Journal of Cancer Research and Clinical Oncology (2019) 145:625–636
https://doi.org/10.1007/s00432-018-2817-z

ORIGINAL ARTICLE – CANCER RESEARCH

TP53 mutations as potential prognostic markers for specific cancers: analysis of data from The Cancer Genome Atlas and the International Agency for Research on Cancer TP53 Database

Victor D. Li[1] · **Karen H. Li**[1] · **John T. Li**[1]

Received: 14 August 2018 / Accepted: 5 December 2018 / Published online: 12 December 2018

Abstract

Purpose Mutations in the tumor suppressor gene TP53 are associated with a variety of cancers. Therefore, it is important to know the occurrence and prognostic effects of TP53 mutations in certain cancers.

Methods Over 29,000 cases from the April 2016 release of the International Agency for Research on Cancer (IARC) TP53 Database were analyzed to determine the distribution of germline and somatic mutations in the TP53 gene. Subsequently, 7,893 cancer cases were compiled in cBioPortal for Cancer Genomics from the 33 most recent The Cancer Genome Atlas (TCGA) studies to determine the prevalence of TP53 mutations in cancers and their effects on survival and disease-free survival times.

Results The data were analyzed, and it was found that the majority of TP53 mutations were missense and the major mutational hotspots were located at codons 248, 273, 175, and 245 in exons 4–8 for somatic mutations with the addition of codon 337 and other mutations in exons 9–10 for germline mutations. Out of 33 TGCA studies, the effects of TP53 mutations were statistically significant in nine cancers (lung adenocarcinoma, hepatocellular carcinoma, head and neck squamous cell carcinoma, acute myeloid leukemia, clear cell renal cell carcinoma (RCC), papillary RCC, chromophobe RCC, uterine endometrial carcinoma, and thymoma) for survival time and in five cancers (pancreatic adenocarcinoma, hepatocellular carcinoma, chromophobe RCC, acute myeloid leukemia, and thymoma) for disease-free survival time. It was also found that the most common p53 mutation in hepatocellular carcinomas (R249S) was a much better indicator for poor prognosis than TP53 mutations as a whole. In addition, in cases of ovarian serous cystadenocarcinoma, the co-occurrence of TP53 and BRCA mutations resulted in longer survival and disease-free survival times than the presence of neither TP53 nor BRCA mutations.

Conclusion TP53 mutations are potential prognostic markers that can be used to further improve the accuracy of predicting survival and disease-free survival times of cancer patients.

Keywords TP53 · p53 · Cancer · Prognostic marker

Introduction

The tumor suppressor gene TP53 encodes for the p53 protein, which serves a role in DNA repair, cell cycle arrest, apoptosis, and other pathways that prevent the development of cancers. The TP53 gene and its corresponding protein are frequently inactivated or partially disabled by mutations that lead to increased risks of developing cancer. Somatic TP53 mutations are very frequent in most human cancers, occurring in 5–80% of them, depending on the cancer type and stage (Petitjean et al. 2007).

Domains of p53

The TP53 gene contains 19,200 nucleotides in its 11 exons and 10 introns. Of the 11 exons, exon one, the first half of exon two, and the majority of exon 11 are non-coding exons (Bouaoun et al. 2016). The two transactivation domains are encoded in exons 2–4, the DNA-binding domain in exons 4–8, the tetramerization domain in exons 9–10, and the basic domain in exons 10–11. Each domain of this 393 amino acid protein has its own distinct function.

✉ Karen H. Li
likhuijie@gmail.com

[1] Department of Science, The Wheatley School, Old Westbury, NY, USA

Transactivation domain one (AD1) and transactivation domain two (AD2) are comprised of amino acids 1–92. AD1 is required for cell cycle arrest, but is dispensable for apoptosis (Harms and Chen 2006). AD2 is responsible for apoptosis and is aided by the proline-rich domain which is now part of AD2 (Edwards et al. 2003; Zhu et al. 2000). The DNA-binding domain (DBD), comprised of amino acids 102–292, is essential for the role of p53 as a sequence-specific transcription factor. The DBD of p53 binds to a specific DNA sequence to activate transcription, mediate apoptosis, and conduct cell cycle arrest to suppress the growth of tumor cells (Pavletich et al. 1993). The DBD is followed by the tetramerization domain (TD), comprised of amino acids 326–356, which aids the DBD in binding to DNA and other proteins by increasing the strength of interactions between p53 and other structures (Harms and Chen 2006).

Li-Fraumeni and Li-Fraumeni-like syndromes

TP53 is the only gene so far identified in which mutations are definitively associated with Li-Fraumeni (LFS) and Li-Fraumeni-like (LFL) syndromes, which predispose patients to certain types of cancers. Over 50% of families with LFS have an inherited mutation in the TP53 gene (Li-Fraumeni syndrome 2017). The most common germline mutations in tumors are located at amino acids 248, 337, 273, and 175 (Bouaoun et al. 2016). It is known that these mutations can inactivate or disrupt the function of the p53 protein, and increase risks of early onset cancer (Lomax et al. 1997).

Objective of study

Past research has determined the most common TP53 mutations, examined the development of p53 alterations, and identified cancers that TP53 mutations were prevalent in. This study attempted to establish TP53 mutations as potential prognostic markers for specific cancers by investigating if the presence of TP53 mutations in certain cancers was beneficial or detrimental to survival time and disease-free survival time. The distribution of TP53 mutations at specific exons/introns and codons was examined, and the potential of using specific mutations as cancer prognostic markers was evaluated.

Methods

Data were downloaded from the April 2016 release of the International Agency for Research on Cancer (IARC) TP53 database on all 28,000 + somatic and 800 + germline mutations (Bouaoun et al. 2016). Python was then used to scan through the IARC data to generate graphs via Matplotlib, an open source plotting library that can be used in IPython (Jupyter Notebook), and Glue, a tool built on top of the standard scientific libraries of Python. Exon/intron distribution maps, along with codon distribution maps, were generated for both somatic and germline mutations. The mutational hotspots were also located, and mutational hotspots were analyzed for germline mutations to see if families with LFS or LFL had mutations at certain codons.

Genomic data from various cancer studies can be found in cBioPortal for Cancer Genomics, available online at cbioportal.org (Cerami et al. 2012; Gao et al. 2013). The data sets of the most recent The Cancer Genome Atlas (TCGA) cancer studies were selected in the portal, which resulted in 33 studies and 7893 cases in total. Then, a query was performed for TP53 mutations, from which cBioPortal generated a summary of the percentage of cases with TP53 mutations for each cancer. Of these studies, survival data and overall survival Kaplan–Meier estimates were downloaded from cBioPortal, and patients with and without TP53 mutations were compared. These data were analyzed to obtain the total number of cases, the number of cases deceased, and the survival times of patients with and without TP53 mutations for individual cancers. The statistical significance of differences in survival time was determined by log-rank p values. A value of 0.05 or less was considered statistically significant.

