Review Article

Alterations of the TP53 Gene in Gastric and Esophageal Carcinogenesis

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TP53 genes is one of more important tumor suppressor gene, which acts as a potent transcription factor with fundamental role in the maintenance of genetic stability. The development of esophageal and gastric cancers is a multistep process resulting in successive accumulation of genetic alterations that culminates in the malignant transformation. Thus, this study highlights the participation of the main genetic alterations of the TP53 gene in esophageal and gastric carcinogenesis. Among these changes, high frequency of TP53 mutations, loss of heterozygosity (LOH), overexpression of the p53 protein, and consequently loss of p53 function, which would be early events in esophageal and gastric cancers, as well as an important biomarker of the prognosis and treatment response. Furthermore, Single Nucleotide Polymorphisms (SNPs) of TP53 have been implicated in the development and prognosis of several cancers, mainly TP53 codon 72 polymorphism whose role has been extensively studied in relation to susceptibility for esophageal and gastric cancer development.

1. Introduction

Gastric and esophageal cancers together are responsible by high rates of incidence and mortality worldwidely [1]. These neoplasms are histologically and genetically heterogeneous, but in the meantime sharing common aspects, such as a multifactorial origin involving risk factors such as smoking consumption and alcohol intake, progression through precancerous lesions, and the occurrence of an inflammatory process [2, 3].

Esophageal cancer is classified in two major histological types as esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). The ESCC may occur as consequence of a premalignant lesion knows as megaesophagus (esophagus dilatation) due achalasia leading to food retention or esophageal stasis. In consequence, chronic esophagitis may occur due increased bacterial proliferation in the liquid stasis [4], acanthosis, parakeratose and leukoplakia [5]. The megaesophagus increases the risk of the 3% to 8% of developing ESCC [6]. The EA is related with Barrett’s esophagus (BE), an acquired metaplastic abnormality in which the normal stratified squamous epithelium of the esophagus is replaced by an intestinal-like columnar epithelium containing goblet cells (intestinal metaplasia). Such condition is widespread and provides a 100-fold increased risk for the development of EA [7].

The gastric adenocarcinoma accounts for approximately 95% of cases of gastric malignancies. It is classified by histopathological characteristics in diffuse and intestinal subtypes [8] and occurs as distinct clinical and epidemiological entities. The gastric cancer (GC) can progress through of multistep process from a chronic gastritis frequently resulting from Helicobacter pylori infection to gastric atrophy, intestinal metaplasia, dysplasia, and finally to carcinoma [9]. This bacterium, due the inflammatory process in gastric mucosa is considered the major risk factor of GC. It is present
in 77% of noncardia gastric cancers [10] and in 90% of all chronic gastritis patients, so has been associated with increased risk of cancer up to nine times [11, 12].

Although different genetic and epigenetic alteration involving oncogenes activation, tumor suppressor genes mutations, DNA repair genes, microsatellite instability, loss of heterozygosity (LOH) have been reported in both esophageal and gastric cancers [2, 3, 13, 14], genetic alterations in TP53 tumor suppressor gene are fundamental events related in both early stage and advanced tumor.

In this study, we summarize the main molecular alterations of the TP53 gene in esophageal and gastric carcinogenesis reported in literature and also our contribution to studies of this gene in precancerous and malignant lesions of the esophagus and stomach, such as frequency and types of TP53 mutations, LOH, overexpression of the mutant p53 protein, and consequently loss of p53 function, which may act as important biomarker of the prognosis and treatment response. In addition, we also focused on the role of TP53 codon 72 polymorphism, which has been extensively studied in relation to risk for esophageal and gastric cancer development.

