A comprehensive pan-cancer study of fibroblast growth factor receptor aberrations in Chinese cancer patients

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Background: The prevalence and types of fibroblast growth factor receptor (*FGFR*) mutations vary significantly among different ethnic groups. The optimal application of FGFR inhibitors depends on these variations being comprehensively understood. However, such an analysis has yet to be conducted in Chinese patients.

Methods: We retrospectively screened the genomic profiling results of 10,582 Chinese cancer patients across 16 cancer types to investigate the frequency and distribution of *FGFR* aberrations.

Results: *FGFR* aberrations were identified in 745 patients, equating to an overall prevalence of 7.0%. A majority of the aberrations occurred on *FGFR1* (56.8%), which was followed by *FGFR3* (17.7%), *FGFR2* (14.4%), and *FGFR4* (2.8%). Further, 8.5% of patients had aberrations of more than 1 *FGFR* gene. The most common types of aberrations were amplification (53.7%), other mutations (38.8%), and fusions (5.6%). *FGFR* fusion and amplification occurred concurrently in 1.9% of the patients. *FGFR* aberrations were detected in 12 of the 16 cancers, with the highest prevalence belonging to colorectal cancer (CRC) (31%). Other *FGFR*-aberrant cancer types included stomach (16.8%), breast (14.3%), and esophageal (12.7%) cancer. Breast tumors were also more likely than other cancer types to have concurrent *FGFR* rearrangements and amplifications (P<0.001). In comparison with the public dataset, our cohort had a significantly higher number of *FGFR* aberrations in colorectal (P<0.001) and breast cancer (P=0.05).

Conclusions: Among the Chinese cancer patients in our study, the overall prevalence of *FGFR* aberrations was 7.0%. *FGFR1* amplification was the most common genetic alteration in CRC, breast cancer, and lung cancer; while *FGFR2* amplification was more commonly observed in gastric cancer than in other cancers in our cohort. Our study advances the understanding of the distribution of *FGFR* aberrations in various cancer types in the Chinese population, which will facilitate the further development of FGFR inhibitors.

Keywords: Fibroblast growth factor receptors (*FGFRs*); *FGFR* amplifications; *FGFR* mutations; *FGFR* fusions; genomic profiling

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Introduction

Fibroblast growth factor receptors (*FGFRs*) are a family of four homologous, highly conserved transmembrane tyrosine kinase receptors (*FGFR*1-4) (1). While FGFRs are widely distributed throughout the body, they are not constitutively active in nonmalignant cells. FGFRs bind to fibroblast growth factor (FGF) ligands, leading to *FGFR* dimerization followed by phosphorylation of tyrosine residues, which triggers a series of intracellular events that activate major signaling pathways including the RAS/MAPK, PI3K/AKT, and JAK/STAT pathways (2,3). *FGFR* signaling plays a role in various biological processes including cellular proliferation, migration, anti-apoptosis, angiogenesis, wound healing, and tissue regeneration (4,5). The constitutive activation of FGFR signaling results in dysregulated proliferation and angiogenesis, the development of drug resistance, and immune evasion (5-8). *FGFR* aberrations, including gene amplification, chromosomal translocation, and/or mutations, have been reported in a broad range of cancers, including breast (9), urothelial (10), gastric (11), lung (8), and prostate cancer, as well as multiple myeloma (12).

There is significant variation in the frequency of different types of *FGFR* aberrations across different cancers (7). For instance, *FGFR1* has been reported to be amplified in as many as 19% of squamous cell lung carcinomas (13), 6% of small cell lung carcinomas, and 1% of lung adenocarcinomas (14). *FGFR1* amplification is also prevalent in breast cancer, with 15% of hormone receptor-positive breast cancers and 5% triple-negative breast cancers (TNBC) have been found to harbor *FGFR1* amplification (15-17). *FGFR2* amplification, which occurs less frequently than *FGFR1* amplification, is present in 4–9% of gastric cancers, especially in diffuse-type gastric cancer (18), and is often associated with poor prognosis (19). *FGFR2* amplification has also been found in 4% of TNBCs. Mutations in *FGFR3* are extremely common in non-muscle invasive bladder cancers (75%) and are also found in 15% of high-grade invasive bladder cancers (20-22).

In recent years, oncogenic fusions in *FGFRs* have been discovered in a number of cancers; to date, more than 40 different *FGFR* fusion proteins have been detected (3,20,23). *FGFR1* rearrangements are rare compared to *FGFR2* or *FGFR3* rearrangements. *FGFR2* fusions have been identified in approximately 13.6% of intrahepatic cholangiocarcinomas (24-26), while *FGFR3* fusions are commonly observed in glioblastomas and bladder cancers (27). Transforming acidic coiled-coil containing protein 3 (TACC3) is the most common fusion partner of *FGFR3* (28,29). The identification of oncogenic aberrations of *FGFR* family members and their potential as therapeutic targets have encouraged the development of multiple *FGFR* inhibitors, which are currently the focus of clinical studies at different phases in various cancers. Erdafitinib (*JNJ-42756493*), a potent tyrosine kinase inhibitor of *FGFR1-4*, has been approved by the US Food and Drug Administration (FDA) as the first targeted therapy for previously-treated patients with locally advanced and metastatic urothelial cancer harboring FGFR alterations (30). Selective *FGFR1-3* tyrosine kinase inhibitors, pemigatinib (INCB05482) and infigratinib (BGJ398) have been granted accelerated approval and fast-track designation, respectively, by the US FDA for the treatment of intrahepatic cholangiocarcinoma with *FGFR2* rearrangements (31-33). Several trials have shed light on the specific patient population who would benefit from *FGFR*-targeted drugs (30-39); however, studies that have investigated the distribution of *FGFR* aberrations in different cancers have focused primarily on Caucasians (20). A few studies investigated *FGFR* mutations in Chinese squamous non-small cell lung cancer patients and their associated clinical significance (40,41). However, there lacks a study that interrogates the *FGFR* mutation spectrum in Chinese cancer patients. In the present study, we examined the frequency of *FGFR* aberrations including amplification, fusions and all non-silent mutations, as well as the distribution of these mutation types across 16 different cancers in Chinese patients. We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/atm-20-5118).

