Histol Histopathol (2015) 30: 1171-1183

http://www.hh.um.es

Histology and Histopathology

Cellular and Molecular Biology

Review

The clinical translational potential of p53-related alterations as cancer biomarkers

Meng Xiao[1,2], Xu Wang[1,2] and Wantao Chen[1,2]

[1]Department of Oral and Maxillofacial-Head and Neck Oncology and Faculty of Oral and Maxillofacial Surgery, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine and [2]Shanghai Research Institute of Stomatology and Shanghai Key Laboratory of Stomatology, Shanghai, China

Summary. We aimed to analyse and summarise the potential value of the clinical use of p53-related alterations as cancer biomarkers. A systematic search and collection of the published meta-analyses on p53-related alterations and cancers in the past 5 years was conducted through appropriate queries in the PubMed database. We then composed "grey-scale" tables to show the significant levels for each variant, and the potential heterogeneity was subsequently discussed. The data show that p53-related alterations are extremely complex biomarkers in terms of their clinical translation. Together with the experimental studies on p53-related alterations, a gold-standard approach is still in need of development, with more evidence from clinical studies with large, prospectively planned cohorts, to fully understand its potential as a cancer biomarker.

Key words: p53, Meta-analysis, Cancer biomarker

Introduction

Cancer is one of the most devastating human diseases, and it leads to a vast number of mortalities worldwide each year. For decades, numerous works have studied the molecular alterations in cancer tissues compared with their normal counterparts, with the aim of revealing biomarkers that are representative of certain cancers (Armitage and Barbas, 2014). This approach has led to the identification of many potential molecules for cancer detection, risk assessment, screening, diagnosis, and prediction (Hayes, 2015).

Since its discovery, p53 has undoubtedly been one of the most extensively studied genes and proteins in cancer research (Levine and Oren, 2009). The TP53 gene (GenBank NM_000546.2) resides on chromosome 17p13.1 and encodes the p53 protein, which mainly acts as a stress response protein and has been widely regarded as a "guardian of the genome" (Brosh and Rotter, 2009; Freed-Pastor and Prives, 2012). After 40 years, it has been well established that p53 exerts a crucial role in cancer suppression through its sequence-specific transcriptional regulation of certain downstream target genes, by cell cycle arrest, senescence, apoptosis and DNA repair, or even by regulating cellular metabolism, stem cell function, invasion and metastasis, as well as cell-cell communication within the cancer microenvironment (Smeenk et al., 2008; Zilfou and Lowe, 2009; Lane and Levine, 2010; Molchadsky et al., 2010; Bieging et al., 2014). Intriguingly, thousands of studies have reported that p53 mutations occur frequently in cancer cells, and it has even been termed as one of the most frequently mutated genes in human cancer (Brosh and Rotter, 2009; Bieging et al., 2014; Duffy et al., 2014). Genetic alterations in TP53 have been reported to contribute to human cancers in different ways (Olivier et al., 2010), and ample data indicate that certain mutant p53 proteins not only lose their cancer suppressive functions but may also gain new oncogenic abilities associated with malignant transformation,

Offprint requests to: Wantao Chen, Department of Oral and Maxillofacial-Head & Neck Oncology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, 639 Zhizaoju Road, Shanghai 200011, China. e-mail: chenwantao196323@sjtu.edu.cn

DOI: 10.14670/HH-11-637

including promoting cancer proliferation, survival, metabolic changes, angiogenesis, and metastasis (Brosh and Rotter, 2009; Muller and Vousden, 2013; Bieging et al., 2014; Duffy et al., 2014; Liu et al., 2015).

Above all, the more detailed identifications of p53-related alterations in human cancers make p53 an extremely attractive target for further clinical use as a cancer biomarker (Olivier et al., 2010; Liu et al., 2014). However, despite the vast knowledge on p53 involvement in tumourigenesis from prior research, its translation to clinical use is still at an early stage (Brosh and Rotter, 2009; Duffy et al., 2014). Therefore, this review includes updated evidence-based studies on p53-related alterations in cancer clinics from the past 5 years and aims at discussing its clinical potential as a cancer biomarker from the view of translational medicine.

Studies included in this review were scanned by searching PubMed with the terms "'p53' or 'TP53'" and "meta-analysis". The last literature search was run on November 20, 2014, and only articles published from January 2010 were included.

The articles were analysed only if they met all the following inclusion criteria: (1) systematic reviews or meta-analysis studies in a peer-reviewed journal; (2) evaluation of the association of p53-related alterations with cancers; (3) human studies; and (4) the publication language was English. Furthermore, conference abstracts, dissertations, comments, letters to the editor, reviews, and case reports were not considered in this review.

As shown in Fig. 1, 293 articles were identified after our primary search. We then read the titles to select the potential meta-analysis on p53 published in the past 5 years, and 119 articles were included for further evaluation. After reading their abstracts, 43 articles were excluded based on the inclusion criteria. For the 76 remaining articles, the full texts of 62 articles were acquired, and 14 articles were included without full text. If an article reported on more than one study, the involved details for each study were extracted separately. In total, 83 studies were eventually included for further analysis.

The following information was collected from each study: p53-related alterations; cancer type; detection technology; clinical purpose; clinical significance; number of included studies; searched databases; and year of publication. After a preliminary review, we identified 7 types of p53-related alterations (Fig. 2A). The articles were evaluated by a meta-analysis over the past 5 years. Additionally, we observed that 18 cancer types (Fig. 2B) were included in the meta-analysis on its clinical association with certain p53-related alterations. Clinical purpose, risk assessment, diagnosis, prediction, and prognosis were evaluated for the clinical potential of

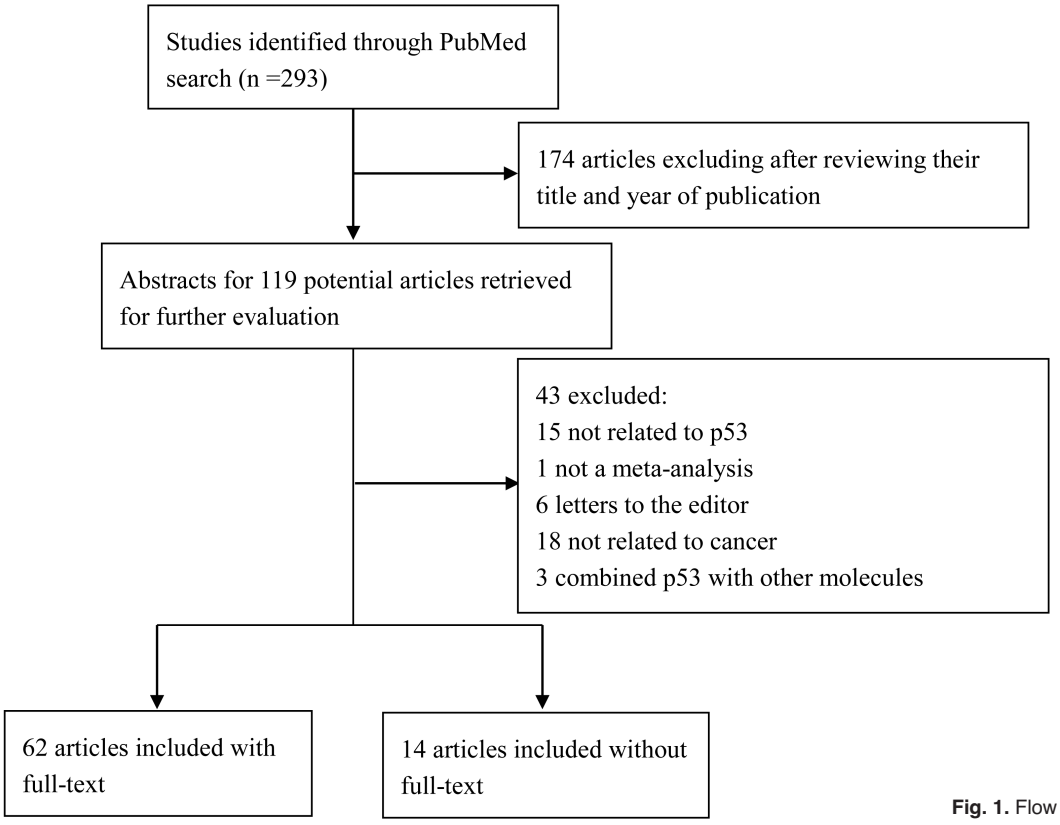

Fig. 1. Flow diagram of article selection.

certain types of p53-related alterations (Fig. 2C). A systematic description and discussion are included in the following sections.