Data on relapse and disease-free survival time were also selected. Disease-free survival Kaplan–Meier estimates were downloaded from cBioPortal for Cancer Genomics and analyzed. Estimates with log-rank p values of 0.05 or less were considered statistically significant. Disease-free survival data included the total number of cases, number of cases relapsed, relapse time of the patients, censored data, and whether a TP53 mutation was present. The data were also compared with the survival data to determine whether relapse affected overall survival.

Then, data were selected for specific TP53 mutations in liver hepatocellular carcinoma cases. Survival data of cases with the most common p53 mutation (R249S) in this cancer were used to generate a Kaplan–Meier estimate using MedCalc, and the survival time of cases with this specific mutation, cases with TP53 mutations, and cases without TP53 mutations were compared.

Finally, a query was performed for TP53 and BRCA mutations in cBioPortal for Cancer Genomics for cases with ovarian serous cystadenocarcinoma. Mutation data were downloaded and the number of cases with no mutation, only one mutation, or both mutations was tallied. Then, survival and disease-free survival time data were downloaded, and cases with neither TP53 nor BRCA mutations, with TP53 mutations but without BRCA mutations, and with both TP53 and BRCA mutations were compared, generating Kaplan–Meier estimates in MedCalc.

Results

Somatic mutations

The percentage of certain types of somatic TP53 mutations is unlike those of other tumor suppressors. Mutations in TP53 are 73.16% missense, 9.06% frameshift, 8.17% nonsense, 3.62% silent, 2.4% splice, 0.74% intronic, 0.17% large deletion, and 2.28% other (Bouaoun et al. 2016) (Fig. 1). Most tumor suppressors are inactivated by frameshift or nonsense mutations. However, due to the low core thermodynamic stability of p53, the protein is most often inactivated by missense mutations in TP53 that cause single amino acid changes (Friedler et al. 2003; Olivier et al. 2010).

Very few somatic mutations occur in AD1 and AD2. Even though the two transactivation domains represent 24% of the length of the gene, only 4% of somatic TP53 mutations occur in AD1 and AD2. The majority of mutations occur in the DBD, which is about the same length as AD1 and AD2. The DBD represents 26% of the TP53 gene, but almost 90% of somatic TP53 mutations occur here. 96% of somatic missense mutations occur in the DBD and 92% of somatic mutations in the DBD are missense. Only about 3% of somatic mutations are located in the TD (Fig. 2a). Mutational hotspots for somatic mutations are located at codons 248, 273, 175, and 245 (Fig. 3a).

Germline mutations

The distribution of germline mutations is different from the distribution of somatic mutations. 94% of all somatic TP53 mutations are located in exons 4–8, whereas only 77% of all germline TP53 mutations are located in exons 4–8. In comparison to somatic mutations, the proportion of germline mutations that occur in the DBD is lower, and the proportion of mutations in the introns and exons of TD, AD1, and AD2 is relatively higher. The percentage of mutations in the TD is approximately 3% in somatic mutations, and approximately 14% in germline mutations. The only section of the DBD that increased in mutation proportion from somatic mutations to germline mutations was exon 4 (Fig. 2b). The top three mutational hotspots occur at codons 248, 337, and 273 (Fig. 3b). All three of these mutational hotspots are associated with LFS or LFL, and about 62% of the 1644 cancer cases with germline mutations had LFS and LFL, or met the TP53 Chompret criteria.

TP53 mutations are common in many different types of cancers. According to "Integrated Genomic Analyses of Ovarian Carcinoma" and "Comprehensive Genomic Characterization of Squamous Cell Lung Cancers," two TCGA papers published in Nature, TP53 mutations occur in 95% of ovarian serous cystadenocarcinomas and 94% of lung squamous cell carcinomas (The Cancer Genome Atlas Network 2011; The Cancer Genome Atlas Network 2012). In this study, almost every sample of the two aforementioned cancers had TP53 mutations, but for other types of cancers such as uveal melanomas, which had a sample size of 80, there were no occurrences of TP53 mutations (Table 1).

Overall survival

Of the 33 cancers analyzed, nine were found to have statistically significant differences in survival time when comparing samples with and without TP53 mutations (Table 1). The cancers were separated into three groups. The first group included cancers in which cases without TP53 mutations survived up to two times longer than cases with TP53 mutations. The second group consisted of cancers in which cases without TP53 mutations survived over three times longer than cases with TP53 mutations. Finally, the third group consisted of cancers in which median survival time could not

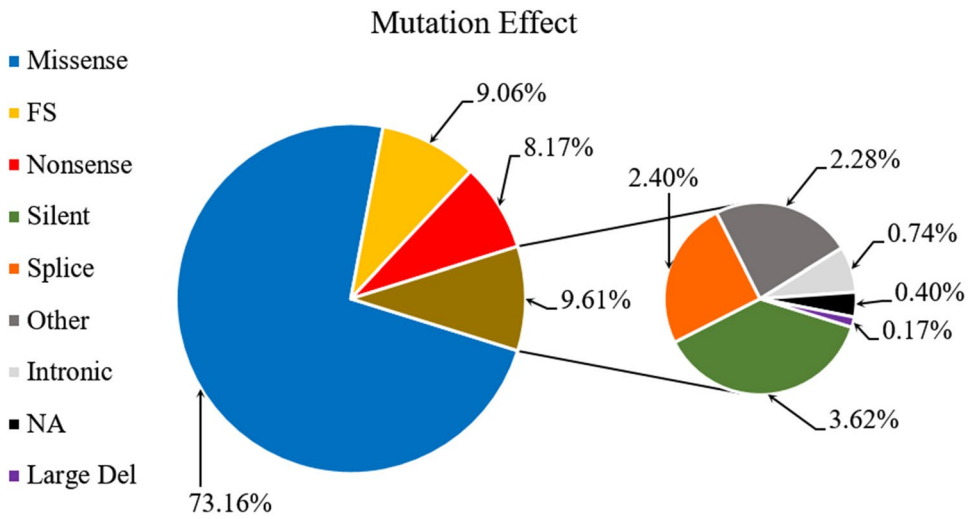

Fig. 1 Pie chart showing the proportion of different types of somatic TP53 mutations. *FS* frameshift, *NA* not available. In total, there were 28,869 cases with mutations. Data from IARC TP53 Database (R18, April 2016)