Methods

Patients

Patients who were diagnosed with any of 16 cancer types

in the 3 participating hospitals: Xiangya Hospital, Hainan General Hospital, and The Seventh Affiliated Hospital, Sun Yat-sen University between September, 2015, and April, 2018, were retrospectively screened for *FGFR* aberrations based on their genomic profiling results from plasma or formalin-fixed paraffin-embedded (FFPE) tumor samples. All of the patients had submitted samples for sequencing to Burning Rock Biotech. The cohort included 10,582 patients across the following 16 cancer types: lung cancer (8,922 patients), breast cancer (750 patients), gastric cancer (149 patients), hepatobiliary cancer (101 patients), pancreatic cancer (87 patients), soft tissue sarcoma (STS, 76 patients), esophageal cancer (71 patients), ovarian cancer (59 patients), colorectal cancer (CRC, 58 patients), head and neck cancer (37 patients), renal carcinoma (32 patients), endometrial cancer (21 patients), osteogenic sarcoma (21 patients), cervical cancer (16 patients), melanoma (10 patients), and lymphoma (10 patients). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Xiangya Hospital (number: 2018121148). Due to the study's retrospective nature, written informed consent was waived.

DNA extraction

Sample processing, NGS library construction, and subsequent sequencing analysis were performed in Burning Rock Biotech, a College of American Pathologists (CAP)-accredited and Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratory. Briefly, circulating cell-free DNA (cfDNA) and tumor DNA were extracted from plasma and FFPE tumor samples using the QIAamp Circulating Nucleic Acid Kit (Qiagen, Hilden, Germany) and the QIAamp DNA FFPE Tissue Kit (Qiagen, UK), respectively, according to the manufacturer's instructions. The DNA concentration was quantified with the Qubit 2.0 Fluorometer and the Qubit dsDNA HS Assay Kit (Life Technologies, Carlsbad, USA).

Library construction and sequencing

DNA shearing was performed on tissue DNA using the M220 Focused-ultrasonicator (Covaris, Woburn, MA, USA), followed by end repair, phosphorylation, and adaptor ligation. Fragments in the range of 200–400 bp were size selected by Agencourt AMPure XP beads (Beckman Coulter, Brea, CA, USA) followed by hybridization with capture probe baits, hybrid selection with magnetic beads, and PCR amplification. Target capture was performed using commercially-available panels consisting of either 168 genes (Lung Plasma), 295 genes (OncoScreen), or 520 genes (OncoScreen Plus), spanning 0.273, 1.44, and 1.64 megabases (Mb) of the human genome, respectively. Finally, a high-sensitivity DNA assay was performed using Bioanalyzer 2100 (Agilent, CA, USA) to assess the quality and size of the fragments and indexed samples were sequenced on Illumina NextSeq 500 paired-end system (Illumina, Inc., Hayward, CA, USA).

Sequencing coverage for FGFR 1-4

Each of the gene panels used for genomic profiling contained capture probes that interrogated the same regions for *FGFR1-4*, including all of the exons for *FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4*, introns 3-4 for *FGFR1*, the intron 17 and 3' untranslated regions (UTR) for *FGFR2*, and introns 16-17 and 3' UTR for *FGFR3*.

Sequence data analysis

Burrows-Wheeler aligner v.0.7.10 was used for mapping the paired-end reads to the human genome (hg19) (42). The Genome Analysis Toolkit (GATK) v.3.2 (43) and VarScan v.2.4.3 (44) were used to perform local alignment optimization, variant calling, and annotation. DNA translocation analysis was performed using Factera v.1.4.3 (45). The variants were filtered using the VarScan filter pipeline, and loci with depths of less than 100 were filtered out. Germline mutations were also filtered out by sequencing matched white blood cells from the patients. At least two and eight supporting reads were needed for calling insertion-deletions (INDELs) and single nucleotide variations (SNVs) in plasma samples, respectively. Variants with population frequencies of over 0.1% on the Exome Aggregation Consortium (ExAC), 1,000 Genomes, dbSNP, and ESP6500SI-V2 databases were grouped as single-nucleotide polymorphisms (SNPs) and excluded from further analysis. The remaining variants were annotated with ANNOVAR (2016-02-01 release) (46) and SnpEff v.3.6 (47). Copy number variation (CNV) was detected using in-house analysis scripts based on the depth of coverage data of capture intervals. Coverage data were corrected against sequencing bias stemming from GC content and probe design. CNV was defined as the coverage data of the gene region that were quantitatively and statistically significantly

different from the corresponding reference control. The limit of detection for CNVs was 1.5 for deletions and 2.64 for amplifications. *FGFR* aberrations were considered novel if they were previously unreported in the somatic variation databases Catalogue of Somatic Mutations in Cancer (COSMIC), cBioPortal for Cancer Genomics (48), or the Atlas of Genetics and Cytogenetics in Oncology and Hematology (49).

Statistical analysis

Continuous variables were presented as either the mean ± standard deviation (SD) or the median with interquartile ranges, and categorical variables were presented as frequencies. Continuous variables were compared with unpaired Wilcoxon signed-rank tests, and two-sided Fisher's exact tests were used to compare categorical data, as appropriate. P<0.05 was considered statistically significant. All bioinformatics analyses were performed with R (v.3.5.3, the R Foundation for Statistical Computing, Vienna, Austria).