2. TP53 Gene

TP53 gene mapped on 17p13.1 [15] is one of more important tumor suppressor gene composed by 11 exons (~20 KB), which genomic integrity of exons 5–8 is particularly important for its activity [16, 17]. TP53 gene encodes a nuclear p53 protein of 393 amino acids, which acts as a potent transcription factor with key role in the maintenance of genetic stability [18]. This protein regulates the expression of hundreds of genes and noncoding RNAs, as well as the RNA processing complexes activity. When activated, in response to cellular stress (Figure 1), p53 triggers adequate cellular response, including cell-cycle arrest, DNA repair and programmed cell death (apoptosis) [19], and preventing the multiplication of damaged cells [20], being named “the guardian of the genome” [21]. The p53 protein has also others biological functions: senescence, DNA metabolism, angiogenesis, cellular differentiation, and the immune response [22].

The function of TP53 gene is usually altered through LOH, mutations, and rarely by DNA methylation. Over 50% of human cancers present inactivated TP53, due loss of function mutations [23], among 95% of them occurred within the genomic region encoding the sequence-specific DNA-binding domain of TP53. These mutations disrupted the proper conformation of that sequence so mutant forms of TP53 lacked the sequence-specific transactivation ability. Thus, impaired TP53 activity promotes the accumulation of DNA damage in cells, which leads to a cancer phenotype.

In general, TP53 exons 5–9 are investigated because they contain the zinc-finger domain and the transactivating domain, which are mutational hotspots; by the way, more than 80% of TP53 mutations are clustered there [24]. The TP53 mutations consist of primarily missense substitutions (75%) nonrandomly distributed along the molecule, particularly the central DNA-binding-domain [25]. These single aminoacid changes affect TP53 transcriptional activity to various degrees. The TP53 mutational spectrum is characterized by the presence of mutations at six discrete hotspot codons within the DNA binding domain of the molecule: codons 175, 245, 248, 249, 273, and 282 [26]. Furthermore, other alterations include frameshift insertions and deletions (9%), nonsense mutations (7%), silent mutations (5%), and some infrequent alterations [27]. More than 27,000 somatic mutation data of TP53 appear in the International Agency for Research on Cancer (IARC) TP53 database version R15 [25, 28].

For the p53 protein expression, the wild type has short-life and the mutant forms have a longer half-life [29, 30], and show the dominant-negative behavior toward wild type [31, 32], so overexpression and accumulation of mutant p53 protein by immunohistochemistry assay has been widely used as marker for detection of p53 abnormalities in neoplasms. More than two decades after the TP53 gene discovery and knowledge about its function in cell cycle control and normal cells homeostasis, mutations of this gene remain the prevalent genetic alteration involved in cancer etiology.

3. Mutations of TP53 Gene in Esophageal and Gastric Carcinogenesis

3.1. Esophageal Adenocarcinoma (EA) and Esophageal Squamous Cell Carcinoma (ESCC). The EA is a multistep process, in which the metaplastic epithelium characteristic of Barrett’s esophagus (BE) is thought to sequentially develop low-grade dysplasia, high-grade dysplasia, early EA, and, eventually, invasive carcinoma [33, 34].

The genetic and epigenetic alteration more common in BE is the inactivation of CDKN2A on chromosome 9p [35, 36]. However, the loss of TP53 is an important event in BE progression [37, 38], because patients with LOH in TP53 are 16 times more likely to progress to EA [39], since both mutations and LOH in TP53 appear to provide a competitive advantage to the mutant clone [40]. Mutations in TP53 can be a predictor of significantly reduced postoperative survival following surgical resection of EA and would appear to be a clinically useful molecular prognostic biomarker. In a study that assessed the prognostic value of TP53 mutations in EA was observed that 47% of the tumors analyzed had TP53 mutations, predominantly G:C to A:T transitions at CpG dinucleotides. Such mutations have been associated with overexpression of p53 protein, tumor differentiation, and significantly reduced postoperative survival following surgical resection of EA [41]. Many studies has also focused on genetic alterations in ESCC at different loci of the chromosomes, because some of the microsatellite markers may be useful for the early detection of this type of cancer. The LOH was found in at least one of the eight markers, including TP53. However, the most of the 38 microsatellite markers analysis did not display microsatellite instability, suggesting these regions are
possible targets of genomic instability in early-stage ESCC carcinogenesis [42].