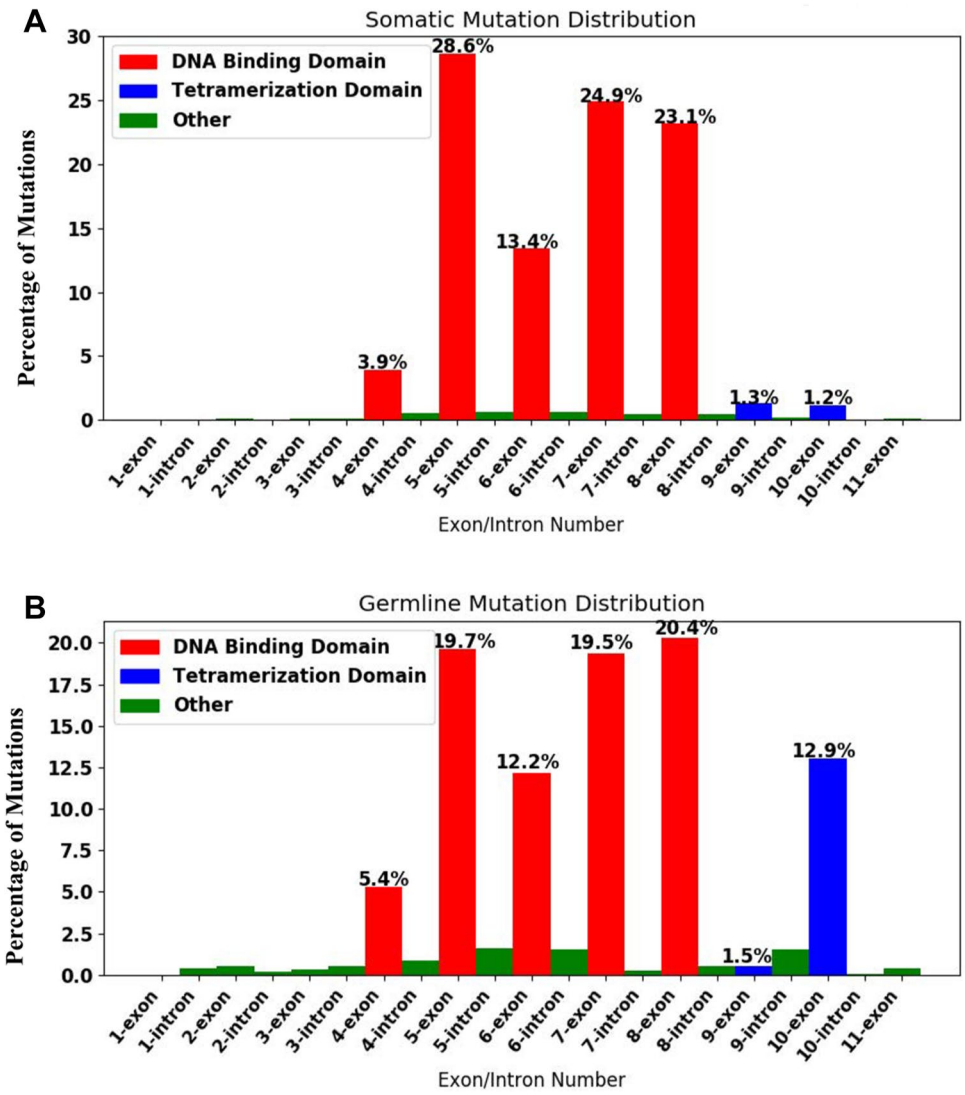

Fig. 2 Intron/exon distributions of somatic and germline mutations. Histograms showing the percentage of mutations in specific exons and introns. Data from IARC TP53 Database (R18, April 2016)

be calculated for either cases with or without TP53 mutations, since > 50% of patients were still alive by the end of the study.

There were two cancers in the first group. The first cancer was lung adenocarcinoma, where about 46.5% of the 230 cases had TP53 mutations. According to median survival time data, cases without mutations survived for 48.99 months and cases with mutations survived for 38.47 months. Those without mutations survived 1.27 times longer. Even though mutations resulted in poor prognosis, only the minority of cases were affected negatively (Fig. 4b). The second cancer was liver hepatocellular carcinoma, where 30.8% of the 373 cases had TP53 mutations. Once again, like in lung adenocarcinomas, the minority of patients were affected negatively. The median survival time was 60.84 months for cases without mutations, and 45.07 months for cases with mutations. Those without mutations survived 1.35 times longer. While it seems like the survival percentage in months 70–80 were equal between those with and without mutations, this occurred because of censoring, which resulted in no points of interest between months 50–80 for samples with TP53 mutations (Fig. 4c).

The next three cancers were in the second group. The first was head and neck squamous cell carcinoma, where TP53 mutations occurred in 74.2% of the 279 cases. Median survival time was 65.77 months for cases without mutations, and 19.19 months for cases with mutations. Those without mutations survived 3.43 times longer. Out of all cancers with statistically significant differences in survival time, this was the only cancer in which the majority of patients possessed detrimental TP53 mutations (Fig. 4d). The second cancer was acute myeloid leukemia, where 8.0% of the 200 cases contained TP53 mutations. By the first 10 months, only 25% of cases with mutations were still alive, and by 17 months, all such cases were deceased. However, for those without mutations, about 66% of cases were alive

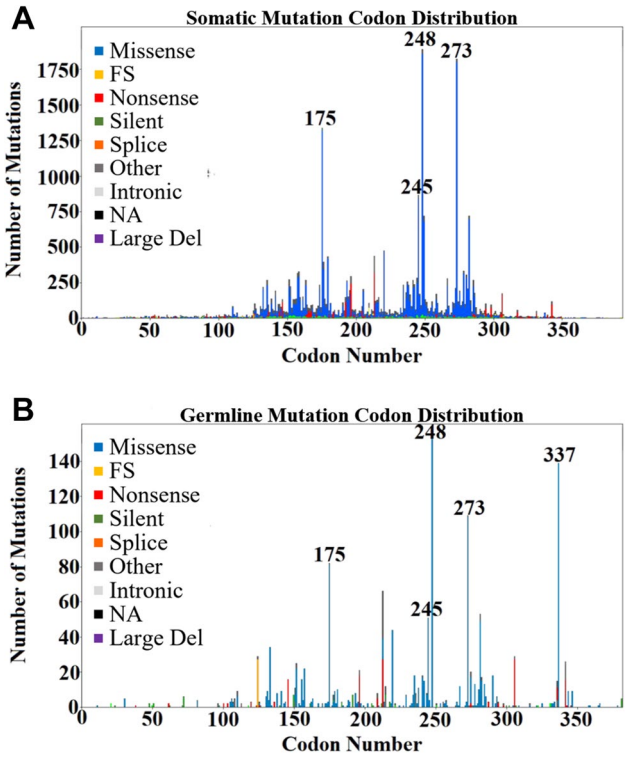

Fig. 3 Codon distributions of somatic and germline mutations. Histogram displaying the frequency and types of mutations at certain codons. *FS* frameshift, *NA* not available. The major mutational hotspots are labeled. Data from IARC TP53 Database (R18, April 2016)

by 10 months, and by 17 months, over 50% of cases were still alive. Median survival time was 20.5 months for cases without mutations, and 4.5 months for cases with mutations. Those without mutations survived 4.56 times longer. Since only 8.0% of cases had TP53 mutations, only the minority of patients were affected negatively (Fig. 4e). The third was clear cell renal cell carcinoma (RCC). Although only 2.1% of the 424 cases had TP53 mutations, the most drastic differences in survival time were seen. Median survival time was 77 months for cases without mutations, and 11 months for cases with mutations. Those without mutations survived 7.02 times longer (Fig. 4f).