Results

Somatic aberrations of FGFRs

Of the 10,582 patients screened, *FGFR* aberrations were detected in 745 patients, showing an overall prevalence of 7.0%. *FGFR* amplification was harbored by 3.8% of the screened population, 0.5% had fusions, and the remaining 2.7% had other mutations. Aberrations of *FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4* were detected in 56.8%, 14.2%, 17.7%, and 2.8% of the 745 patients, respectively, and 8.5% of them had concurrent *FGFR* aberrations (>1 *FGFR* aberration, *Figure 1A*). Amplification was the predominant mutation type and was detected in 53.7% of the patients. Rearrangements were observed in 5.6% of patients. Non-amplification, non-fusion mutations including insertions or deletions, single base substitutions, multiple-nucleotide substitutions, and copy number deletions, which hereafter are referred to collectively as mutations or other mutations, were detected in 38.8% of the patients. Furthermore, 1.9% of patients had concurrent *FGFR* fusion and amplification (*Figure 1B*). The mutation types were distributed significantly differently across the four *FGFRs* (P<0.01). Of the *FGFR1* aberrations, 70% were amplifications, 28% were mutations, 1% were fusions, and 1% were concurrent fusions and amplifications. Amplifications were more likely to be detected in *FGFR1* than in any of the other *FGFR* genes (P<0.001). Of the *FGFR2* aberrations, 57% were mutations, 35% were amplifications, 3% were fusions, and 5% were concurrent fusions and amplifications. *FGFR2* had significantly more concurrent fusions and amplifications than the other genes (P=0.003). Of the *FGFR3* aberrations, 56% were mutations, 24% were amplifications, 19% were fusions, and 1% were concurrent fusions and amplifications. *FGFR3* fusions occurred more frequently than fusions in the other 3 *FGFR* genes (P<0.001). The predominant aberration in *FGFR4* was mutations (69%), followed by amplifications (28%), and fusions (3%) (*Figure 1C*). Moreover, 86 novel non-amplification, non-fusion mutations were identified from our cohort; these are listed in *Table S1*. A total of 24, 25, 25, and 12 novel mutations were identified in *FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4*, respectively. Taken together, these data revealed an overall *FGFR* aberration prevalence of 7.0% in Chinese patients across 16 different cancers. Also, distinct mutation frequencies and distributions of mutation types were observed in the four *FGFR* genes.

Somatic aberrations of FGFRs across the 16 cancer types

Next, we investigated the mutation frequencies and distribution of mutation types of the four *FGFR* genes based on cancer type. Our cohort comprised of patients with 16 different types of cancer. In the following four types of cancer, no *FGFR* aberrations were identified: head and neck cancer, osteogenic sarcoma, renal carcinoma, and lymphoma. Detailed mutation frequencies and the distribution of mutation types of the 4 *FGFR*s in the other 12 cancers are summarized in *Table 1*.

Among the cancer types analyzed in this study, CRC (18/58, 31.0%) had the highest frequency of *FGFR* aberrations, with the majority of these aberrations identified in *FGFR1* (12/18, 8 amplifications and 4 other mutations). Mutations in the other *FGFR* genes included *FGFR2* amplification (n=1), *FGFR3* amplification (n=1), *FGFR3* mutation (n=1), *FGFR4* mutation (n=1), and concurrent mutations in multiple *FGFR* genes (n=2).

Of the 10 patients with melanoma in our cohort, 2 patients harbored *FGFR1* aberrations, amplification, and a fusion (*FGFR1* Exon10-*ADAM9* Intron 11). However, due to the extremely limited number of patients with melanoma included in our cohort, this prevalence (20.0%, 2/10) may not accurately reflect the prevalence of *FGFR1* aberrations in the broader population of Chinese melanoma patients.

Meanwhile, of the 149 patients with gastric cancer, 16.8% (25/149) had *FGFR* aberrations, with a majority of

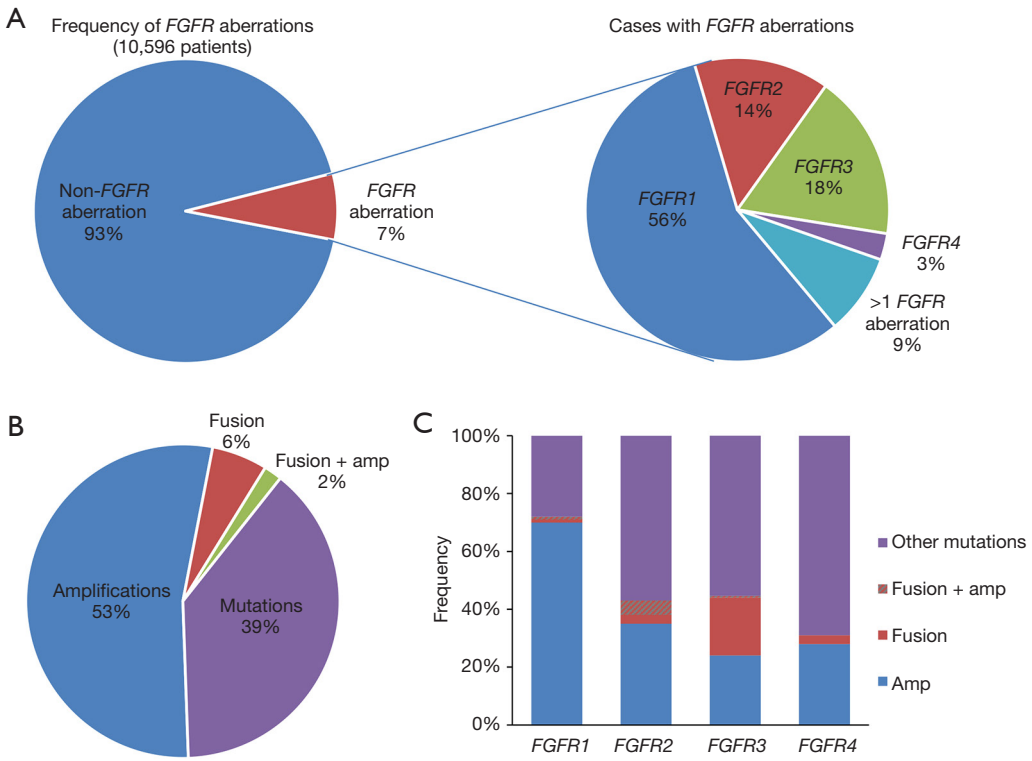

Figure 1 *FGFR* aberrations in 10,582 cancer patients across 16 cancer types. (A) The prevalence of *FGFR* aberrations among all cancer patients (left), the percentages of patients with aberrations in *FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4*, and the percentages of patients with aberrations in more than one *FGFR* gene (right); (B) the distribution of mutation types in patients with *FGFR* alterations; (C) the distribution of mutation types for each *FGFR* gene. Different types of alterations are denoted in different colors.

the patients harboring mutations in *FGFR2* (64.0%, 16/25). Amplification was the most frequently observed mutation type, occurring in 68.0% (17/25) of the gastric cancer patients.