TP53 polymorphisms

To date, although the frequencies of cancer-associated TP53 mutations vary considerably, TP53 has been widely reported to be the most frequently mutated gene in almost every type of human cancer (Bertheau et al., 2008; Brosh and Rotter, 2009; Olivier et al., 2010; Rivlin et al., 2011; Liu et al., 2014). Due to the great development of detection methods and their practical implementations, an extensive body of data has highlighted the fact that TP53 mutants, typically single-nucleotide polymorphisms (SNPs), are a hallmark of most human cancers (Whibley et al., 2009; Grochola et al., 2010; Olivier et al., 2010). TP53 harbours high-frequency SNPs, and approximately 2000 different single amino acid changes in the p53 protein have been identified in human cancers; certain SNPs have been tested in functional assays or found to cause measurable alterations of p53 cancer-suppressor function (Whibley et al., 2009; Olivier et al., 2010; Leroy et al., 2013). Further identification of the molecular mechanisms behind the clinically relevant SNPs in TP53 has provided insight for its translation into cancer treatment (Grochola et al., 2010). Indeed, although thousands of studies have reported that TP53 polymorphisms are possible risk factors for many cancer varieties, the results remain inconclusive. These data must be summarised in detail to elicit a clear idea of the current evidence-based studies on TP53 polymorphisms in cancer clinics before this information can be applied clinically. In this study, meta-analysis studies on 4 types of TP53 polymorphisms associated with cancers were searched for and collected.

TP53 codon 72 SNP (rs1042522)

The TP53 codon 72 polymorphism was the most widely studied p53-related alteration in both experimental and population studies. In this study, 55 meta-analysis studies associated with TP53 codon 72 polymorphism were finally analysed among the 83 included studies (Fig. 2A), all of which reported the association between TP53 codon 72 polymorphism and risk assessments for different cancers.

TP53 codon 72 is located within a proline-rich region between the transactivation and DNA-binding domains, which has been shown to be important for wild-type p53 function, especially for its ability to induce cellular apoptosis (Grochola et al., 2010; Olivier et al., 2010). As first reported in 1988 by Buchman and colleagues, the TP53 codon 72 SNPs exist in exon 4 with a transition between CGC and CCC, leading to an arginine(R)-to-proline(P) substitution in position 72 of the amino acid sequence (Grochola et al., 2010; Weng et al., 2012). The current consensus on TP53 codon 72 SNPs from a large number of studies is that these two different p53 isoforms are not functionally equivalent (Olivier et al., 2010). TP53 codon 72R was observed to have a stronger capacity to induce apoptosis than TP53 codon 72P, which was observed to be more efficient at both suppressing malignant transformation resulting from E7 or EJ-ras and responding to chemotherapy through interactions with p73 (Bergamaschi et al., 2003; Bertheau et al., 2008; Grochola et al., 2010). Interestingly, some studies showed that the TP53 codon 72P is possibly associated with higher levels of apoptosis (Grochola et al., 2010).

A large number of studies have reported the association between TP53 codon 72 SNP and the risk or susceptibility to certain cancers; in this study a "grey-scale" table was generated to show the clinical

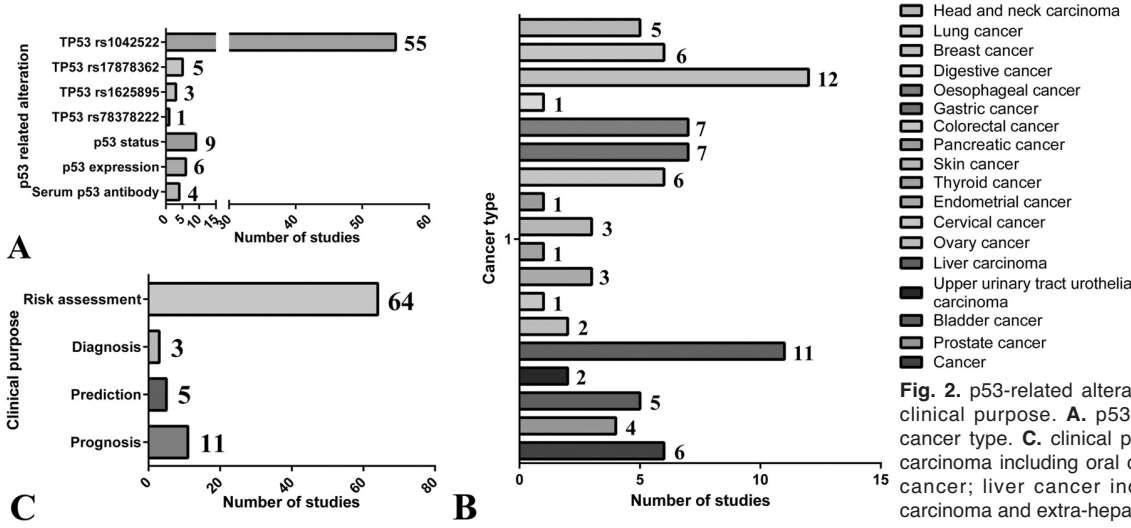

Fig. 2. p53-related alterations, cancer types and clinical purpose. **A.** p53 related alterations. **B.** cancer type. **C.** clinical purpose. Head and neck carcinoma including oral cancer and nasophageal cancer; liver cancer including hepatocellular carcinoma and extra-hepatic bile duct cancer.

significance for the potential clinical use of TP53 codon 72 SNPs. Judging from the table (Table 1), significance was observed in all included meta-analyses for nasopharyngeal cancer, oesophageal cancer, and gastric cancer. Comparatively, no "significant signals" were observed for prostate cancer, colorectal cancer, thyroid cancer, endometrial cancer, cervical cancer, head and neck carcinoma, or digestive tract cancer without subtyping. For ovarian cancer, oral cancer, and skin cancer, even non-significance was shown in all the included meta-analyses. Additionally, significance may have been found when the subgroup meta-analysis was conducted for race (Hu et al., 2010a; Jiang et al., 2010; Chen et al., 2011; Gu et al., 2011; He et al., 2011; Liu et al., 2011a,b; Xu et al., 2012a,b; Zhou et al., 2012a,b; Liu and Bao, 2013; Yang et al., 2013a,b; Lu et al., 2014), cancer subtype (Francisco et al., 2011; Liu et al., 2011a,b; Dahabreh et al., 2013; Zhou et al., 2013; Ren et al., 2014), and genetic analysis model (Zhou et al., 2012b; Wu et al., 2014).

Table 1. TP53 rs1042522 (TP53 codon 72 polymorphism) for risk assessment.

Cancer Type	S	PS	NS
Cancer		Dahabreh et al., 2013; Francisco et al., 2011	Mandal et al., 2014
Prostate cancer		Lu et al., 2014	Zhu et al., 2011; Li et al., 2011; Zhang et al., 2011
Lung cancer	Wang et al., 2013; Ye et al., 2014	Zhou et al., 2013	
Breast cancer	Zhang et al., 2010	Hu et al., 2010a; He et al., 2011	Ma et al., 2011; Cheng et al., 2012; Hou et al., 2013
Esophageal cancer	Wang et al., 2010; Zhao et al., 2010, 2013; Jiang et al., 2011c		
Gastric cancer	Su and Jin, 2012; Xiang et al., 2012; Liu et al., 2012b; Tang et al., 2012b; Zhang et al., 2013a		
Colorectal cancer		Liu et al., 2011b	Tang et al., 2010; Dahabreh et al., 2010; Economopoulos et al., 2010; Wang et al., 2011b
Digestive tract cancer		Liu et al., 2011a	
Skin cancer			Jiang et al., 2011b; Ye et al., 2013; Yang et al., 2013a
Bladder cancer	Li et al., 2010	Jiang et al., 2010; Xu et al., 2012b; Yang et al., 2013b; Liu and Bao, 2013	
Thyroid cancer		Wu et al., 2014	
Endometrial cancer		Gu et al., 2011	Jiang et al., 2011a; Tang et al., 2012a
Cervical cancer		Zhou et al., 2012b	
Ovarian cancer			Shen et al., 2012; Alqumber et al., 2014
Head and neck carcinoma		Ren et al., 2014	Xia et al., 2013
Nasopharyngeal cancer	Cai et al., 2014		
Oral cancer			Jiang, 2013
Liver cancer	Ding et al., 2012; Lv et al., 2013; Hu et al., 2014	Chen et al., 2011; Xu et al., 2012a	

S: Statistical significance; NS: no statistical significance; PS: statistical significance for certain subgroup analysis.

Table 2. TP53 rs17878362, rs1625895, and rs78378222 for risk assessment.