The next four cancers were in third group. The first was papillary RCC. Out of 282 samples, only 2.5% were mutated. According to the Kaplan–Meier estimate, the upper quartile survival time was 8.48 months for cases with TP53 mutations and 67.12 months for cases without TP53 mutations. The second was chromophobe RCC, which had TP53 mutations in 30.8% of its cases. Out of the cases sequenced, 20 out of 65 cases contained TP53 mutations. For cases with TP53 mutations, the upper quartile survival time was 30.22 months. However, for cases without TP53 mutations, an estimated 93.5% of the people were still alive by the end of the study in 136.96 months, and thus, even an upper quartile survival time could not be calculated. The third was uterine endometrial carcinoma, with 27.8% of its 248 cases containing TP53 mutations. The upper quartile survival time was 36.37 months for cases with TP53 mutations, which was 83.91 months for cases without TP53 mutations. The fourth was thymoma, with 3.3% of its 123 cases containing TP3 mutations. Although this was a small percentage, the survivability of a patient was drastically decreased by the presence of a TP53 mutation. For cancers with TP53 mutations, the median survival time was 25.46 months, and the upper quartile survival time was 12.45 months. In cases without TP53 mutations, the upper quartile survival time was 114.59 months.

In the majority of the cancers analyzed, there were almost no differences in survival for cases with and without TP53 mutations during months 1–10. Only four of the nine cancers that had statistically significant differences in survival had notable differences in survival during months 1–10. The first was lung adenocarcinoma, where the difference in survival probability between those with and without TP53 mutations (~ 10%) stayed around the same throughout the whole Kaplan–Meier estimate. By the 10th month, the difference in survival probability was about 7%. The second cancer was acute myeloid leukemia, whereby the 10th month, there was about a 45% difference in survival probability. The third was kidney RCC, in which the survival probability difference was around 40% by the 10th month. Finally, in papillary RCC, the difference in survival probability was around 30% by the 10th month. For the rest of the 10 cancers, there were almost no differences during months 1–10.

Disease-free survival

Out of the 33 cancers studied, five were found to have statistically significant differences in disease-free survival time. In these cancers (pancreatic adenocarcinoma, liver hepatocellular carcinoma, chromophobe RCC, acute myeloid leukemia, and thymoma), TP53 mutations led to earlier relapse. In pancreatic adenocarcinoma, 69.3% of the 150 cases were found to have TP53 mutations. The median disease-free survival time was 13.53 months in cases with TP53 mutations, and 20.37 months in cases without TP53 mutations. Those without TP53 mutations remained disease-free for 1.51 times longer. However, longer time before relapse did not indicate longer overall survival, because, although the difference in the time of disease-free survival among those with and without TP53 mutations was statistically significant, there was no statistically significant difference in overall survival time in pancreatic adenocarcinomas. Therefore, cases with TP53 mutations may require more frequent screening and treatment than cases without TP53 mutations due to shortened periods between relapses, but overall survival time would be the same (Fig. 5b).

Table 1 Percentage of TP53 mutations and median survival time of 33 cancers

Cancer type	Total cases	# Cases mutated	% Cases mutated	Median survival with TP53 mutations (months)	Median survival without TP53 mutations (months)	p value < 0.05
Ovarian serous cystadenocarcinoma[a]	242	231	95.45%	41.99	42.02	No
Lung squamous cell carcinoma	178	167	93.80%	N/A	N/A	N/A
Uterine carcinosarcoma	57	52	91.20%	N/A	N/A	N/A
Esophageal carcinoma	185	153	82.70%	28.09	25.1	No
Head and neck squamous cell carcinoma	279	207	74.20%	19.19	65.77	Yes
Pancreatic adenocarcinoma	150	104	69.30%	19.65	19.94	No
Esophagus-stomach cancers	518	303	58.50%	36.02	28.59	No
Colorectal adenocarcinoma	224	121	54%	N/A	39.03	No
Brain lower grade glioma	286	146	51%	65.7	95.5	No
Bladder urothelial carcinoma	130	64	49.20%	20.47	20.28	No
Stomach adenocarcinoma	289	138	47.80%	35.98	30.88	No
Lung adenocarcinoma	230	107	46.50%	38.47	48.99	Yes
Breast invasive carcinoma	816	280	34.30%	212.09	128.98	No
Sarcoma	254	85	33.5%	64.16	76.35	No
Liver hepatocellular carcinoma	373	115	30.80%	45.07	60.84	Yes
Chromophobe renal cell carcinoma (RCC)	65	20	30.80%	N/A	N/A	Yes
Uterine endometrial carcinoma	248	69	27.80%	N/A	N/A	Yes
Glioblastoma	291	59	20.30%	13.6	13.1	No
Adrenocortical carcinoma	90	18	20%	N/A	N/A	N/A
Skin cutaneous melanoma	368	56	15.20%	107.29	66.43	No
Cholangiocarcinoma	35	5	14.30%	63.7	24.34	No
Diffuse large B-cell lymphoma	48	5	10.40%	N/A	211.07	No
Mesothelioma	87	9	10.30%	N/A	N/A	N/A
Acute myeloid leukemia	200	16	8%	4.5	20.5	Yes
Prostate adenocarcinoma	333	23	6.90%	N/A	N/A	N/A
Cervical squamous cell carcinoma and endocervical adenocarcinoma	194	9	4.60%	N/A	101.74	No
Thymoma	123	4	3.30%	25.46	N/A	Yes
Papillary renal cell carcinoma (RCC)	282	7	2.50%	N/A	N/A	Yes
Clear cell renal cell carcinoma (RCC)	424	9	2.10%	10.97	76.98	Yes
Testicular germ cell cancer	155	2	1.30%	N/A	N/A	No
Papillary thyroid carcinoma	401	3	0.70%	N/A	N/A	No
Pheochromocytoma and paraganglioma	184	1	0.50%	N/A	N/A	N/A
Uveal melanoma	80	0	0%	N/A	N/A	N/A

Data from TCGA studies compiled in cBioPortal for Cancer Genomics

[a]Data exclude BRCA mutants

In liver hepatocellular carcinoma, the median disease-free survival time was 11.79 months for cases with TP53 mutations and 25.3 months for cases without TP53 mutations. Overall, those without TP53 mutations lived disease-free for 2.15 times longer. According to the Kaplan–Meier estimates, 20.5% of cases with mutations remained disease-free, while only 10.9% of cases without mutations remained disease-free at the end of the study (Fig. 5c).