Of the 750 breast cancer patients included in the cohort, 14.7% (107/750) had *FGFR* alterations, and the majority harbored mutations in *FGFR1* (75.7%, 81/107), followed by *FGFR2* (17.8%, 19/107). Only 1 patient had a mutation in *FGFR3*, and 2 patients had aberrations of *FGFR4*. Amplification was also the predominant mutation type among breast cancer patients, with 84.1% of the patients harboring amplifications (84.1%, 90/107).

The prevalence rates of *FGFR* aberrations between esophageal (9/71, 12.7%), cervical (2/16, 12.5%), and ovarian (7/59, 11.9%) cancer were comparable. In contrast to the other cancer types, the predominant mutation type in esophageal carcinoma was non-amplification, non-fusion mutations. Of the 16 patients with cervical cancer, 2 had *FGFR3* fusions. Due to the small number of patients with cervical cancer included in our cohort, this prevalence (12.5%, 2/16) may not be representative of the actual prevalence of *FGFR3* fusion among Chinese cervical cancer patients. From a screening pool of 59 patients with ovarian cancer, 7 had *FGFR* alterations spanning all 4 *FGFR* genes. Two patients had concurrent mutations in two *FGFR* genes.

Among the 101 patients with hepatobiliary cancer, 7 patients had *FGFR* mutations, equating to a prevalence of 6.9%; 3 patients had *FGFR1* aberrations, 3 patients harbored *FGFR2* aberrations, and 1 patient had a concurrent *FGFR1/3* amplification. Of these seven patients, two had fusions, three had other mutations, and two had amplifications.

FGFR aberrations were harbored by 6.2% (552/8,922) of the patients with lung cancer in our study, with the majority of aberrations occurring in *FGFR1* (59.6%, 311/552), followed by *FGFR3* (119/552) and *FGFR2* (60/552). *FGFR4* aberrations were detected in 16 (2.9%, 16/552) patients

Table 1 Frequencies and distributions of *FGFR* aberrations detected in our cohort

Cancer type	N	Frequency of aberrations per cancer type (%)									
		All	Distribution per gene					Distribution per mutation type			
			FGFR1	*FGFR2*	*FGFR3*	*FGFR4*	Multiple *FGFR*s	Amp	Mutation	Fusion	Fusion + amp
Lung	8,922	6.19	3.49	0.67	1.33	0.18	0.52	3.08	2.71	0.36	0.03
Breast	750	14.27	10.8	2.53	0.13	0.27	0.53	11.07	2.0	0.13	1.07
Gastric	149	16.78	2.01	10.74	2.01	0	2.01	10.07	5.37	0	1.34
Colorectal	58	31.03	20.69	1.72	3.45	1.72	3.45	17.24	13.79	0	0
Soft tissue sarcoma	76	5.26	1.32	3.95	0	0	0	2.63	1.32	1.32	0
Ovarian	59	11.86	3.39	1.69	1.69	1.69	3.39	6.78	3.39	1.69	0
Esophageal	71	12.68	2.82	0	5.63	0	4.23	2.82	7.04	2.82	0
Pancreatic	87	4.60	2.3	1.15	0	1.15	0	2.3	2.3	0	0
Hepatobiliary	101	6.93	2.97	1.98	0	0	0	0.99	1.98	1.98	0
Melanoma	10	20	20	0	0	0	0	10	0	10	0
Endometrial	21	4.76	4.76	0	0	0	0	4.76	0	0	0
Cervical	16	12.5	0	0	12.5	0	0	0	0	12.5	0

Mutation refers to all non-amplification, non-fusion mutations including insertions or deletions, single base substitutions, multiple-nucleotide substitutions, and copy number deletion. N, screened population; amp, amplification.

including 7 with amplifications and 9 with other mutations. The most common mutation type among the lung cancer patients in our study was amplification.

Among the 76 patients with STS, 4 *FGFR* aberrations were identified, including 3 in *FGFR2* and 1 in *FGFR1*, revealing a prevalence of 5.3%. Of the 21 patients with endometrial cancer screened, only 1 patient with an *FGFR1*-amplified tumor was identified (4.8%, 1/21). Of the 87 patients with pancreatic cancer, 4 (5%) had *FGFR* aberrations; these were *FGFR1* amplification, *FGFR2* amplification, *FGFR1* mutation; and *FGFR4* mutation, respectively.

Collectively, our analysis revealed distinct prevalence and distribution of mutation types of *FGFR* aberrations in 12 cancer types. *FGFR1* amplification was the most common genetic alteration in CRC, breast cancer, and lung cancer, while *FGFR2* amplification was more commonly observed in gastric cancer than in other cancers in our cohort.

Comparison with publicly available pan-cancer dataset

To better understand the distinct distribution of *FGFR* aberrations in Chinese patients with cancer, we compared our cohort with that of the Memorial Sloan Kettering Cancer Center (MSKCC) dataset obtained from cBioPortal (48,50). The coverage for the 4 *FGFR* genes was comparable between our panel and the panels used in the MSKCC cohort (50,51). The results are shown in *Figure 2* and are summarized in *Table S2*. Since the MSKCC dataset does not include patients with gastric cancer, we only compared the distribution of *FGFR* aberrations between 11 cancers. Collectively, our cohort had a significantly higher number of *FGFR* aberrations in CRC (P<0.001) and breast cancer (P=0.05) than the cohort in the MSKCC dataset (*Figure 2*). Moreover, *FGFR1* aberrations were more common in patients with CRC (20.7% *vs.* 3.1%; P<0.001) and melanoma (20.0% *vs.* 1.1%; P=0.01) in our cohort. *FGFR2* aberrations were more frequently observed in patients with STS in our cohort (4.0% *vs.* 0.2%; P=0.01). *FGFR3* aberrations occurred less frequently in patients with breast cancer (0.1% *vs.* 1.2%; P=0.01) and more frequently in patients with esophageal cancer (5.6% *vs.* 0.6%; P=0.01) in our cohort compared with the MSKCC cohort. Meanwhile, *FGFR4* aberrations were significantly less common in patients with lung (0.2% *vs.* 1.2%; P<0.001) and breast (0.3% *vs.* 1.3%; P=0.03) cancer in our cohort. Concurrent