Cancer Type	S	PS	NS
TP53 rs17878362 (IVS 3 16bp Del/Ins) for risk assessment			
Breast cancer	Hu et al., 2010a; He et al., 2011; Wu et al., 2013		
Lung cancer	Ye et al., 2014		
Cancer	Hu et al., 2010b		
TP 53 rs1625895 (IVS6 +62 A>G) for risk assessment			
Breast cancer			Hu et al., 2010a; He et al., 2011
Lung cancer	Ye et al., 2014		
TP53 rs78378222 (A to C change) for risk assessment			
Cancer		Guan et al., 2013	

S: Statistical significance; NS: no statistical significance; PS: statistical significance for certain subgroup analysis.

TP53 intron 3 16bp Del/Ins (rs17878362), TP53 intron 6 A/G transition (rs1625895)

*TP*53 intron 3 16bp Del/Ins and intron 6 A/G transition are two intronic TP53 polymorphisms (Hrstka et al., 2009). Although intron polymorphisms were originally believed to have no function because they do not code for proteins, further studies have revealed that some of these sequences show certain associations with increased cancer risk (Hrstka et al., 2009; Marcel et al., 2009; He et al., 2011; Ye et al., 2014). However, the results were inconclusive; some original studies found that these polymorphisms were associated with cancer risk, but other studies drew different conclusions.

We found that 8 related meta-analysis studies were conducted to further explore the association between TP 53 intron 3 or intron 6 polymorphisms with the risk of certain cancers (Table 2). For TP53 intron 3 16bp Del/Ins, significant conclusions were found in all 5 included studies for the risk assessment of breast cancer, lung cancer, or cancer without further subtyping (Hu et al., 2010a,b; He et al., 2011; Wu et al., 2013; Ye et al., 2014). However, with regard to the TP53 intron 6 A/G transition, 3 included studies showed that the potential significance for cancer risk assessment was only found in lung cancer (Ye et al., 2014), but not breast cancer (Hu et al., 2010a; He et al., 2011).

TP53 A-to-C change in the 3'-untranslated region (rs78378222)

The TP53 A-to-C change polymorphism was identified as a rare variant in the 3' untranslated region of TP53, changing the AATAAA polyadenylation region to AATACA (Stacey et al., 2011; Zhou et al., 2012a,b). It has been suggested that rs7837222 can impair the proper termination and polyadenylation of the TP53 mRNA, and the rs7837222A/C heterozygotes was observed to express somewhat less TP53 transcript than the wild-type homozygotes (Stacey et al., 2011). Although the potential mechanisms might not be clear, rs78378222 was reported to be associated with prostate cancer, glioma, colorectal adenoma, and oesophageal squamous cell carcinoma, while no effect was observed for breast cancer (Stacey et al., 2011; Egan et al., 2012).

In this study, one meta-analysis was included regarding rs78378222 (Table 2). After a systematic review, there was no significant association between rs78378222 and an increased risk of skin melanoma and lung cancer, and a possible protective effect for HNSCC was shown in the study (Guan et al., 2013).

p53 expression

Due to the tight regulation by the MDM2 E3 ubiquitin ligase, wild-type p53 is continually produced and degraded to be maintained at very low levels under non-stressed conditions (Freed-Pastor and Prives, 2012; Muller and Vousden, 2013; Liu et al., 2014). However, in most cases, the TP53 gene is mutated, and the majority of TP53 mutations are missense mutations in human cancers (Brosh and Rotter, 2009; Rivlin et al., 2011; Liu et al., 2014). As the results of the structural alterations of the mutated p53 protein or additional events occur during tumourigenesis (Freed-Pastor and Prives, 2012; Zong et al., 2012), it is possible that mutant-type p53 has a prolonged half-life and accumulates in the nucleus of cancer cells, which shows its potential to be a hallmark of certain cancer cells (Rivlin et al., 2011). Therefore, many studies aimed to detect mutant p53 as a candidate biomarker for further prognostic or predictive information of certain cancers, and immunohistochemical (IHC) staining is commonly used as a surrogate for detecting a missense mutation in TP53 (Bertheau et al., 2008; Brosh and Rotter, 2009; Freed-Pastor and Prives, 2012).

IHC was the only detection technology used for p53 expression in the 5 included studies that reported on detection technology (Smith et al., 2011; Ku et al., 2013; Ji et al., 2014; Wei et al., 2015; Zhan and Ji, 2014). For the studies on the association between p53 expression and prognosis (Table 3), significant conclusions were acquired for gastric cancer (Wei et al., 2015), hepatocellular carcinoma (Ji et al., 2014; Zhan and Ji, 2014), and upper urinary tract urothelialcarcinoma (Ku et al., 2013), but not for pancreatic cancer (Smith et al., 2011). With regard to prediction (Table 3), a significant association was found for upper urinary tract

Table 3. p53 expression for prognosis and prediction.

Cancer Type	S	PS	NS
p53 expression for prognosis			
Gastric cancer	Wei et al., 2015		
Hepatocellular carcinoma	Ji et al., 2014; Zhan and Ji, 2014		
Upper urinary tract urothelial carcinoma	Ku et al., 2013		
Pancreatic cancer			Smith et al., 2011
p53 expression for prediction			
Upper urinary tract urothelial carcinoma	Lee et al., 2015		

S: Statistical significance; NS: no statistical significance; PS: statistical significance for certain subgroup analysis.

urothelialcarcinoma (Lee et al., 2015). Indeed, the accumulation of p53 detected by IHC does not always indicate a TP53 mutation; certain abnormal proteins caused by some mutations are not detectable by IHC, especially for frameshift, nonsense, or splicing mutations, and wild-type p53 may also accumulate in some cancers in response to DNA damage (Norberg et al., 1998; Bertheau et al., 2008; Brosh and Rotter, 2009). A large number of studies revealed that p53 expression detected by IHC is not a powerful surrogate marker for TP53 mutation; at the same time, an unacceptable number of false-positive and false-negative cases or inter-study variability caused by a lack of standard protocols and cut-off thresholds for IHC detection of p53 have been noted (Brosh and Rotter, 2009; Olivier et al., 2010). Therefore, further consideration should be taken when p53 expression is solely chosen as a biomarker for certain cancers.

TP53 status

Considering the lack of evidence for p53 expression as a potential biomarker, some studies have examined the detection of TP53 status by gene sequencing or related methods (Brosh and Rotter, 2009). The mutational status of TP53 was suggested to serve as an independent prognostic or predictive indicator in certain cancers (Shi et al., 2009; Grochola et al., 2010). Additionally, it should be noted that TP53 status is a factor with many parameters, consisting of the type of mutation, the level and subcellular location of the mutant protein, as well as the status of TP53 LOH, codon 72 SNP, and other TP53-related alterations (Brosh and Rotter, 2009). In this study, p53 status was concluded to be significant for the prognostic evaluation of hepatocellular carcinoma (Liu et al., 2012c; Zhan et al., 2013), oesophageal cancer(Chen et al., 2013), extra-hepatic bile duct cancer (Wang et al., 2011a), and head and neck carcinoma (Tandon et al., 2010), and significant for the prediction of oesophageal cancer (Zhang et al., 2013), gastric cancer (Xu et al., 2014), rectal cancer (Chen et al., 2012a), and breast cancer (Chen et al., 2012b) (Table 4). It should be noted that the predictive significance of TP53 status is extremely variable according to the treatment regimens for each included study; therefore, further studies should be conducted to provide a powerful and reliable conclusion to assess the TP53 status with homogeneous chemotherapy to homogeneous cancer types (Bertheau et al., 2008; Olivier et al., 2010).

Serum p53 antibodies

It has been revealed that mutated or aberrantly expressed proteins following cancer onset and progression are able to act as antigens and evoke an immune response, which subsequently results in the production of autoantibodies (Luna Coronell et al.,

Table 4. TP53 status for prognosis and prediction.

Cancer Type	S	PS	NS
p53 status for prognosis			
Hepatocellular carcinoma	Liu et al., 2012c; Zhan et al., 2013		
Esophageal cancer	Chen et al., 2013		
Extra-hepatic bile duct cancer	Wang et al., 2011a		
Head and neck carcinoma	Tandon et al., 2010		
p53 status for prediction			
Esophageal cancer	Zhang et al., 2013		
Gastric cancer	Xu et al., 2014		
Rectal cancer	Chen et al., 2012a		
Breast cancer	Chen et al., 2012b		

S: Statistical significance; NS: no statistical significance; PS: statistical significance for certain subgroup analysis.

Table 5. Serum p53 antibody for diagnosis and prognosis.

Cancer Type	S	PS	NS
Serum p53 antibody for diagnosis			
Esophageal cancer	Zhang et al., 2012		
Cancer	Zhang et al., 2014		
Lung cancer	Lei et al., 2013		
Serum p53 antibody for prognosis			
Hepatocellular carcinoma		Liu et al., 2012c	

S: Statistical significance; NS: no statistical significance; PS: statistical significance for certain subgroup analysis.