The esophagus is most frequently exposed to carcinogens as the stomach or colon, such carcinogens present in food or dietary factors act as inducers of TP53 mutations in ESCC in some areas considered high risk, such as China, Southern Brazil, and Taiwan [43]. A high frequency of TP53 mutations and p53 protein expression in the ESCC has been reported,
and loss of p53 function would be the early events in ESCC development [44]. The study performed in ESCC patients in Japanese population reported mutations in exons 5–9 of the TP53 gene in 48% of them, whereas transversions were the most prevalent, followed by translocations. Transversion G:C to T:A occurred preferentially at codons 157, 248, and 273, considered known sites of adducts formation on DNA. Among the sources of transversion, oxidative DNA damage, and metabolites of benzo(a)pyrene are associated with esophageal carcinogenesis, since smoking is the major risk factor for the development of this neoplasm and the fact that this substance is an important component of cigarette smoke [43].

One of the highest incidences of ESCC in the world is found in northeastern Iran, Golestan Province, with rates over 50 per 100,000 person-years in both genders [45]. In this high-risk geographic area was found a total of 120 TP53 mutations in 107/119 cases (89.9%), including 11 patients with double or triple mutations, which mutation pattern was heterogeneous with infrequent mutations at common TP53 “hotspots,” but with frequent transversions attributable to environmental carcinogens forming bulky DNA adducts, including 40% at bases known as site of mutagenesis by polycyclic aromatic hydrocarbons (PAHs). The authors no observed relation of the mutation pattern with ethnicity, tobacco or opium use, and alcoholic beverage consumption or urban versus rural residence. Thus, the multiple environmental carcinogens seem to be the cause of this heterogeneous mutation pattern [45].

Our research group, in a small sample of ESCC patients of southeastern Brazil described two novel mutations in the TP53 exons 5 (codon 147) and 6 (codon 197) in 2/10 cases of ESCC, but no mutation was found in the 30 cases of chronic esophagitis assessed. While one of them was a silent mutation (codon 147) the other was a missense mutation (codon 197) resulting in a change from valine to alanine that could affect the structure and function of the p53 protein [46]. In addition, Egashira et al. [24] identified several mutations in exons 2, 3, 10, and 11 of TP53 gene in ESCC and some of these mutations might be deleterious because they are expected to lead to a truncated protein. A significant correlation between the presence of TP53 gene mutation and LOH was found, whereas there was no significant correlation between LOH and protein expression.

Recently, 10 esophageal cancer cell lines and 91 surgically resected specimens were examined for LOH at the TP53 using microsatellite analysis, CGH (comparative genomic hybridization), FISH (fluorescence in situ hybridization), and SNP-CGH (single nucleotide polymorphism-CGH) [47]. It was verified that LOH without copy number change at the TP53 locus was observed in TP53 mutant ESCC, suggesting that copy-neutral LOH occurring as a result of chromosomal instability might be the major mechanism for inactivation of the intact allele in esophageal squamous cell carcinogenesis associated with TP53 mutation. These results emphasize the pivotal role of genetic alterations in TP53 in the esophageal carcinogenesis, with serious consequences for the deregulation of the cell cycle.

3.2. Gastric Carcinogenesis. Molecular studies have supplied important information on the genetic events in GC involving a number of genetic and epigenetic alterations including oncogenes as amplification of c-MYC, c-ERBB2, c-MET, E-cadherin (CDH1), tumor suppressor genes with mutations of APC, TP53, and cell cycle regulators, cell adhesion molecules and DNA repair genes [13, 48, 49]. Other genetic factors, such as DNA polymorphisms and genetic instability, may also be implicated in the two distinct major genetic pathways of gastric carcinogenesis [50]. However, LOH at chromosome 17p and TP53 mutations are implicated in the development of both intestinal and diffuse type gastric cancer [50].