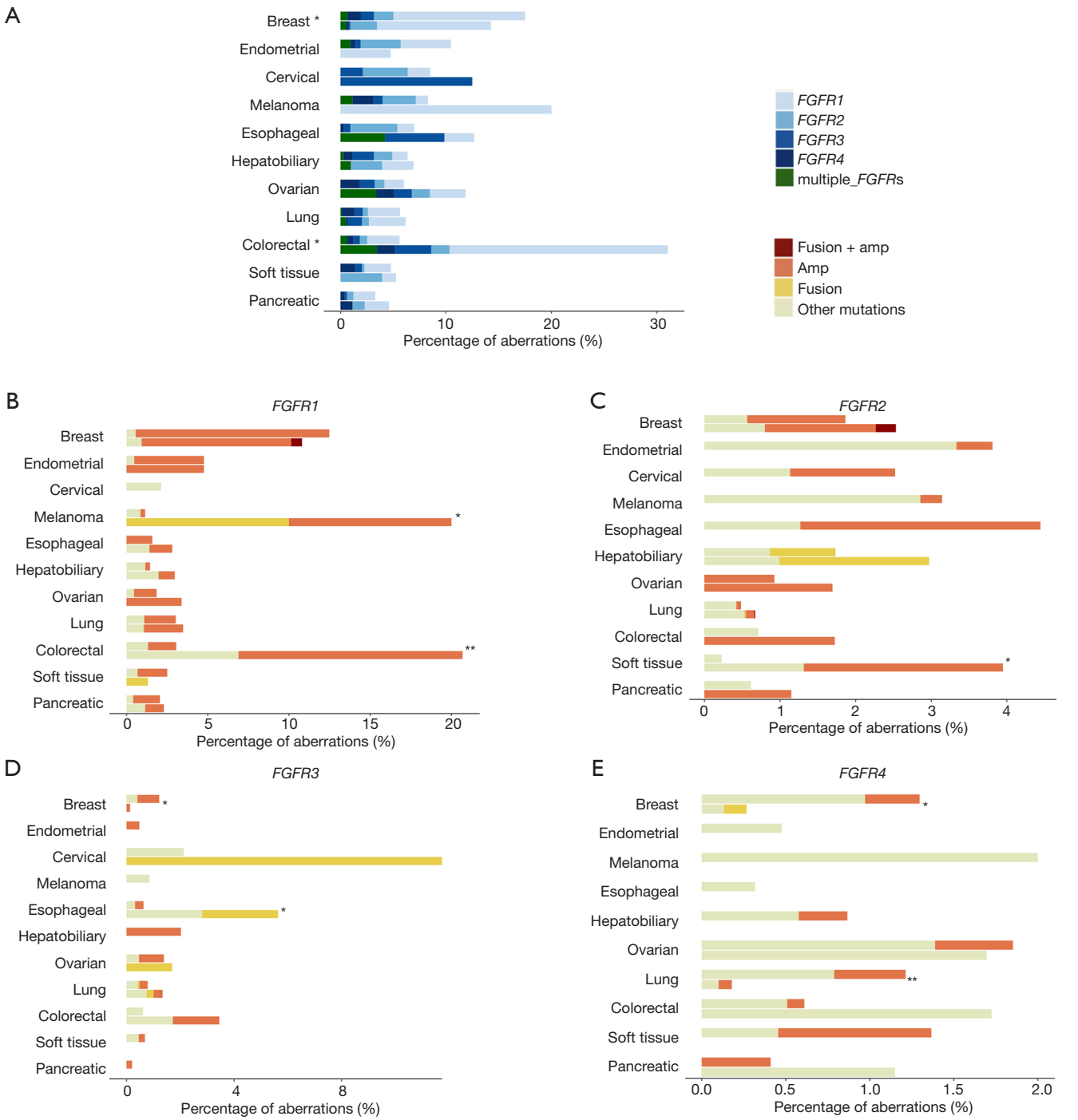

Figure 2 The prevalence and relative distributions of all *FGFR* aberrations (A), and in *FGFR1* (B), *FGFR2* (C), *FGFR3* (D), and *FGFR4* (E) in 11 cancer types. The frequency of *FGFR* aberrations is reported as the percentage of all cases screened per cancer type. The distribution of alteration types is shown as the proportion within each *FGFR* gene. Different *FGFR* genes (A) and alteration types (B,C,D,E) are denoted in different colors. The top bar reflects the data from the MSKCC data set for that particular cancer type; the bottom bar reflects the data from our cohort. (B,C,D,E) The single bars reflect only the data from our cohort due to the absence of corresponding data from the MSKCC cohort for some *FGFR*/cancer types. *, denotes statistical significance of P=0.05–0.01; **, denotes statistical significance of P<0.001.

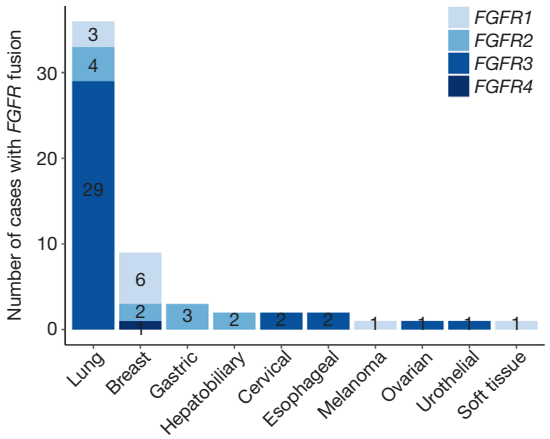

Figure 3 The distribution of *FGFR* fusions in our cohort. The frequency of *FGFR* fusions is reported as the number of all cases screened per cancer type. Different *FGFR* genes are denoted in different colors.

FGFR aberrations were also more frequent among lung (0.5% *vs.* 0.1%; P=0.03), esophageal (4.2% *vs.* 0%; P=0.01), and ovarian (3.4% *vs.* 0%; P=0.045) cancer patients in our cohort in comparison with the MSKCC cohort. No significant differences were found between our data and the MSKCC dataset in the distribution of *FGFR* aberrations in urothelial, hepatobiliary, endometrial, or cervical cancer. Overall, our findings revealed the distinct distribution of *FGFR* aberrations in our cohort in certain cancer types.