2012). Autoantibodies as serological tools have always been expected to be translated into the early diagnosis and management of cancer as a potential marker with a minimal invasive testing method and only a few microliters of serum. For p53, antibodies in the serum were shown to be frequently found in human cancer patents, and the increased incidence of anti-p53 antibodies was also observed to correlate with TP53 missense mutations and the accumulation of mutant protein in cancer (Lubin et al., 1995a,b; Ralhan et al., 1998; Lutz and Nowakowska-Swirta, 2002). Some studies showed that the presence of p53 antibodies might have resulted from the humoral immune response against accumulated p53, and p53-HSP70 complex, while the underlying mechanisms still require further investigation (Kaur et al., 1997). The results of previous studies ascertained that the presence of p53 antibodies is an early event associated with some cancer preconditioning or the subsequent development of cancers, showing potential clinical significance as an early serological marker (Ralhan et al., 1998; Li et al., 2005; Rivlin et al., 2011). Herein, from the meta-analysis on serum p53 antibodies (Table 5), significance was concluded for the diagnosis of oesophageal cancer (Zhang et al., 2012), lung cancer (low sensitivity) (Lei et al., 2013), and cancer without subtyping (Zhang et al., 2014). Considering the prognosis of hepatocellular carcinoma, elevated p53 antibody levels were only found to be associated with poor overall survival (OS) with a high proportion of hepatitis C virus infection (Liu et al., 2012a,b).

Because p53 antibodies are truly rare in the normal population, and accumulated mutant p53 protein only exists in the nucleus of cancer cells after gene mutation, p53 antibodies are found predominantly in human cancer with a specificity approaching 95% (Soussi, 2000; Rivlin et al., 2011). Conversely, the low sensitivity of p53 antibodies absolutely precludes its further clinical use (Soussi, 2000). Therefore, increased attention should be paid to the clinical translation of p53 antibodies on its action as a biomarker for evaluating the efficiency of certain cancer treatments or for monitoring possible cancer relapse (Soussi, 2000).

Heterogeneity analysis of p53-related alterations

Heterogeneity from TP53/p53

Indeed, even with the thorough investigation of p53 over the past few decades, things appear ever more complicated. We know that the function of p53 as a transcriptional factor is crucial for cancer suppression; a TP53 mutation may result in complete p53 deficiency, which can enhance the initiation or progression of malignancy (Bieging et al., 2014). However, the biological effects of certain numbers of TP53-related mutations are not yet understood clearly; the clinical value of the TP53 status may also depend on the type of mutation (Bertheau et al., 2008). Notably, the notion that TP53 mutations may occur at different stages along the process of malignant transformation raises the question that p53 mutations might not be an exact or rational biomarker with convincing clinical values (Brosh and Rotter, 2009; Rivlin et al., 2011). Considering p53 expression, not all cancers with missense TP53 mutations are IHC positive, and it may not be favourable to utilise p53 expression as a sole biomarker (Brosh and Rotter, 2009). Although the p53 protein is frequently referred to as a single entity, at least 12 isoforms have been identified, and the discovery of p53 isoforms has introduced new perspectives in the p53 research field (Surget et al., 2013; Duffy et al., 2014). The transcriptional activities of p53 show the ability to alter the expression of hundreds of genes, and it is difficult to determine whether the identified p53 isoforms exert identical effects (Levine and Oren, 2009). In addition, the abnormal expression of p53 isoforms was observed to contribute actively to cancer formation and progression in cancer cells, regardless of TP53 mutation (Surget et al., 2013). Therefore, for the clinical observations associated with p53-related alterations and cancer clinics, further research is required for its eventual translation.

Heterogeneity from different cancer types

As shown in this study, the clinical significance of p53-related alterations is extremely variable among different cancer types. In conclusion, we would like to describe such heterogeneity in two aspects. For the occurrence of TP53 mutations, it has been found that the variation in the number of TP53 mutations along with the frequency of specific cancer types results from the impact of mutational factors on TP53 in a cancer- and tissue-selective manner (Freed-Pastor and Prives, 2012). For the effect of p53, as a transcription factor, its cancer suppressor functions are context dependent and may be influenced by numerous factors, including the local chromatin environment, genetic background, and microenvironment of the cell, rather than follow a global cell-type invariant response program (Bertheau et al., 2008; Zilfou and Lowe, 2009; Sammons et al., 2015). Clinical observations have shown that the prognostic and predictive significance of mutant p53 is extremely variable according to cancer types (Olivier et al., 2010); studies of different cancer types will certainly improve our understanding of p53 function in the process of their malignancy. In this study, for TP53 codon 72 SNP, significance was observed for the risk assessment of nasopharyngeal cancer, oesophageal cancer, and gastric cancer with similar local microenvironments in the upper digestive tract, which might trigger further studies for the underlying mechanisms.

Heterogeneity from ethnicity or geography

In this study, although some p53-related alterations showed non-significance in the primary meta-analysis,

we observed that significance could be obtained after further analysis by subgroups among different ethnicities. The heterogeneity from ethnicity is another factor that should not be neglected; various factors, such as a normal genetic background, other genetic alterations in cancer, gene-environment interactions in different cancer types, and other unknown factors have the ability to influence p53-related alterations (Bertheau et al., 2008). This result can be exemplified by the finding that hepatocellular carcinoma in certain developing nations has a substantially higher frequency of p53-R249 mutations than other cancer types or even liver cancer in developed nations (Freed-Pastor and Prives, 2012). Additionally, geographic differences have also been reported in relation to environmental exposures (Shi et al., 2009; Olivier et al., 2010). Shi et al. reported that winter temperature and ultraviolet are tightly linked to genetic changes of *TP53* in eastern Asia (Shi et al., 2009). Thus, more attention should be paid to the heterogeneity from population groups of different ethnicities or different areas, which is sure to be more meaningful for clinical translation among different ethnicities.

Heterogeneity from detecting methods

For the past few decades, rapid and considerable progress has been made in molecular detection methods, which greatly promotes the experimental and clinical development of p53-related alterations (Brosh and

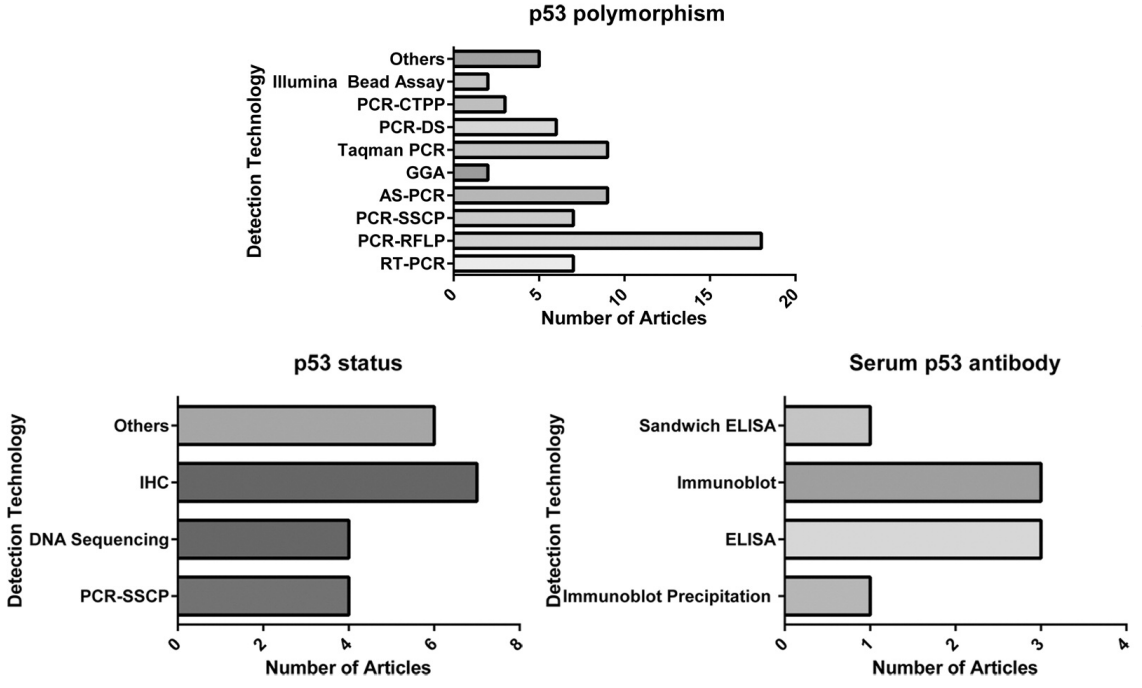

Fig. 3. Heterogeneity analysis of the detection methods PCR: polymerase chain reaction; PCR-RFLP: PCR-restriction fragment length polymorphism; PCR-SSCP: PCR-single-strand conformation polymorphism analysis; PCR-CTPP: PCR-confronting two-pair primer; AS-PCR: allele-specific PCR; PCR-DS: PCR-direct sequencing; GGA: golden gate assay; IHC: Immunohisto-chemical staining; ELISA: enzyme-linked immunosorbent assay.