TP53 mutation is one of the most prevalent genetic alterations in GC. More than one mutation may be present in a single tumor resulting in heterogeneity of the TP53 mutational status. There are conflicting results with respect to the prevalence of TP53 mutations and their relationship to histological type or tumor stage of GC. Some studies showed that mutations tend to affect mainly intestinal-type tumors, while others found that the incidence of mutation is similar in both intestinal and diffuse-type tumors, ranging between 25% and 40% of the cases studied. According tumor stage, TP53 abnormalities appear to occur early in intestinal-type cancers, but some studies showed that the frequency of TP53 mutation in both early and advanced intestinal-type is consistent at around 40% each, similar to that observed in advanced diffuse-type, while in early diffuse-type TP53 mutations are uncommon [43, 51–53].

In Japanese patients with GC, Oki et al. [43] found TP53 mutations in 16% (18/112) of the cases, more often in intestinal-type. The TP53 mutational spectrum was wide, including in a decreasing order of frequency, codons 175, 248, 273, 282, 245, and 213, all of which are CpG sites. Transitions of the G:C to A:T are the most common type of mutation, regardless of the histological type of the tumor, followed by transversions. Interestingly, it appears to be a difference in the frequency of G:C to A:T and A:T to G:C transitions in European compared to Asian populations [53]. The observed pattern of mutations are consistent with that for dietary mutagens associated with the metabolism of nitro- genous compounds involved in gastric carcinogenesis, thus resulting in the deamination of nucleic acids. C to T mutations are also induced by nitric oxide, a substance produced during infection by H. pylori bacterium [54].

Similarly, in Chinese population, Chen et al. [55] reported TP53 mutations in GC occurring in four exons affecting codons 131, 132, 133, 135, 149, 151, 162, 167, 173, 174, and 175 of exon 5, codons 193, 197, 213, and 215 of exon 6, codons 245, 246, 248, 249, and 270 of exon 7, and codons 271, 272, 273, and 282 of exon 8. Among the mutations, G:C to A:T transitions was the highest (41.7%), followed by A:T to G:C (25%), G:C to C:G (11.1%), G:C to T:A (8.3%), A:T to T:A (2.8%), and frameshift mutation. The authors also reported an association between TP53 mutation and patients with high/high-middle differentiated type-GC, indicating that these mutations are responsible for the initiation stages of gastric carcinoma, rather than the slowing of differentiation.
The tumor suppressor functions of p53 protein are largely demonstrated by its apoptosis-inducing ability that may be dependent or independent of de novo gene transcription. As a transcription factor, p53 targets multiple elements involved in the apoptotic pathway [56].

Apart from transcriptionally targeting elements, p53 is also able to mediate transcription-independent apoptosis. Under cellular stress, p53 accumulates in the cytosol or mitochondria and leads to the direct activation of proapoptotic Bcl-2 family members, such as Bax and/or Bak [57, 58], so it selectively activates p53-mediated apoptosis. This selectivity may help to avoid the unwanted side effects associated with conventional p53 treatment based on transcription [59, 60].

Several studies have assessed the relationship between apoptosis and TP53 alterations. In gastric epithelium a balance between cell proliferation rate and programmed cell death or apoptosis maintain the homeostasis. An imbalance of these two processes leading to increased proliferation of the gastric epithelial cells may enhance the effect of carcinogens on DNA, increasing the risk of mutational changes, and the development of gastric cancer [61, 62].

In focus, we investigated the association of apoptosis with infection by H. pylori in benign gastric lesions and GC [63]. Although not observed significant differences in apoptotic index (AI) between the different groups of benign gastric lesions, whether by the TUNEL technique or by the CPP32 (caspase-3 activated) antibody, the CAG (chronic atrophic gastritis) group showed a statistically increased AI, compared to normal mucosa (NM), as well as a higher number of TUNEL-positive cases. Furthermore, the CG (chronic gastritis) group had a statistically higher AI than did the NM, as well as a higher number of CPP32-positive cases. However, the GC group displayed a low AI, and no significant differences were found regarding the histological subtypes, intestinal or diffuse. Also in this study, was found statistically higher AI in individuals infected by H. pylori in GU (gastric ulcer) and IM (intestinal metaplasia) groups compared to NM from patients without infection. In general, this study showed high AI in both groups of CG and CAG regardless of infection by H. pylori, aneuploidy, and overexpression of the protein p53. However, the precise involvement of H. pylori infection in the balance between apoptosis and proliferation has yet to be elucidated.

