively, these data along with ours highlight again that never-smoking women with lung adenocarcinoma represent a unique subset of patients with the disease.

\( \text{HER2} \) mutations were found to be more prevalent in East Asian ethnicity, adenocarcinoma histology, females, and never-smokers (14, 15). According to a meta-analysis of published studies, \( \text{HER2} \) mutations were present in a small proportion of patients with NSCLC, namely 2.1% and 1.5% of Asian and Caucasian cases, respectively (23). Consistent with our data, this study also showed that \( \text{HER2} \)-mutated patients were significantly younger at diagnosis (23). Here, we report a mutation rate of 4.6% in Chinese never-smoking females with adenocarcinoma. When limited to the youngest one third of patients, the frequency of \( \text{HER2} \) mutation was 9.1% in all the patients and 27.3% in \( \text{EGFR} \) wild-type patients. These data have implications for clinical trials seeking to enrich for patients with \( \text{HER2} \) mutant tumors.

To our knowledge, however, a mechanistic basis to explain an association between the occurrence of driver mutations and age at diagnosis is unclear. As this relationship was revealed in female never-smokers, female hormones might play a role. Estrogens potentially played a role in promoting lung cancer (24). Increased estrogen levels were significantly associated with poorer survival among patients with lung cancer (25). Immunohistochemical studies showed that \( \text{EGFR} \) mutations correlated with higher expression of estrogen receptors (26, 27). In a cohort study, women experiencing a longer fertile life (measured as period from age of menarche to age of menopause or age at diagnosis) were found to have a higher proportion of \( \text{EGFR} \) mutations (28). Although these data are not sufficient to support our findings, future studies on female hormones might help to elucidate the mechanisms underlying the relationship between somatic mutations and age at diagnosis in lung adenocarcinoma from female never-smokers.

With regard to histologic molecular correlations, previous studies revealed a high prevalence of \( \text{EGFR} \) mutations in adenocarcinomas formerly classified as nonmucinous BAC or with nonmucinous BAC patterns (29, 30), which probably fell into AIS, MIA, and lepidic predominant subtype in the new classification (13). Our study showed that all the AIS and MIA (all were nonmucinous in this study), and lepidic predominant subtype had also been reported (31, 32). Mottii and colleagues (32) showed that \( \text{EGFR} \) mutations were present in 9.1% (3 of 33) of the acinar subtype, without statistical significance. However, we could not find a related study enrolling East Asian patients. To our...
knowledge, our study is the first to report a positive association between EGFR mutations and the acinar predominant subtype.

It has been well shown that IMA (formerly mucinous BAC) is correlated with an absence of EGFR mutations and the presence of KRAS mutations (29, 33–35). The present study confirmed these molecular histologic correlations. Casali and colleagues (35) reported that HER2/neu immunohistochemical expression significantly characterized mucinous BAC. However, they did not analyze HER2 mutation in their study (35). Our study is the first to show that IMA subtype was significantly correlated with the presence of HER2 mutations. A possible explanation is the high frequency of HER2 mutations in our series of nearly 350 East Asian female never-smoking patients with lung adenocarcinoma which contributed to achieving statistical significance. Together with the findings that EGFR mutations were frequently detected in AIS, MIA, and lepidic predominant adenocarcinomas, our study confirmed the distinctive molecular nature between formerly mucinous BAC and adenocarcinoma formerly classified as nonmucinous BAC or with a nonmucinous BAC component, thus supporting the removal of the term BAC in the new classification (13).

In addition to our previous study (17), we also detected 2 V600E BRAF mutations in lung adenocarcinoma from never-smoking women, accounting for a mutation rate of 0.6%. Paik and colleagues (36) screened 697 patients with lung adenocarcinoma for BRAF mutations and found that this molecular alteration was only present in current or former smokers. However, Marchetti and colleagues (37) also detected V600E BRAF mutations in never-smokers and revealed that this mutation subtype was more prevalent in females than in males.

A major limitation of this study was the lack of survival data. Since the cases were collected from 2007 to 2011, survival data of these patients were far from maturity. However, it would be of interest to evaluate the prognostic impact of clinical variables, histologic patterns, and mutation types, and further research in this aspect is warranted.

In summary, through analyses of 349 Chinese female never-smokers with lung adenocarcinoma, we found that the frequency of driver mutations varies with histologic subtypes and age at diagnosis. Given the potential effectiveness of TKIs, our findings have implications for translational research as well as clinical therapeutic strategies.

### Disclosure of Potential Conflicts of Interest

W. Pao is a Consultant/Advisory Board for AstraZeneca, Bristol-Myers Squibb, MolecularMD, Symphony Evolution, and Clovis Oncology. No potential conflict of interest were disclosed by the other authors.

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References


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