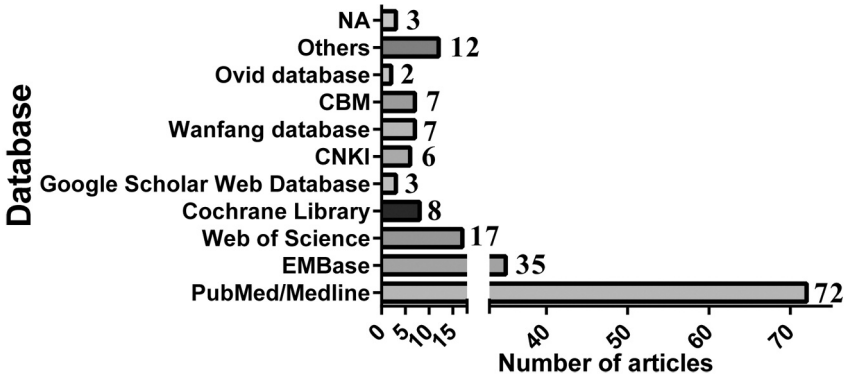

Fig. 4. The database distributions CNKI: China national knowledge infrastructure; CBM: China biology medicine database; NA: not available.

Rotter, 2009). We conclude that a variety of detection methods were adopted for each p53-related alteration in this study (Fig.3); meanwhile, we observed that the detection methods used for each study varied considerably. Therefore, differences in sensitivity or specificity and potential limitations for each method should not be ignored (Brosh and Rotter, 2009; Tandon et al., 2010). Additionally, no standard method of analysis for each could be acquired, which limits the referring values for certain studies. Before we can utilise the benefits from the great improvements of detection technology, the use of consistent methodology or assays, the exact definition of relevant cut-off points, and the standard analysis and reporting of results may clarify many of the conflicting data and help with future studies relevant to p53-related alterations (Soussi, 2000).

Discoveries concluded from small or single studies are prone to overestimation (false positive) or underestimation (false negative) of the actual bio-effect of target biomarkers. A meta-analysis appears to be a more convincing method, as it pools data from multiple studies with an increase in the statistical power and the precision of effect estimates. For the meta-analysis studies included in this study, valuable observations have been acquired for the potential use of p53-related alterations as cancer biomarkers. Additionally, caution should be paid to the potential limitations of each study. First, considerable variations were found in the number of included studies, even for articles published in the same year. A total summary for the database searched in each study was conducted (Fig. 4), which might explain the potential heterogeneity from the number of included studies. Additionally, obtaining all of the published and unpublished pertinent data is necessary for a complete systematic review. However, considering the language barrier or other potential difficulties, meta-analyses concentrating on certain ethnicities or geographical areas may be a convincing choice for the further or updated evaluation of p53-related alterations. Second, some of the works that addressed contradictory results could also be traced back to the different designs of their studies, including differences among search strategies, inclusion or exclusion criteria, and the analysis model used for calculating pooled effect estimates. Third, for TP53 alterations, the mutant status can be analysed in recessive/dominant models or homozygous/heterozygous mode (Francisco et al., 2011). It is still inconsistent to conclude a rational interpretation of these results, and further laboratory studies are needed before we can have a clear understanding. Fourth, differences from the control were also potential origins of heterogeneity. Misclassification bias may have existed depending on whether the controls were hospital based or population based, or whether they coincided with Hardy-Weinberg equilibrium (HWE). A prior test for the controls may be necessary to avoid the underlying bias of meta-analysis. Given the remarkable potential heterogeneity in the reported meta-analysis study, more well-designed prospective large-scale studies with different ethnicities are desirable for the translation of p53-related alterations as cancer biomarkers.

Herein, we collected the published meta-analyses on p53-related alterations and cancers in the past 5 years through queries in the PubMed database. We aimed to systematically summarise both the potential value of the clinical use of p53-related alterations as cancer biomarkers and the underlying heterogeneity from the view of evidence-based medicine. P53-related alterations have been proven to be extremely complex biomarkers in terms of p53's clinical translation; many of the included studies must be interpreted cautiously, at least concerning clinical use as a sole cancer biomarker. Together with the experimental studies on p53-related alterations, a gold-standard approach is still being developed, with more evidence-based medicine studies with large, prospectively planned cohorts and clinical studies required. Above all, we hope that p53 will eventually be used as an effective biomarker in the clinic.

Acknowledgements. Natural Science Foundation of China (91229103, 81472515) and Shanghai Science and Technology Committee project (13140902600, 11DZ2291800).

References

Alqumber M.A., Akhter N., Haque S., Panda A.K. and Mandal R.K. (2014). Evaluating the association between p53 codon 72 arg>pro polymorphism and risk of ovary cancer: A meta-analysis. PloS one 9, e94874.

Armitage E.G. and Barbas C. (2014). Metabolomics in cancer biomarker discovery: Current trends and future perspectives. J. Pharmaceut. Biomed. Anal. 87, 1-11.

Bergamaschi D., Gasco M., Hiller L., Sullivan A., Syed N., Trigiante G., Yulug I., Merlano M., Numico G., Comino A., Attard M., Reelfs O., Gusterson B., Bell A.K., Heath V., Tavassoli M., Farrell P.J., Smith P., Lu X. and Crook T. (2003). P53 polymorphism influences response in cancer chemotherapy via modulation of p73-dependent apoptosis. Cancer Cell 3, 387-402.

Bertheau P., Espie M., Turpin E., Lehmann J., Plassa L.F., Varna M., Janin A. and de The H. (2008). Tp53 status and response to chemotherapy in breast cancer. Pathobiology 75, 132-139.

Bieging K.T., Mello S.S. and Attardi L.D. (2014). Unravelling mechanisms of p53-mediated tumour suppression. Nat. Rev. Cancer 14, 359-370.

Brosh R. and Rotter V. (2009). When mutants gain new powers: News from the mutant p53 field. Nature Rev. Cancer 9, 701-713.

Cai K., Wang Y., Zhao X. and Bao X. (2014). Association between the p53 codon 72 polymorphism and nasopharyngeal cancer risk. Tumour Biol. 35, 1891-1897.

Chen X., Liu F., Li B., Wei Y.G., Yan L.N. and Wen T.F. (2011). P53 codon 72 polymorphism and liver cancer susceptibility: A meta-analysis of epidemiologic studies. World J. Gastroenterol. 17, 1211-1218.

Chen M.B., Wu X.Y., Yu R., Li C., Wang L.Q., Shen W. and Lu P.H. (2012a). P53 status as a predictive biomarker for patients receiving neoadjuvant radiation-based treatment: A meta-analysis in rectal

cancer. PloS one 7, e45388.

Chen M.B., Zhu Y.Q., Xu J.Y., Wang L.Q., Liu C.Y., Ji Z.Y. and Lu P.H. (2012b). Value of tp53 status for predicting response to neoadjuvant chemotherapy in breast cancer: A meta-analysis. PloS one 7, e39655.

Chen M., Huang J., Zhu Z., Zhang J. and Li K. (2013). Systematic review and meta-analysis of tumor biomarkers in predicting prognosis in esophageal cancer. BMC Cancer 13, 539.

Cheng H., Ma B., Jiang R., Wang W., Guo H., Shen N., Li D., Zhao Q., Wang R., Yi P., Zhao Y., Liu Z. and Huang T. (2012). Individual and combined effects of mdm2 snp309 and tp53 arg72pro on breast cancer risk: An updated meta-analysis. Molecular Biol. Rep. 39, 9265-9274.

Dahabreh I.J., Linardou H., Bouzika P., Varvarigou V. and Murray S. (2010). Tp53 arg72pro polymorphism and colorectal cancer risk: A systematic review and meta-analysis. Cancer Epidemiol. Biomark. Prevent. 19, 1840-1847.

Dahabreh I.J., Schmid C.H., Lau J., Varvarigou V., Murray S. and Trikalinos T.A. (2013). Genotype misclassification in genetic association studies of the rs1042522 tp53 (arg72pro) polymorphism: A systematic review of studies of breast, lung, colorectal, ovarian, and endometrial cancer. American J. Epidemiol. 177, 1317-1325.