In acute myeloid leukemia, the median disease-free survival time was 10.3 months for cases with TP53 mutations,

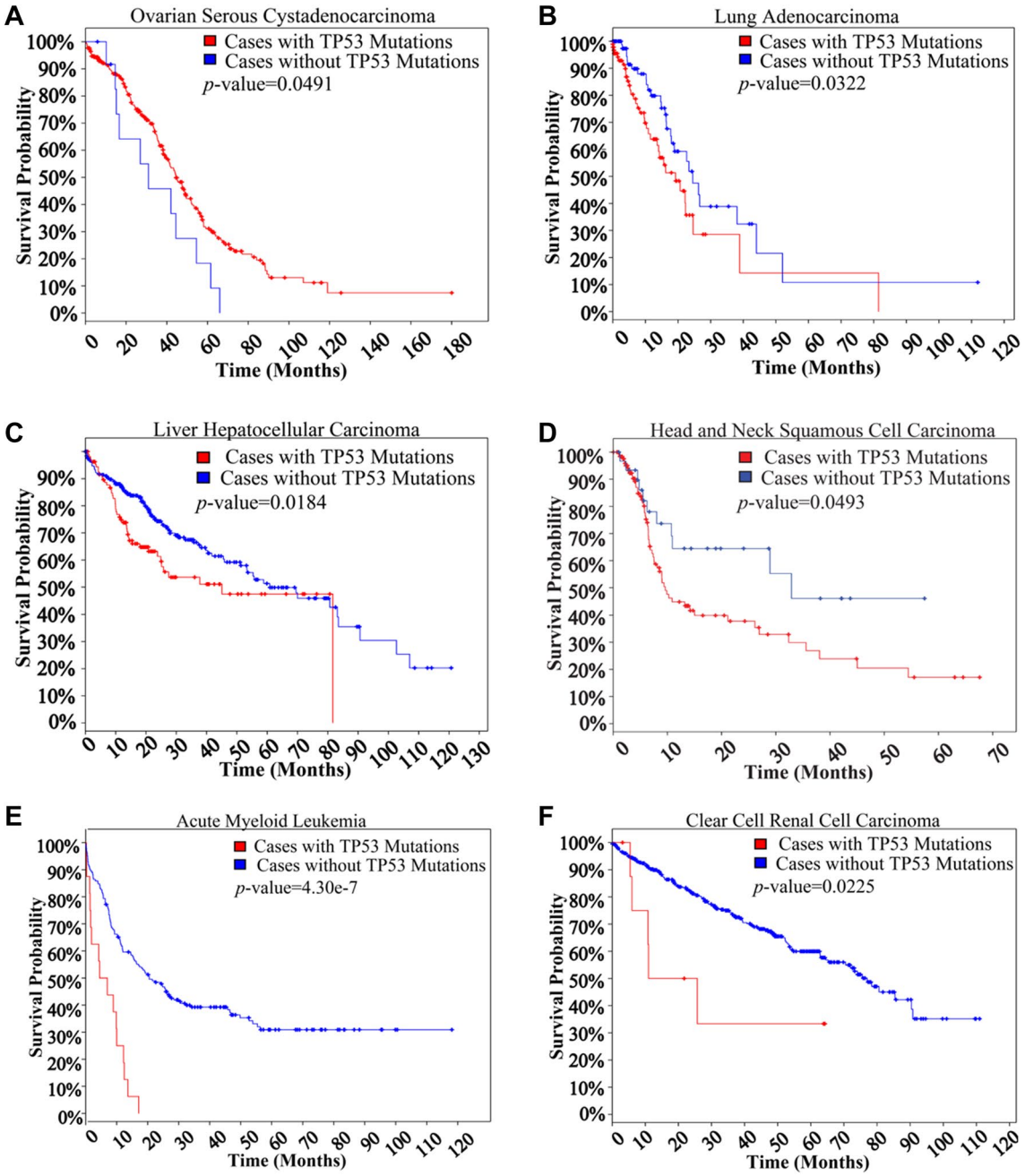

Fig. 4 Survival Kaplan–Meier estimates of select cancers. Data from TCGA studies compiled in cBioPortal for Cancer Genomics

and 17.3 months for cases without TP53 mutations. Those without mutations were disease-free for 1.68 times longer than those with mutations (Fig. 5d).

Chromophobe RCC tended to not relapse in cases without TP53 mutations. In the first 26.84 months, while 32.1% of cases with TP53 mutations relapsed, 100% of cases without TP53 mutations remained disease-free. After 65.34 months, 32.1% of cases with TP53 mutations relapsed, while 92.2% of cases without TP53 mutations remained disease-free.

In thymoma, although TP53 mutations were less frequent than in other tumors, having TP53 mutations significantly decreased time before relapse. The median disease-free survival time was 9.72 months and the upper quartile time was 7.36 months in cases with TP53 mutations. For cases without TP53 mutations, no median disease-free survival time could be calculated, since < 50% of cases relapsed. The upper quartile time for cases without TP53 mutations was 115.05 months, which was greater than the median time for cases with TP53 mutations. In addition,