Distribution of FGFR fusion across cancer types

Next, we performed a detailed analysis of *FGFR* fusions. Fifty-nine *FGFR* fusions were distributed in 57 patients, spanning 9 of the 12 cancer types analyzed (*Figure 3*). Concurrent fusions were detected in two patients including one patient with STS harboring concurrent *FGFR1-CREM* (Intron4-intergenic region) and *FGFR1-FN1* (Intron 4-Intron 20), and one patient with gastric cancer harboring concurrent *FGFR2-MIR5694* (Exon 18-intergenic region) and *FGFR2-PDHX* (Intron 3-Exon 18). Furthermore, 13 patients had concurrent *FGFR* fusions and amplifications (*Figures 4*,*S1*). The majority of fusions involved *FGFR3* (59.3%, 35/59), followed by fusions in *FGFR1* (20.3%, 12/59), *FGFR2* (18.6%, 11/59), and *FGFR4* (1.7%, 1/59). Of the 59 *FGFR* fusions, the majority were (61.0%, 36/59) observed in patients with lung cancer; while the others were detected in patients with breast cancer (n=9), gastric cancer (n=3), hepatobiliary cancer (n=2), cervical cancer (n=2), and esophageal cancer (n=2), as well as in individual patients with melanoma, ovarian cancer, or STS. Of the cancer types with a reasonably large screening population (excluding melanoma and cervical cancer), esophageal cancer had the highest prevalence (2.8%) of *FGFR* fusions, followed by gastric cancer and hepatobiliary carcinoma, which each had a prevalence of 2%. In contrast, low frequencies of *FGFR* fusions were observed in lung and breast cancer, with fusions occurring in 0.4% and 1.2% of patients, respectively. The majority of fusions in lung cancer involved *FGFR3* (80.6%, 29/36); while for breast cancer, the majority involved *FGFR1* (66.7%, 6/9) (*Figure 3*). Meanwhile, a previously unreported rearrangement between *FGFR4* and *MAP1B* (*MAP1B* intergenic region-*FGFR4* Exon 7) was detected in a patient with breast cancer. Interestingly, in our analysis, *FGFR*-rearranged breast tumors were more likely to exist with concurrent *FGFR* amplifications (8/9) than other tumor types (P<0.001).

Overall, 31 fusion partners were identified from our cohort, including *TACC3*, *MIR5694*, and *MIR1286A*, which were detected in 26, 2, and 2 patients, respectively. The remaining 28 fusion partners were only detected once. *TACC3-FGFR3* fusions were predominantly detected in patients with lung cancer (21/26), but were also in patients with esophageal (n=2), cervical (n=2), and ovarian (n=1) cancer. *Table 2* summarizes the *FGFR* fusions detected in the cohort. Twenty-eight of the fusion partners detected were previously unreported. Additionally, breakpoints of fusion partners were detected in various regions including 22 in intergenic regions and 3 in the kinase domain of *FGFR*, while 3 had noncoding fusion partners. A further 31 breakpoints occurred outside of the abovementioned regions and thus may potentially be functional.

The panels we used for targeted sequencing not only interrogated critical regions of *FGFR1-4*, but also included various genes associated with the development and progression of cancer. Hence, we further analyzed the genomic profiles of patients with *FGFR*-rearranged tumors for concurrent mutations (*Figures 4*,*S1*). Since the sequencing was performed using panels comprising different numbers of genes, only the genes that were common across all of the panels were analyzed. Among the 36 patients with *FGFR*-rearranged lung cancer, concurrent *TP53* mutations were detected in a majority (80.56%, 29/36) of the patients. Furthermore, classic lung cancer driver mutations were detected in 20 patients; these included *EGFR* mutations (n=15), *ALK* fusion (n=1), *RET* fusion (n=1), *MET* amplification (n=1), *ERBB2* amplification

Table 2 List of the *FGFR* fusions detected in our study

Cancer type	*FGFR* family	Fusion partner	Breakpoint information for fusion partners (excluding TACC3)
Lung	*FGFR1*	*MIR1268A*	MIR1268A intron2-FGFR1 Exon16
		*C20orf26**	FGFR1 Intron6-C20orf26 intergenic
		*MIR3148**	FGFR1 Intron4-MIR3148 intergenic
	FGFR2	*DPRX**	DPRX intergenic-FGFR2 Intron10
		*ZWINT**	FGFR2 Intron17-ZWINT intergenic
		*LRRC49**	FGFR2 Exon18-LRRC49 Intron8
		MIR5694	MIR5694 intergenic-FGFR2 Intron17
	FGFR3	*PYGL**	PYGL Intron3-FGFR3 intergenic
		TACC3	FAM53A Intron2-FGFR3 intergenic
		*FAM53A**	MUM1 intergenic-FGFR3 Exon18
		*MUM1**	LOC101928201 intergenic-FGFR3 Exon3
		*LOC101928201**	IDUA intergenic-FGFR3 Exon18
		*IDUA**	FGFR3 Exon6-SLBP Intron3
		*SLBP**	FGFR3 Intron13-LOC100507175 intergenic
		*LOC100507175**	
Breast	*FGFR1*	*KCNU1**	KCNU1 intergenic-FGFR1 Exon19
		MIR1268A	MIR1268A Intron2-FGFR1 Exon9
		LZTS1-AS1	LZTS1-AS1 intergenic-FGFR1 Exon6
		*LINC01605**	LINC01605 Intron1-FGFR1 Exon4
		TACC1	TACC1 Intron6-FGFR1 Exon6
		*RNF5P1**	RNF5P1 intergenic-FGFR1 Intron18
	FGFR2	*EPHA6**	EPHA6 Intron5-FGFR2 Exon3
		*ARMT1**	ARMT1 Exon1-FGFR2 Intron11
	FGFR4	*MAP1B**	MAP1B intergenic-FGFR4 Exon7
Gastric	*FGFR2*	*MIR99AHG**	MIR99AHG intergenic-FGFR2 Exon18
		MIR5694[1]	FGFR2 Exon18-MIR5694 intergenic
		*PDHX**[1]	PDHX Intron3-FGFR2 Exon18
		*ATE1**	FGFR2 Intron17-ATE1 Intron10
Hepatobiliary	*FGFR2*	*BICC1*	FGFR2 Intron17-BICC1 Intron2
		*LINC00251**	FGFR2 Intron17-LINC00251 intergenic
Cervical	*FGFR3*	*TACC3*	
Esophageal	*FGFR3*	*TACC3*	
Melanoma	*FGFR1*	*ADAM9**	FGFR1 Exon10-ADAM9 Intron11
Ovarian	*FGFR3*	*TACC3*	
Soft tissue sarcoma	*FGFR1*	*CREM**[2]	CREM intergenic-FGFR1 Intron4
		FN1[2]	FGFR1 Intron4-FN1 Intron20

Asterisks (*) denote fusion partners unreported in publications and absent in somatic variation databases; [1] denotes two novel fusion partners detected from the same gastric cancer patient; [2] denotes two novel fusion partners detected from the same soft tissue sarcoma patient.