Ding C., Yu H., Yu H. and Qin H. (2012). Tp53 codon 72 polymorphism with hepatocellular carcinoma: A metaanalysis. J. Internat. Med. Res. 40, 446-454.

Duffy M.J., Synnott N.C., McGowan P.M., Crown J., O'Connor D. and Gallagher W.M. (2014). P53 as a target for the treatment of cancer. Cancer Treat. Rev. 40, 1153-1160.

Economopoulos K.P., Sergentanis T.N., Zagouri F. and Zografos G.C. (2010). Association between p53 arg72pro polymorphism and colorectal cancer risk: A meta-analysis. Onkologie 33, 666-674.

Egan K.M., Nabors L.B., Olson J.J., Monteiro A.N., Browning J.E., Madden M.H. and Thompson R.C. (2012). Rare tp53 genetic variant associated with glioma risk and outcome. J. Med. Genet. 49, 420-421.

Francisco G., Menezes P.R., Eluf-Neto J. and Chammas R. (2011). Arg72pro tp53 polymorphism and cancer susceptibility: A comprehensive meta-analysis of 302 case-control studies. International journal of cancer. J. Internat. Cancer 129, 920-930.

Freed-Pastor W.A. and Prives C. (2012). Mutant p53: One name, many proteins. Genes Dev. 26, 1268-1286.

Grochola L.F., Zeron-Medina J., Meriaux S. and Bond G.L. (2010). Single-nucleotide polymorphisms in the p53 signaling pathway. Cold Spring Harbor Perspect. Biol. 2, a001032.

Gu Y., Zhou X. and Zhang S.L. (2011). Meta-analysis of an association of codon 72 polymorphisms of the p53 gene with increased endometrial cancer risk. Genet. Mol. Res. 10, 3609-3619.

Guan X., Wang L.E., Liu Z., Sturgis E.M. and Wei Q. (2013). Association between a rare novel tp53 variant (rs78378222) and melanoma, squamous cell carcinoma of head and neck and lung cancer susceptibility in non-hispanic whites. J. Cell. Mol. Med. 17, 873-878.

Hayes D.F. (2015). Biomarker validation and testing. Mol. Oncol. 9, 960-966.

He X.F., Su J., Zhang Y., Huang X., Liu Y., Ding D.P., Wang W. and Arparkorn K. (2011). Association between the p53 polymorphisms and breast cancer risk: Meta-analysis based on case-control study. Breast Cancer Res. Treat. 130, 517-529.

Hou J., Jiang Y., Tang W. and Jia S. (2013). P53 codon 72 polymorphism and breast cancer risk: A meta-analysis. Exp. Therap. Med. 5, 1397-1402.

Hrstka R., Beranek M., Klocova K., Nenutil R. and Vojtesek B. (2009). Intronic polymorphisms in tp53 indicate lymph node metastasis in breast cancer. Oncol. Rep. 22, 1205-1211.

Hu Z., Li X., Yuan R., Ring B.Z. and Su L. (2010a). Three common tp53 polymorphisms in susceptibility to breast cancer, evidence from meta-analysis. Breast Cancer Res. Treat. 120, 705-714.

Hu Z., Li X., Qu X., He Y., Ring B.Z., Song E. and Su L. (2010b). Intron 3 16 bp duplication polymorphism of tp53 contributes to cancer susceptibility: A meta-analysis. Carcinogenesis 31, 643-647.

Hu S., Zhao L., Yang J. and Hu M. (2014). The association between polymorphism of p53 codon72 arg/pro and hepatocellular carcinoma susceptibility: Evidence from a meta-analysis of 15 studies with 3,704 cases. Tumour Biol. 35, 3647-3656.

Ji Y.N., Wang Q. and Xue J. (2014). Tp53 immunohistochemical expression is associated with the poor outcome for hepatocellular carcinoma: Evidence from a meta-analysis. Tumour Biol. 35, 1653-1659.

Jiang D.K., Ren W.H., Yao L., Wang W.Z., Peng B. and Yu L. (2010). Meta-analysis of association between tp53 arg72pro polymorphism and bladder cancer risk. Urology 76, 765.e1-765.e7.

Jiang D.K., Yao L., Ren W.H., Wang W.Z., Peng B. and Yu L. (2011a). Tp53 arg72pro polymorphism and endometrial cancer risk: A meta-analysis. Med. Oncol. (Northwood, London, England) 28, 1129-1135.

Jiang D.K., Wang W.Z., Ren W.H., Yao L., Peng B. and Yu L. (2011b). Tp53 arg72pro polymorphism and skin cancer risk: A meta-analysis. J. Invest. Dermatol. 131, 220-228.

Jiang D.K., Yao L., Wang W.Z., Peng B., Ren W.H., Yang X.M. and Yu L. (2011c). Tp53 arg72pro polymorphism is associated with esophageal cancer risk: A meta-analysis. World J. Gastroenterol. 17, 1227-1233.

Kaur J., Srivastava A. and Ralhan R. (1997). Serum p53 antibodies in patients with oral lesions: Correlation with p53/hsp70 complexes. Int. J. Cancer 74, 609-613.

Ku J.H., Byun S.S., Jeong H., Kwak C., Kim H.H. and Lee S.E. (2013). The role of p53 on survival of upper urinary tract urothelial carcinoma: A systematic review and meta-analysis. Clin. Genitourinary Cancer 11, 221-228.

Lane D. and Levine A. (2010). P53 research: The past thirty years and the next thirty years. Cold Spring Harbor. Persp. Biol. 2, a000893.

Lee J.Y., Cho K.S., Diaz R.R., Choi Y.D. and Choi H.Y. (2015). P53 expression as a prognostic factor in upper urinary tract urothelial carcinoma: A systematic review and meta-analysis. Urol. Int. 94, 50-57.

Lei Q.Q., Liu J.W. and Zheng H. (2013). Potential role of anti-p53 antibody in diagnosis of lung cancer: Evidence from a bivariate meta-analysis. European review for medical and pharmacological Sciences 17, 3012-3018.

Leroy B., Fournier J.L., Ishioka C., Monti P., Inga A., Fronza G. and Soussi T. (2013). The tp53 website: An integrative resource centre for the tp53 mutation database and tp53 mutant analysis. Nucleic Acids Res. 41, D962-969.

Levine A.J. and Oren M. (2009). The first 30 years of p53: Growing ever more complex. Nat. Rev. Cancer 9, 749-758.

Li Y., Karjalainen A., Koskinen H., Hemminki K., Vainio H., Shnaidman M., Ying Z., Pukkala E. and Brandt-Rauf P.W. (2005). P53 autoantibodies predict subsequent development of cancer.

International journal of cancer. Int. J. Cancer 114, 157-160.

Li D.B., Wei X., Jiang L.H., Wang Y. and Xu F. (2010). Meta-analysis of epidemiological studies of association of p53 codon 72 polymorphism with bladder cancer. Genet. Mol. Res. 9, 1599-1605.

Li M.S., Liu J.L., Wu Y., Wang P. and Teng H. (2011). Meta-analysis demonstrates no association between p53 codon 72 polymorphism and prostate cancer risk. Genet. Mol. Res. 10, 2924-2933.

Liu Z.H. and Bao E.D. (2013). Quantitative assessment of the association between tp53 arg72pro polymorphism and bladder cancer risk. Mol. Biol. Rep. 40, 2389-2395.

Liu L., Wang K., Zhu Z.M. and Shao J.H. (2011a). Associations between p53 arg72pro and development of digestive tract cancers: A meta-analysis. Arch. Med. Res. 42, 60-69.

Liu Y., Qin H., Zhang Y., Shi T., Liu B., Sun Y. and Ma Y. (2011b). P53 codon 72 polymorphism and colorectal cancer: A meta-analysis of epidemiological studies. Hepato-gastroenterology 58, 1926-1929.

Liu J., Ma Q., Zhang M., Wang X., Zhang D., Li W., Wang F. and Wu E. (2012a). Alterations of tp53 are associated with a poor outcome for patients with hepatocellular carcinoma: Evidence from a systematic review and meta-analysis. Eur. J. Cancer 48, 2328-2338.

Liu K.J., Qi H.Z., Yao H.L., Lei S.L., Lei Z.D., Li T.G. and Zhao H. (2012b). An updated meta-analysis of the p53 codon 72 polymorphism and gastric cancer risk. Mol. Biol. Rep. 39, 8265-8275.

Liu J., Zhang C. and Feng Z. (2014). Tumor suppressor p53 and its gain-of-function mutants in cancer. Acta Biochem. Biophys. Sinica 46, 170-179.