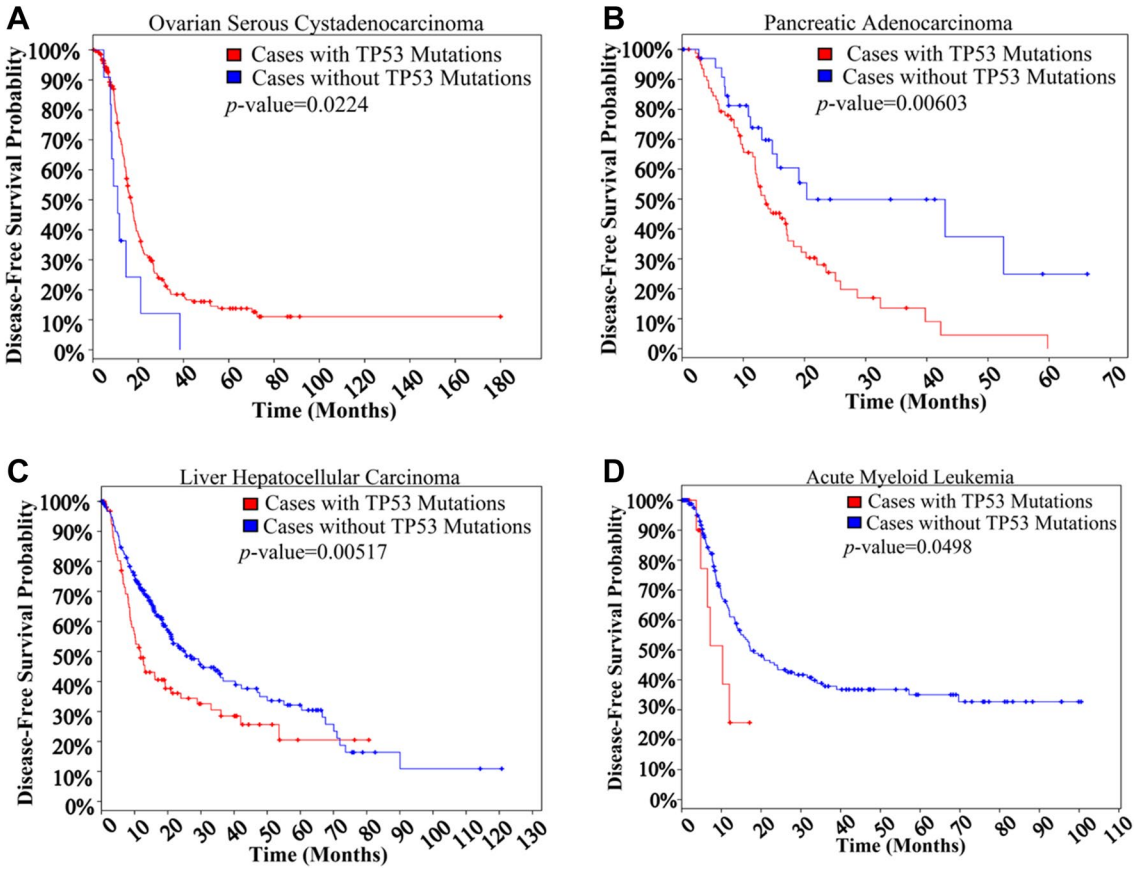

Fig. 5 Disease-free survival Kaplan–Meier estimates of select cancers. Data from TCGA studies compiled in cBioPortal for Cancer Genomics

the upper quartile value for cases without TP53 mutations was 15.63 times of that for cases with TP53 mutations. Therefore, the presence of TP53 mutations was very detrimental in thymoma cases.

Specific TP53 mutations as prognostic markers

For some cancers, specific TP53 mutations can be used as prognostic markers. This can be done in cancers with a large number of samples containing TP53 mutations. One Kaplan–Meier estimate was generated for liver hepatocellular carcinomas, showing the effect of the R249S mutation (the most common p53 mutation in liver hepatocellular carcinoma) on survival compared to cases with and without TP53 mutations. The median survival time for cases with the p53 R249S mutation was 11.30 months compared to 45.07 months for cases with TP53 mutations (including R249S) and 60.84 months for cases without TP53 mutations. Since the differences in survival time among the three groups were statistically significant, this specific mutation is an indicator for poor prognosis in liver hepatocellular carcinoma (Fig. 6).

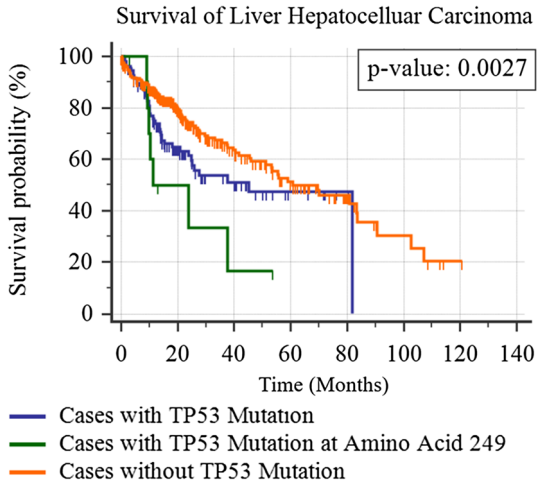

Fig. 6 Survival Kaplan–Meier estimate of liver hepatocellular carcinoma cases with p53 R249S mutation. Data from TCGA studies compiled in cBioPortal for Cancer Genomics

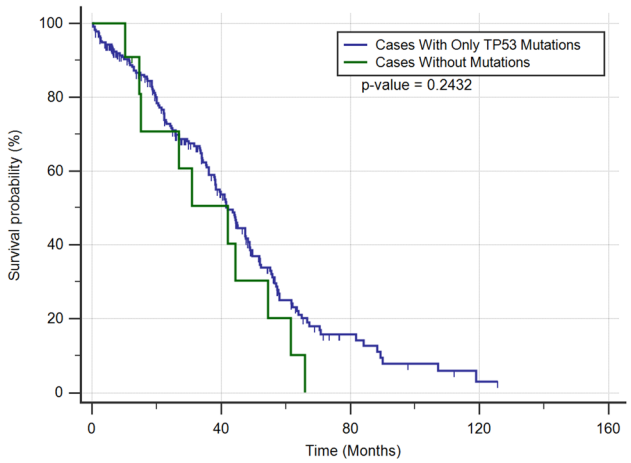

Fig. 7 Survival Kaplan–Meier estimate of ovarian serous cystadenocarcinoma cases with TP53 mutations but without BRCA mutations vs. cases with neither TP53 nor BRCA mutations

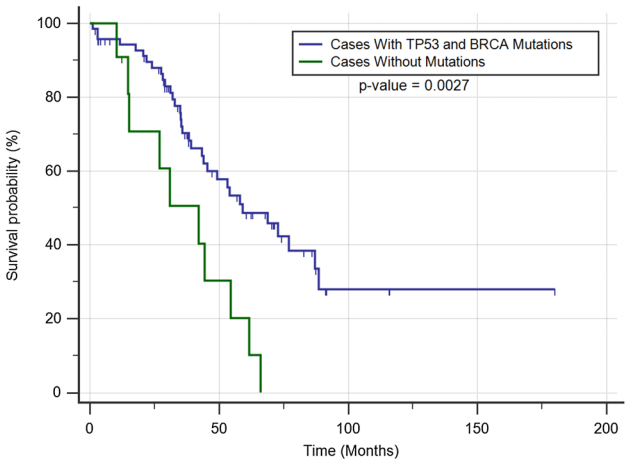

Fig. 9 Survival Kaplan–Meier estimate of ovarian serous cystadenocarcinoma cases with both TP53 and BRCA mutations vs. cases with neither TP53 nor BRCA mutations

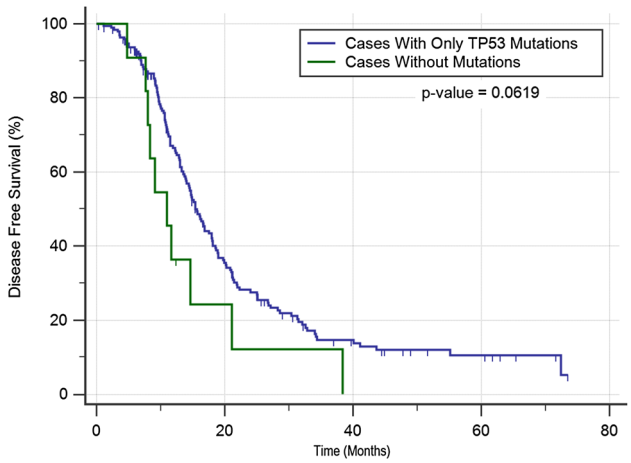

Fig. 8 Disease-free survival Kaplan–Meier estimate of ovarian serous cystadenocarcinoma cases with TP53 mutations but without BRCA mutations vs. cases with neither TP53 nor BRCA mutations