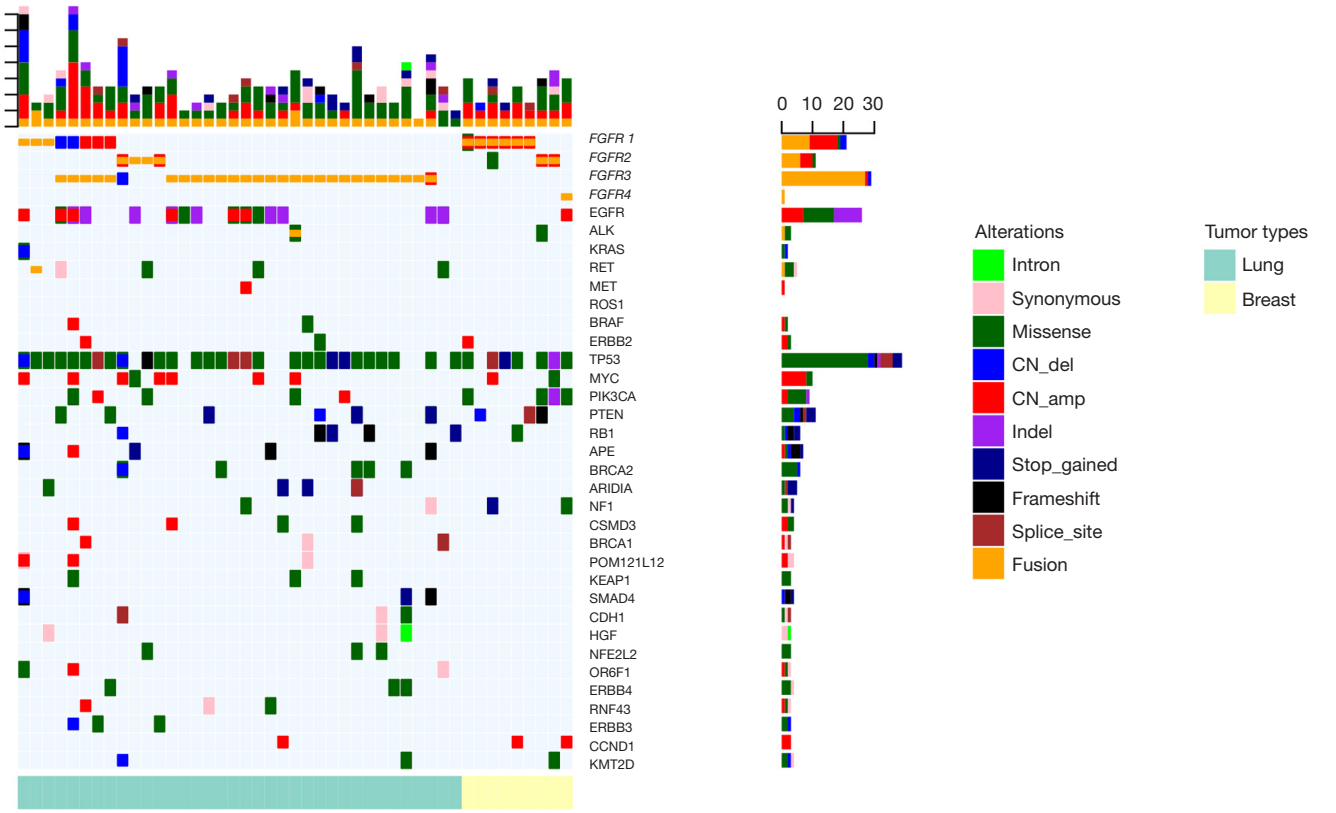

Figure 4 The comprehensive somatic mutation spectrum of *FGFR*-rearranged lung and breast cancer patients. Each column represents a patient; each row represents a gene. The number on the left represents the percentage of patients with mutations in a specific gene. The top plot represents the overall number of mutations detected in a patient. Different types of mutations are denoted in different colors. The colored annotation at the bottom of the oncoprint specifies the cancer type of the patient.

(n=1), and *KRAS Q61* mutation (n=1) (*Figure 4*). Among the 9 patients with *FGFR*-rearranged breast cancer, concurrent *TP53* mutations were also detected in 7 patients (7/9). Other frequently mutated genes included *PIK3CA* (4/9) and *PTEN* (3/9). One patient had *ERBB2* amplification (*Figure 4*). Moreover, concurrent *TP53* mutations were also detected in patients with various *FGFR*-rearranged tumors including gastric (2/3), hepatobiliary (1/2), esophageal (2/2), ovarian (1/1), and urothelial (1/1) cancer (*Figure S1*). Taken together, our data revealed that the genomic profiles of patients who harbored *FGFR* fusions were comparable to those of patients with the same cancer type but without *FGFR* fusions.

Discussion

FGFR aberrations have been shown to be drivers of cancer development and progression, which makes them attractive therapeutic targets (5,7,8). The optimal application of FGFR inhibitors demands a comprehensive understanding of the prevalence and types of *FGFR* mutations. However, studies on the prevalence of *FGFR* aberrations, as well as the distribution of the mutation types across multiple cancer types, have only focused on Western populations (20), and similar research on Chinese cancer patients is limited. Herein, we conducted a pan-cancer retrospective study to investigate the prevalence and distribution of mutation types in Chinese patients with different cancers. Of the 16 cancer types included in our cohort, we revealed the overall prevalence of *FGFR* aberrations to be 7.0%. Consistent with the findings of a study on Caucasian cancer patients (20), in our cohort, *FGFR1* and *FGFR4* aberrations were found to be the most and least frequent, respectively. A majority of the *FGFR* aberrations in our cohort were amplifications (53.7%). In contrast, *FGFR* rearrangements are relatively rare, with a frequency of 7.5%, which is comparable to the

prevalence reported by other studies (20,52). Furthermore, our findings revealed the distinct distribution of *FGFR* mutations across various cancers.