Liu J., Zhang C., Hu W. and Feng Z. (2015). Tumor suppressor p53 and its mutants in cancer metabolism. Cancer Lett. 356, 197-203.

Lu Y., Liu Y., Zeng J., He Y., Peng Q., Deng Y., Wang J., Xie L., Li T., Qin X. and Li S. (2014). Association of p53 codon 72 polymorphism with prostate cancer: An update meta-analysis. Tumour Biol. 35, 3997-4005.

Lubin R., Schlichtholz B., Teillaud J.L., Garay E., Bussel A. and Wild C.P. (1995a). P53 antibodies in patients with various types of cancer: Assay, identification, and characterization. Clinical Cancer Res. 1, 1463-1469.

Lubin R., Zalcman G., Bouchet L., Tredanel J., Legros Y., Cazals D., Hirsch A. and Soussi T. (1995b). Serum p53 antibodies as early markers of lung cancer. Nature Med. 1, 701-702.

Luna Coronell J.A., Syed P., Sergelen K., Gyurjan I. and Weinhausel A. (2012). The current status of cancer biomarker research using tumour-associated antigens for minimal invasive and early cancer diagnostics. J. Proteomics 76, 102-115.

Lutz W. and Nowakowska-Swirta E. (2002). Gene p53 mutations, protein p53, and anti-p53 antibodies as biomarkers of cancer process. Int. J. Occupat. Med. Environ. Health 15, 209-218.

Lv L., Wang P., Zhou X. and Sun B. (2013). Association between the p53 codon 72 arg/pro polymorphism and hepatocellular carcinoma risk. Tumour Biol. 34, 1451-1459.

Ma Y., Yang J., Liu Z., Zhang P., Yang Z., Wang Y. and Qin H. (2011). No significant association between the tp53 codon 72 polymorphism and breast cancer risk: A meta-analysis of 21 studies involving 24,063 subjects. Breast Cancer Res. Treat. 125, 201-205.

Mandal R.K., Yadav S.S. and Panda A.K. (2014). No evidence of correlation between p53 codon 72 g > c gene polymorphism and cancer risk in indian population: A meta-analysis. Tumour Biol. 35, 8607-8613.

Marcel V., Palmero E.I., Falagan-Lotsch P., Martel-Planche G., Ashton-Prolla P., Olivier M., Brentani R.R., Hainaut P. and Achatz M.I. (2009). Tp53 pin3 and mdm2 snp309 polymorphisms as genetic modifiers in the li-fraumeni syndrome: Impact on age at first diagnosis. J. Med. Genet. 46, 766-772.

Molchadsky A., Rivlin N., Brosh R., Rotter V. and Sarig R. (2010). P53 is balancing development, differentiation and de-differentiation to assure cancer prevention. Carcinogenesis 31, 1501-1508.

Muller P.A. and Vousden K.H. (2013). P53 mutations in cancer. Nat. Cell Biol. 15, 2-8.

Norberg T., Lennerstrand J., Inganas M. and Bergh J. (1998). Comparison between p53 protein measurements using the luminometric immunoassay and immunohistochemistry with detection of p53 gene mutations using cdna sequencing in human breast tumors. International journal of cancer. Int. J. Cancer 79, 376-383.

Olivier M., Hollstein M. and Hainaut P. (2010). Tp53 mutations in human cancers: Origins, consequences, and clinical use. Cold Spring Harbor Perspect. Biol. 2, a001008.

Ralhan R., Nath N., Agarwal S., Mathur M., Wasylyk B. and Shukla N.K. (1998). Circulating p53 antibodies as early markers of oral cancer: Correlation with p53 alterations. Clin. Cancer Res. 4, 2147-2152.

Ren W.H., Jiang D.K., Pei Y., Wang S.Q., Yang X.M. and Yu L. (2014). Meta-analysis of associations between the tp53 arg72pro polymorphism with risk of head and neck carcinomas based on case-control studies. Genet. Mol. Res. 13, 103-114.

Rivlin N., Brosh R., Oren M. and Rotter V. (2011). Mutations in the p53 tumor suppressor gene: Important milestones at the various steps of tumorigenesis. Genes Cancer 2, 466-474.

Sammons M.A., Zhu J., Drake A.M. and Berger S.L. (2015). Tp53 engagement with the genome occurs in distinct local chromatin environments via pioneer factor activity. Genome Res. 25, 179-188.

Shen S.Q., Jiang D.K., Liu G.Y., Chen F. and Yu L. (2012). Meta-analysis shows significant association of the tp53 arg72pro with ovarian cancer risk. Mol. Biol. Rep. 39, 4683-4690.

Shi H., Tan S.J., Zhong H., Hu W., Levine A., Xiao C.J., Peng Y., Qi X.B., Shou W.H., Ma R.L., Li Y., Su B. and Lu X. (2009). Winter temperature and uv are tightly linked to genetic changes in the p53 tumor suppressor pathway in eastern asia. Am. J. Human Genet. 84, 534-541.

Smeenk L., van Heeringen S.J., Koeppel M., van Driel M.A., Bartels S.J., Akkers R.C., Denissov S., Stunnenberg H.G. and Lohrum M. (2008). Characterization of genome-wide p53-binding sites upon stress response. Nucleic Acids Res. 36, 3639-3654.

Smith R.A., Tang J., Tudur-Smith C., Neoptolemos J.P. and Ghaneh P. (2011). Meta-analysis of immunohistochemical prognostic markers in resected pancreatic cancer. Br. J. Cancer 104, 1440-1451.

Soussi T. (2000). P53 antibodies in the sera of patients with various types of cancer: A review. Cancer Res. 60, 1777-1788.

Stacey S.N., Sulem P., Jonasdottir A., Masson G., Gudmundsson J., Gudbjartsson D.F., Magnusson O.T., Gudjonsson S.A., Sigurgeirsson B., Thorisdottir K., Ragnarsson R., Benediktsdottir K.R., Nexo B.A., Tjonneland A., Overvad K., Rudnai P., Gurzau E., Koppova K., Hemminki K., Corredera C., Fuentelsaz V., Grasa P., Navarrete S., Fuertes F., Garcia-Prats M.D., Sanambrosio E., Panadero A., De Juan A., Garcia A., Rivera F., Planelles D., Soriano V., Requena C., Aben K.K., van Rossum M.M., Cremers R.G., van Oort I.M., van Spronsen D.J., Schalken J.A., Peters W.H., Helfand B.T., Donovan J.L., Hamdy F.C., Badescu D., Codreanu O., Jinga M., Csiki I.E., Constantinescu V., Badea P., Mates I.N., Dinu D.E.,

Constantin A., Mates D., Kristjansdottir S., Agnarsson B.A., Jonsson E., Barkardottir R.B., Einarsson G.V., Sigurdsson F., Moller P.H., Stefansson T., Valdimarsson T., Johannsson O.T., Sigurdsson H., Jonsson T., Jonasson J.G., Tryggvadottir L., Rice T., Hansen H.M., Xiao Y., Lachance D.H., BP O.N., Kosel M.L., Decker P.A., Thorleifsson G., Johannsdottir H., Helgadottir H.T., Sigurdsson A., Steinthorsdottir V., Lindblom A., Sandler R.S., Keku T.O., Banasik K., Jorgensen T., Witte D.R., Hansen T., Pedersen O., Jinga V., Neal D.E., Catalona W.J., Wrensch M., Wiencke J., Jenkins R.B., Nagore E., Vogel U., Kiemeney L.A., Kumar R., Mayordomo J.I., Olafsson J.H., Kong A., Thorsteinsdottir U., Rafnar T. and Stefansson K. (2011). A germline variant in the tp53 polyadenylation signal confers cancer susceptibility. Nat. Genet. 43, 1098-1103.

Su X.L. and Jin J.J. (2012). Pro variant of tp53 arg72pro contributes to gastric cancer risk in asians: Evidence from a meta-analysis. Asian Pacific J. Cancer Prevent. 13, 915-921.

Surget S., Khoury M.P. and Bourdon J.C. (2013). Uncovering the role of p53 splice variants in human malignancy: A clinical perspective. OncoTargets Therapy 7, 57-68.

Tandon S., Tudur-Smith C., Riley R.D., Boyd M.T. and Jones T.M. (2010). A systematic review of p53 as a prognostic factor of survival in squamous cell carcinoma of the four main anatomical subsites of the head and neck. Cancer Epidemiol. Biomarkers Prevent. 19, 574-587.

Tang N.P., Wu Y.M., Wang B. and Ma J. (2010). Systematic review and meta-analysis of the association between p53 codon 72 polymorphism and colorectal cancer. Eur. J. Surg. Oncol. 36, 431-438.