Regarding the histological subtypes of GC, Triantafyllou et al. [64] investigated both apoptotic and proliferation indices and found higher AI in advanced intestinal type tumors, as well as p53 protein expression significantly higher in advanced cancers and in the nondysplastic tissue adjacent. According to the authors these data indicate similar cell turnover during tumorigenesis between both tumors types.

Considering the variation of the prognosis among patients with the same tumor stage, Liu et al. [65] assessed the relationship between some apoptotic markers, such as p53, bcl-2, bax, and c-myc expression to clinicopathological characteristics and their prognostic significance in GC. The authors observed a strong correlation between the expression of p53, bax, and c-myc, as well as with histological grade, but a reverse correlation between histological type and p53 expression, so demonstrating that deregulation of p53 might result in uncontrolled proliferation in gastric cancer.

So far, many efforts have been applied for understanding the mechanisms involving TP53 mutations in carcinogenesis and development of the gastrointestinal tract; it is clear participation of TP53 gene alterations in early stages and progression of these tumor types.

4. p53 Protein Overexpression in Esophageal and Gastric Carcinogenesis

The expression analysis on p53 protein level by immunohistochemical staining has been performed on routine paraffin embedded material and the overexpression and an accumulation of protein is used as an indicator of mutant form of TP53 gene, which has been shown to be a powerful marker of malignancy.

One of the most common abnormality detected in EA is overexpression of p53 protein, that is restricted to more advanced areas of dysplasia and malignancy [66, 67]. Among 137 primarily resected EA samples, after immunohistochemical staining, showed accumulation of p53 in 52% cases [68]. Increased p53 expression, as measurement of TP53 mutations, was observed also in BE with high-grade dysplasia (HGD) and in BE-associated to EA suggesting the involvement of the TP53 in the pathogenesis of this entity [69]. Moreover, p53 expression confirmed multifocal dysplasia in BE esophageal mucosectomies and the patients displayed increased aneuploidy for chromosome 17 along the sequence of cancer progression [70].

Other esophageal precursor lesions have also evidenced alterations in p53 expression. For example, study performed by researchers of our laboratory [71] observed that the proportion of p53-positive cases increased progressively according to the severity of the esophageal pathology. Positive immunostaining for p53 protein was observed in a few cells in the normal mucosa, which was interpreted as expression of wild-type p53 protein. However, a progressive increase of p53 protein expression was observed as follows: chagasic megaesophagus (26.1%), chronic esophagitis (52.2%), and ESCC (100%). A strong and diffuse nuclear staining in the ESCC probably arose from the high expression of mutant p53 protein, whereas in chronic esophagitis and chagasic megaesophagus, it was not possible to indicate p53 as mutated protein. It may also have been due to the expression of wild-type p53 that accumulates in the cells as a consequence of the physiological and inflammatory processes in the esophageal epithelium [71].

To characterize p53 alterations in multiple esophageal carcinomas and to study their roles in carcinogenesis, p53 immunohistochemical and mutation analyses using laser capture microdissection on surgically resected were performed in esophageal carcinomas. p53 protein accumulation was observed in 72.7% of tumors. In the 9 cases of multiple esophageal carcinomas, TP53 mutations were detected in the whole tumor in 1 (11.1%) case, in the microdissected tumor samples of main lesions in 3 (33.3%) cases, and in the microdissected tumor samples of concomitant lesions in 3
In ESSC, the aberrant expression of p53 protein has been observed during the tumoral progression and appears to be associated with lymph node metastasis [73, 74]. When p53 protein expression was examined in 148 ESSC cases using immunohistochemistry combined with tissue microarray, Lin et al. [75] showed p53 protein accumulation in 86% high-grade dysplasia/carcinoma in situ (HGD/CIS), 81% of low-grade dysplasia (LGD), and in none of reactive atypical epithelium (RAE) and normal epithelium (NE). Of HGD/CIS and LGD with p53 protein accumulation, similar percentages had mutations (83% and 82%, resp.), p53 expression has also been reported in 65.5% lymph node metastasis, whereas p53 was in 50% of cases of ESSC, with the specificity of 90.9% and sensitivity rate of 65.5% in detected lymph node metastasis and positive predictive value was 95%. Expression of p53 was significantly correlated with stage and lymph node metastasis, suggesting that when preoperative staging has been insufficient in ESSC, immunohistochemical analysis of p53 in tissues could be an aid to clinicians regarding lymph node metastasis [73].