Multiple studies have investigated the prevalence of *FGFR* aberrations. Compared to the published data (20,26), we revealed comparable prevalence across cancers including lung, breast, STS, ovarian, and pancreatic cancer, as well as hepatobiliary carcinoma. However, we also revealed a significantly higher incidence of *FGFR* aberrations in Chinese patients with gastric/esophageal cancer (15.45% *vs.* 6.7%, P<0.001) and CRC (31.03% *vs.* 4.4%, P<0.001) (20). To further analyze the prevalence and the distribution of *FGFR* aberrations between our cohort and Caucasian patients, we compared the sequencing data from our cohort with the MSKCC dataset (51), which revealed a statistically distinct distribution of *FGFR* aberrations in certain cancer types between the two populations. Our cohort had a significantly higher number of *FGFR* aberrations in CRC (P<0.001) and breast (P=0.05) cancer than the MSKCC cohort. The prevalence of mutations in each *FGFR* gene also differed in some cancer types between the two populations. Interestingly, concurrent *FGFR* aberrations were also more frequent in Chinese patients with lung (0.52% *vs.* 0.12%), esophageal (4.23% *vs.* 0%), and ovarian (3.39% *vs.* 0%) cancers than in their Western counterparts.

Furthermore, based on our findings, *FGFR1* amplification was the most frequently observed genomic aberration in several types of cancer, including CRC, lung, breast, and ovarian cancers. *FGFR1* amplifications were detected in 13.8% (9/58) of Chinese patients with CRC in our cohort and have been reported to have a prevalence of 5.3% (24/454) in CRC primary tumors and 97.9% (92/94) of patients with CRC who have lymph node metastases (53). In our cohort, 2.4% of patients with lung cancer, 97% of whom had lung adenocarcinoma, were found to harbor *FGFR1* amplifications, which is comparable to the prevalence of 1.5% reported for lung adenocarcinoma in Western population (20). The incidence of *FGFR1* amplifications in lung cancer varies according to histology and tumor grade, with other studies reporting a prevalence of 20% in squamous cell carcinoma of the lung (54,55) and 6% in small cell lung carcinoma (14). In our cohort, *FGFR1* amplifications were also prevalent (9.2%) among the patients with breast cancer, which is consistent with the prevalence of 9.7% reported from the Breast Cancer International Research Group (BCIRG) trials (56). *FGFR2* amplifications commonly occurred in gastric cancer and breast cancer, with prevalence rates of 9.4% and 1.7%, respectively. These data were highly consistent with the rates reported in earlier studies (18,57). *FGFR3* and *FGFR4* amplifications were rarely observed; patients were far more likely to harbor other types of mutations. Surprisingly, in contrast to previous reports that found 10–12% of patients with endometrial cancer harbored *FGFR2* mutations (excluding amplifications and fusions) and 5% of patients with cervical cancer harbored *FGFR3* mutations (excluding amplifications and fusions) (20,21,58,59), we did not observe any *FGFR2* and *FGFR3* mutations in our patients with endometrial and cervical cancers. This discrepancy may be attributable to the limited size of our screening population in these two gynecological cancers.

FGFR fusions, which represent 8% of *FGFR* aberrations, have been considered as drivers of cancer development and progression (28,60,61). In our study, the majority of *FGFR* fusions in four cancer types (lung, cervical, esophageal, and ovarian cancer) involved *FGFR3*. *FGFR3* fusions have also been commonly observed in bladder cancer and glioblastoma (6,62). *FGFR2* fusions, the second most commonly observed fusion, were found in breast, gastric, hepatobiliary, and lung cancer. *FGFR2* fusion-driven tumor cells are sensitive to FGFR inhibitors, infigratinib (BGJ398) and PD173074, thus *FGFR2* fusions are recognized as a promising target (25,31-33). Despite their rarity, *FGFR1* fusions were observed in breast cancer, melanoma, lung cancer, and STS in our study. We also detected a previously unreported *FGFR4* fusion in a patient with breast cancer. Meanwhile, *TACC3* was revealed as the most frequently observed fusion partner, which can potentially be explained by its close proximity to *FGFR*, and this is consistent with the results of other studies (63,64). In addition to previously reported fusion partners, including *TACC3*, *TACC1*, *BICC1*, and *FN1* (20,23,25,27,62,63,65), we also identified numerous novel fusion partners from our cohort.

Our study has several limitations. Firstly, patients were selected for NGS-based genetic testing at the physicians' discretion, which may have introduced sampling bias. Secondly, the size of the screening population was extremely limited for some cancer types, especially endometrial cancer, cervical cancer, and melanoma. Thirdly, due to the retrospective nature of our study, data such as detailed clinicopathological characteristics, treatment history, and survival outcomes were not available for most of the patients; hence, association analysis could not be performed. A nationwide multi-center, prospective study to evaluate the association between *FGFR* aberrations and the clinical outcomes of patients with various cancers is called for.

Fourth, our study does not include the functional analysis of the oncogenicity of the novel *FGFR* fusions identified in our cohort. *In vitro* experiments are needed to elucidate the functionality of novel fusions. Despite these limitations, to the best of our knowledge, our study is the first to comprehensively investigate the prevalence and distribution of *FGFR* aberrations in a large cohort of Chinese patients spanning 16 cancer types.

Conclusions

In conclusion, our study revealed an overall prevalence of *FGFR* aberrations of 7.0% in Chinese patients with cancer. Our findings also demonstrate a distinct distribution of certain *FGFR* aberration in Chinese patients with certain types of cancer. Our study facilitates a better understanding of *FGFR* mutations in various cancer types in the Chinese population.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures involving human participants were performed in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Xiangya Hospital (approval number: 2018121148). Due to the study's retrospective nature, written informed consent was waived.

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