Tang W., He X., Chan Y. and Luo Y. (2012a). Lack of association between p53 codon 72 polymorphism and endometrial cancer: A meta-analysis. Cancer Epidemiol. 36, e153-157.

Tang W., Zhou X., Nie S., Yang Z., Zhu H., Wu X., Zhao R. and Luo Y. (2012b). Association of p53 arg72pro polymorphism with gastric cancer: A meta-analysis. Biomarkers 17, 597-603.

Wang B., Wang D., Zhang D., Li A., Liu D., Liu H. and Jin H. (2010). Pro variant of tp53 arg72pro contributes to esophageal squamous cell carcinoma risk: Evidence from a meta-analysis. Eur. J. Cancer Prevent. 19, 299-307.

Wang J., Wang X., Xie S., Yan Z., Li Z., Li Y., Wang L. and Jiao F. (2011a). P53 status and its prognostic role in extrahepatic bile duct cancer: A meta-analysis of published studies. Digest. Dis. Sci. 56, 655-662.

Wang J.J., Zheng Y., Sun L., Wang L., Yu P.B., Dong J.H., Zhang L., Xu J., Shi W. and Ren Y.C. (2011b). Tp53 codon 72 polymorphism and colorectal cancer susceptibility: A meta-analysis. Mol. Biol. Rep. 38, 4847-4853.

Wang S., Lan X., Tan S., Wang S. and Li Y. (2013). P53 codon 72 arg/pro polymorphism and lung cancer risk in asians: An updated meta-analysis. Tumour Biol. 34, 2511-2520.

Wei K., Jiang L., Wei Y., Wang Y., Qian X., Dai Q. and Guan Q. (2015). The prognostic significance of p53 expression in gastric cancer: A meta-analysis. J. Cancer Res. Clin. Oncol. 14, 735-748.

Weng Y., Lu L., Yuan G., Guo J., Zhang Z., Xie X., Chen G. and Zhang J. (2012). P53 codon 72 polymorphism and hematological cancer risk: An update meta-analysis. PloS one 7, e45820.

Whibley C., Pharoah P.D. and Hollstein M. (2009). P53 polymorphisms: Cancer implications. Nat. Rev. Cancer 9, 95-107.

Wu D., Zhang Z., Chu H., Xu M., Xue Y., Zhu H. and Zhang Z. (2013). Intron 3 sixteen base pairs duplication polymorphism of p53 contributes to breast cancer susceptibility: Evidence from meta-analysis. PloS one 8, e61662.

Wu B., Guo D. and Guo Y. (2014). Association between p53 arg72pro polymorphism and thyroid cancer risk: A meta-analysis. Tumour Biol. 35, 561-565.

Xia L.Y., Zeng X.T., Li C., Leng W.D. and Fan M.W. (2013). Association between p53 arg72pro polymorphism and the risk of human papillomavirus-related head and neck squamous cell carcinoma: A meta-analysis. Asian Pacific J. Cancer Prevent. 14, 6127-6130.

Xiang B., Mi Y.Y., Li T.F. and Liu P.F. (2012). Updated meta-analysis of the tp53 arg72pro polymorphism and gastric cancer risk. Asian Pacific J. Cancer Prevent. 13, 1787-1791.

Xu C.T., Zheng F., Dai X., Du J.D., Liu H.R., Zhao L. and Li W.M. (2012a). Association between tp53 arg72pro polymorphism and hepatocellular carcinoma risk: A meta-analysis. Asian Pacific J. Cancer Prevent. 13, 4305-4309.

Xu T., Xu Z.C., Zou Q., Yu B. and Huang X.E. (2012b). P53 arg72pro polymorphism and bladder cancer risk--meta-analysis evidence for a link in asians but not caucasians. Asian Pacific J. Cancer Prevent. 13, 2349-2354.

Xu H.Y., Xu W.L., Wang L.Q., Chen M.B. and Shen H.L. (2014). Relationship between p53 status and response to chemotherapy in patients with gastric cancer: A meta-analysis. PloS one 9, e95371.

Yang X., Yang B., Liu Y., Xu S. and Li B. (2013a). The association between tp53 arg72pro polymorphism and non-melanoma skin cancer risk: A meta-analysis including 7,107 subjects. Indian J. Dermatol. 58, 175-180.

Yang Z., Nie S., Zhu H., Wu X., Jia S., Luo Y. and Tang W. (2013b). Association of p53 arg72pro polymorphism with bladder cancer: A meta-analysis. Gene 512, 408-413.

Ye J., Li X.F., Wang Y.D. and Yuan Y. (2013). Arg72pro polymorphism of tp53 gene and the risk of skin cancer: A meta-analysis. PloS one 8, e79983.

Ye X.H., Bu Z.B., Feng J., Peng L., Liao X.B., Zhu X.L., Sun X.L., Yu H.G., Yan D.F. and Yan S.X. (2014). Association between the tp53 polymorphisms and lung cancer risk: A meta-analysis. Mol. Biol. Rep. 41, 373-385.

Zhan P. and Ji Y.N. (2014). Prognostic significance of tp53 expression for patients with hepatocellular carcinoma: A meta-analysis. Hepatobiliary Surg. Nutrit. 3, 11-17.

Zhan P., Ji Y.N. and Yu L.K. (2013). Tp53 mutation is associated with a poor outcome for patients with hepatocellular carcinoma: Evidence from a meta-analysis. Hepatobiliary Surg. Nutrit. 2, 260-265.

Zhang Z., Wang M., Wu D., Wang M., Tong N., Tian Y. and Zhang Z. (2010). P53 codon 72 polymorphism contributes to breast cancer risk: A meta-analysis based on 39 case-control studies. Breast Cancer Res. Treat. 120, 509-517.

Zhang L., Shao N., Yu Q., Hua L., Mi Y. and Feng N. (2011). Association between p53 pro72arg polymorphism and prostate cancer risk: A meta-analysis. J. Biomed. Res. 25, 25-32.

Zhang J., Xv Z., Wu X. and Li K. (2012). Potential diagnostic value of serum p53 antibody for detecting esophageal cancer: A meta-analysis. PloS one 7, e52896.

Zhang Q., Ma Y.Y., Wang H.J., Shao C.M., Zhang J. and Ye Z.Y. (2013a). Meta-analysis of the association between p53 codon 72 polymorphisms and gastric cancer. J. Surg. Oncol. 107, 360-366.

Zhang S.S., Huang Q.Y., Yang H., Xie X., Luo K.J., Wen J., Cai X.L., Yang F., Hu Y. and Fu J.H. (2013b). Correlation of p53 status with the response to chemotherapy-based treatment in esophageal

cancer: A meta-analysis. Ann. Surg. Oncol. 20, 2419-2427.

Zhang J., Xu Z., Yu L., Chen M. and Li K. (2014). Assessment of the potential diagnostic value of serum p53 antibody for cancer: A meta-analysis. PloS one 9, e99255.

Zhao Y., Wang F., Shan S., Zhao Y., Qiu X., Li X., Jiao F., Wang J. and Du Y. (2010). Genetic polymorphism of p53, but not gstp1, is association with susceptibility to esophageal cancer risk - a meta-analysis. Int. J. Med. Sci. 7, 300-308.

Zhao L., Zhao X., Wu X. and Tang W. (2013). Association of p53 arg72pro polymorphism with esophageal cancer: A meta-analysis based on 14 case-control studies. Genetic Test. Mol. Biomarkers 17, 721-726.

Zhou L., Yuan Q. and Yang M. (2012a). A functional germline variant in the p53 polyadenylation signal and risk of esophageal squamous cell carcinoma. Gene 506, 295-297.

Zhou X., Gu Y. and Zhang S.L. (2012b). Association between p53 codon 72 polymorphism and cervical cancer risk among asians: A huge review and meta-analysis. Asian Pacific J. Cancer Prevent. 13, 4909-4914.

Zhou C., Chen H. and Wang A. (2013). P53 codon 72 polymorphism and lung cancer risk: Evidence from 27,958 subjects. Tumour Biol. 34, 2961-2969.

Zhu Y., Wang J., He Q. and Zhang J.Q. (2011). Association of p53 codon 72 polymorphism with prostate cancer: A meta-analysis. Mol. Biol. Rep. 38, 1603-1607.

Zilfou J.T. and Lowe S.W. (2009). Tumor suppressive functions of p53. Cold Spring Harbor Perspect. Biol. 1, a001883.

Zong L., Chen P. and Xu Y. (2012). Correlation between p53 expression and malignant risk of gastrointestinal stromal tumors: Evidence from 9 studies. Eur. J. Surg. Oncol. 38, 189-195.

Accepted June 10, 2015