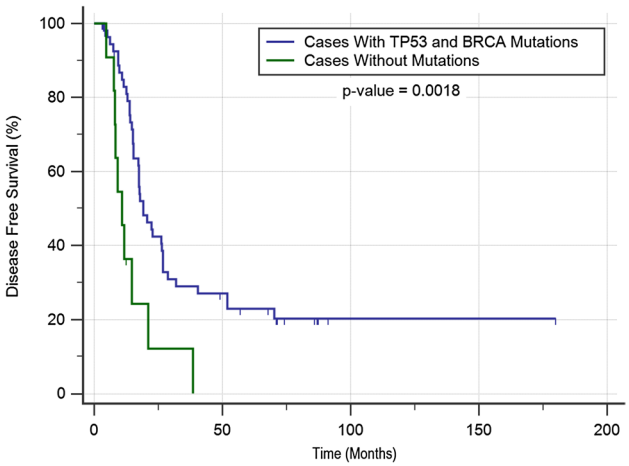

Fig. 10 Disease-free survival Kaplan–Meier estimate of ovarian serous cystadenocarcinoma cases with both TP53 and BRCA mutations vs. cases with neither TP53 nor BRCA mutations

Analysis of TP53 and other genes

In some cancers, there were a high proportion of mutations in genes other than TP53. This occurred in ovarian serous cystadenocarcinoma, in which 74 out of 316 cases (23.4%) had mutations in BRCA1 or BRCA2. In addition, out of the BRCA mutants, 73 out of 74 (98.6%) had TP53 mutations. Although when comparing survival and disease-free survival times between cases with and without TP53 mutations, those with TP53 mutations seemed to live longer (Figs. 4a, 5a), there were no statistically significant differences in survival or disease-free times between cases with TP53 mutations but without BRCA mutations and cases with neither TP53 nor BRCA mutations (Figs. 7, 8). However, when comparing cases with both TP53 and BRCA mutations and cases with neither TP53 nor BRCA mutations, the presence of TP53 and BRCA mutations conferred longer survival and disease-free survival times (Figs. 9, 10).

Discussion

This study used TP53 mutations instead of immunohistochemistry (IHC) data, even though both were available. Since the p53 protein sometimes accumulates when there is no mutation and sometimes does not accumulate when there is a mutation present, the presence of false-positives and false-negatives makes IHC less reliable than sequencing for TP53 mutations (Ross and Hortobagyi 2005). Older research uses IHC, but, due to the availability of faster and

cheaper modern sequencing methods, more genetic data on TP53 have become available for analysis.

Some mutations affected the survival time or time before relapse, while others had no effect. In 26 of the 33 cancers studied, there were data on survival time. Nine cancers (lung adenocarcinoma, liver hepatocellular carcinoma, head and neck squamous cell carcinoma, acute myeloid leukemia, clear cell RCC, papillary RCC, chromophobe RCC, uterine endometrial carcinoma, and thymoma) had statistically significant differences in survival time between patients with and without TP53 mutations. Of the 33 cancers studied, there were 21 cancers with relapse data, and five cancers (pancreatic adenocarcinoma, liver hepatocellular carcinoma, chromophobe RCC, acute myeloid leukemia, and thymoma) had statistically significant differences in disease-free survival time between patients with and without TP53 mutations.

With these data, TP53 mutations can be predictive markers as to how long patients will survive, and when the cancer may relapse. For example, in cases of acute myeloid leukemia, one can predict that if a patient does not have a TP53 mutation, then she will have a 66% chance of surviving to month 10, while another patient with the same disease will only have a 30% chance of surviving to month 10 if she has a TP53 mutation (Fig. 4e). This adds accuracy to preexisting survival estimates that do not consider TP53 mutations as a factor. The same applies to disease-free survival time. In cases of acute myeloid leukemia, there is a 38% chance that patients without TP53 mutations will relapse by month 12, while there is a 74% chance that patients with TP53 mutations will relapse by month 12 (Fig. 5d).

Past studies have determined the function of the p53 protein and studied the development TP53 mutations. Since the establishment of the IARC TP53 Database in 1991, many researchers have analyzed and used its data to identify the different TP53 polymorphisms that exist in human populations (Credits 2017). Researchers have also identified the causes of TP53 mutations, including geographic differences and known carcinogens (Olivier et al. 2010). In addition, the effects of TP53 mutations on the function and structure of the p53 protein were studied, which led to the identification of the functional domains of p53 in 2006 (Harms and Chen 2006; Kato et al. 2003).

Using TP53 mutation data from the newest IARC Database, which is the April 2016, R18 release, and data on cBioPortal, which compiles all of the data from the most recent TCGA cancer studies, this study is the first to represent the newest data available. Applying the previous knowledge of p53 functional domains and their locations, we were able to identify the distribution of mutations at exons/introns to determine that the DBD, which is responsible for binding p53 to DNA to regulate cell growth, was affected the most by TP53 mutations. By separating mutations into somatic and germline mutations, we found that germline mutations were common at introns and in the TD, AD1, and AD2, which was rare among somatic mutations.

Using survival and genomic data from multiple TCGA studies on cancers, this study compared Kaplan–Meier estimates of cases with and without TP53 mutations to predict survival time and disease-free survival time. Unlike preexisting studies, we examined the prognostic effect of TP53 mutations in a whole variety of cancers, instead of one specific cancer, and found that survival was significantly affected in nine different kinds of cancers. This study is also one of the only studies that looked at the significance of TP53 mutations on the time before relapse. The distribution of TP53 mutations was also used to identify the most prevalent mutations in certain cancers. The mutations in liver hepatocellular carcinoma were analyzed and the most common one was R249S. Survival data for cases with this specific mutation showed that it negatively affected the prognosis of patients significantly. Due to a previous lack of data, specific TP53 mutations were not considered to be utilized as prognostic markers until now.

According to the previous literature, mutations in the TP53 gene are associated with genomic instability which leads to oncogene amplification and the loss of tumor suppressor genes (Alidousty et al. 2018; Kim et al. 2017). The co-occurrence of TP53 and BRCA mutations in ovarian serous cystadenocarcinoma indicates that TP53 mutations might play an important role in the development of BRCA mutations, since only 1.4% of BRCA mutants do not have TP53 mutations. As indicated in cases of ovarian serous cystadenocarcinoma, although TP53 mutations might not confer differences in survival and disease-free survival, TP53-induced mutations in other genes may be key drivers in the progression of cancers and, therefore, should be studied to more clearly predict prognosis. In addition, future studies should investigate the co-occurrence of TP53 and BRCA mutations and the factors underlying better prognosis in cases with both mutations than in cases without either mutation.

Nevertheless, for some of the cancers, more data are necessary. For seven of the cancers, survival data were not available, and for 12 of the cancers, disease-free survival time data were not available either. In addition, for some of the cancers, only small amounts of data were available, since only a small percentage of cases had TP53 mutations. In addition, some Kaplan–Meier estimates could be misleading because of censoring that results in horizontal and vertical lines which indicate loss of data (Rich et al. 2010). More data can lead to a better accuracy for cancers like clear cell RCC, where there were only nine cases of TP53 mutations and four of them were censored.

Conclusion

The presence of TP53 mutations resulted in poor survival prognosis in nine cancers (lung adenocarcinoma, liver hepatocellular carcinoma, head and neck squamous cell carcinoma, acute myeloid leukemia, clear cell RCC, papillary RCC, chromophobe RCC, uterine endometrial carcinoma, and thymoma) and poor disease-free survival prognosis in five cancers (pancreatic adenocarcinoma, hepatocellular carcinoma, chromophobe RCC, acute myeloid leukemia, and thymoma). The most common p53 mutation (R249S) in liver hepatocellular carcinomas was found to be an indicator for poor prognosis. In addition, in cases of ovarian serous cystadenocarcinoma, those with co-occurring TP53 and BRCA mutations were found to survive longer than their wild-type counterparts. Therefore, with the increasing availability of genomic sequencing, TP53 mutations can be used as prognostic markers to increase the accuracy of survival and relapse estimates. These results are supported with past research on TP53 and its clinical value (Olivier et al. 2006).

In future studies, when more data become available, by identifying and analyzing the most common TP53 mutations and the cancers that they are prevalent in, it will be possible to predict the invasiveness or aggressiveness of cancers based upon whether they contain TP53 mutations or not, and in cases with TP53 mutations, based upon which specific TP53 mutations are present (Salnikova 2014). This information can be useful in determining the progression of cancers, which is crucial when deciding the type of treatment to be used. In addition, the effects of specific mutations in cancers can be investigated to a deeper extent on the molecular level to improve the accuracy of TP53 mutations as prognostic markers. This study demonstrated that TP53 mutations have statistically significant effects on survival and disease-free survival times, and, thus, can be successfully used as prognostic markers.

Specific germline TP53 mutations and the cancers that they are associated with can be identified to predict the cancers which certain individuals and their children are predisposed to, which can help to implement screening procedures that allow for earlier detection and treatment. Individuals with a certain germline TP53 mutation can be screened for specific cancers that they are at risk of developing, thus increasing the likelihood of finding and successfully treating premalignant tumors and growths through preventative care. However, more data on germline TP53 mutations are required to establish reliable criteria for screening. Nevertheless, with increasing data availability, future studies may yield further insights.

Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Alidousty C et al (2018) Genetic instability and recurrent MYC amplification in ALK-translocated NSCLC: a central role of TP53 mutations. J Pathol 246:67–76. https://doi.org/10.1002/path.5110

Bouaoun L, Sonkin D, Ardin M, Hollstein M, Byrnes G, Zavadil J, Olivier M (2016) TP53 variations in human cancers: new lessons from the IARC TP53 database and genomics data. Hum Mutat 37:865–876. https://doi.org/10.1002/humu.23035

Cerami E et al (2012) The cBio cancer genomics portal: an open platform for exploring multidimensional. Cancer Genom Data Cancer Discov 2:401–404. https://doi.org/10.1158/2159-8290.cd-12-0095

Credits (2017) IARC. http://p53.iarc.fr/Credits.aspx. Accessed 1 Sep 2017

Edwards SJ, Hananeia L, Eccles MR, Zhang YF, Braithwaite AW (2003) The proline-rich region of mouse p53 influences transactivation and apoptosis but is largely dispensable for these functions. Oncogene 22:4517–4523

Friedler A, Veprintsev DB, Hansson LO, Fersht AR (2003) Kinetic instability of p53 core domain mutants: implications for rescue by small molecules. J Biol Chem 278:24108–24112. https://doi.org/10.1074/jbc.M302458200

Gao J et al (2013) Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 6:pl1. https://doi.org/10.1126/scisignal.2004088

Harms KL, Chen X (2006) The functional domains in p53 family proteins exhibit both common and distinct properties. Cell Death Differ 13:890–897

Kato S, Han SY, Liu W, Otsuka K, Shibata H, Kanamaru R, Ishioka C (2003) Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. Proc Natl Acad Sci USA 100:8424–8429. https://doi.org/10.1073/pnas.1431692100

Kim Y, Cho M-Y, Kim J, Kim SN, Oh SC, Lee K-A (2017) Profiling cancer-associated genetic alterations and molecular classification of cancer in Korean gastric cancer patients. Oncotarget 8:69888–69905. https://doi.org/10.18632/oncotarget.19435

Li-Fraumeni syndrome (2017) USA.gov. https://ghr.nlm.nih.gov/condition/li-fraumeni-syndrome#genes. Accessed 23 Aug 2017

Lomax ME, Barnes DM, Gilchrist R, Picksley SM, Varley JM, Camplejohn RS (1997) Two functional assays employed to detect an unusual mutation in the oligomerisation domain of p53 in a Li-Fraumeni like family. Oncogene 14:1869–1874. https://doi.org/10.1038/sj.onc.1201133

Olivier M et al (2006) The clinical value of somatic TP53 gene mutations in 1794 patients with breast cancer. Clin Cancer Res 12:1157

Olivier M, Hollstein M, Hainaut P (2010) TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harbor Perspect Biol 2:a001008 https://doi.org/10.1101/cshperspect.a001008

Pavletich NP, Chambers KA, Pabo CO (1993) The DNA-binding domain of p53 contains the four conserved regions and the major mutation hot spots. Genes Dev 7:2556–2564

Petitjean A, Mathe E, Kato S, Ishioka C, Tavtigian SV, Hainaut P, Olivier M (2007) Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: lessons from recent developments in the IARC TP53 database. Hum Mutat 28:622–629. https://doi.org/10.1002/humu.20495

Rich JT, Neely JG, Paniello RC, Voelker CCJ, Nussenbaum B, Wang EW (2010) A practical guide to understanding Kaplan-Meier

curves. Otolaryngol Head Neck Surg 143:331–336. https://doi.org/10.1016/j.otohns.2010.05.007

Ross J, Hortobagyi G (2005) Molecular oncology of breast cancer. Jones & Bartlett Learning, Burlington

Salnikova LE (2014) Clinicopathologic characteristics of brain tumors are associated with the presence and patterns of TP53 mutations: evidence from the IARC TP53. Database Neuromol Med 16:431–447. https://doi.org/10.1007/s12017-014-8290-1

The Cancer Genome Atlas Network (2011) Integrated genomic analyses of ovarian carcinoma. Nature 474:609–615. https://doi.org/10.1038/nature10166

The Cancer Genome Atlas Network (2012) Comprehensive genomic characterization of squamous cell lung cancers. Nature 489:519–525. https://doi.org/10.1038/nature11404

Zhu J, Zhang S, Jiang J, Chen X (2000) Definition of the p53 functional domains necessary for inducing apoptosis. J Biol Chem 275:39927–39934. https://doi.org/10.1074/jbc.M005676200