The p53 status, both gene mutation and immunohistochemical staining, was assessed as potential predictive markers of chemotherapy response and prognosis for ESSC [76]. The results of retrospective study showed mutant TP53 and p53-positive protein in 46.8% and 55.8% of patients, respectively, which was not associated with clinicopathological findings of patient including initial tumor stage. Response to chemotherapy was observed in only 16.7% of patients with mutation of TP53 gene, which showed significantly poorer prognosis. However, there was no correlation of p53 protein status with response to chemotherapy, curative resection rate, or prognosis. These parameters were also investigated in a group of patients in the prospective study. Similarly to the retrospective study, TP53 mutation was associated with poorer response to chemotherapy and prognosis. Thus, these findings showed that TP53 genotype is a potentially useful predictor of poorer response to chemotherapy and prognosis in ESSC patients.

In gastric benign lesions and gastric cancer, our research group assessed the p53 overexpression and occurrence of aneuploidy for chromosome 17 and TP53 gene deletion [77, 78]. In intestinal metaplasia (IM) from cancer-free patients, immunohistochemistry revealed p53 overexpression in 12% of the analyzed cases, as well as TP53 gene deletion in 60% of the cases. All GC cases presented higher frequencies of trisomy or tetrasomy of chromosome 17 and TP53 deletion, and immunohistochemistry detected overexpression of p53 protein in 80% of the assessed cases. These results suggest that IM and GC may share the same genetic alterations [77]. Similarly, Khayat et al. [79] evidenced positive immunoreactivity of p53 in IM samples and, in these cases, the frequency of cells with two chromosome 17 and two TP53 signals was higher than in p53-negative cases. In other benign lesions as chronic gastritis (CG) and gastric ulcer (GU) has also been reported p53-positive immunoreactivity, that is, in 45% and 12% of cases, respectively [78]. In this study, trisomy of 17 was increasingly found from CG to GU, but no TP53 deletion was found in these gastric lesions. The occurrence of aneuploidies in benign lesions evidences chromosomal instability in early stages of gastric carcinogenesis.

Overexpression of p53 protein and aneuploidy of chromosome 17 has been observed in GC and nontumoral tissues in others studies. Lu et al. [80] showed that in tumor tissues aneuploidy of chromosome 17 occurred in 58.6% of cases and 45.5% of GC samples overexpressed p53 protein, significantly higher than those in nontumor strict mucosa (0 and 12.1%, resp.). The expression of p53 in nontumor gastric mucosa with dysplasia was significantly higher than that in the mucosa without dysplasia. Overexpression of p53 protein was associated with the size of tumors that may help in diagnosis and prognostic prediction of GC [80].

In addition, association of p53 expression with the tumor biological behavior and prognosis of GC patients was also reported. However, the prognostic impact of p53 abnormalities in this neoplasm remains controversial. It was described that the degree of p53 expression correlates with the proliferative rate of the gastric cancer. Furthermore, a significant association between p53 overexpression and the metastatic spread to lymph nodes or shortened survival has been described by some studies on GC, but not by others [81, 82].

Although H. pylori eradication has some inhibitory effects on the subsequent development of GC, there are sporadic cases of malignant progression even after successful eradication. The pathogenesis of GC emerging after H. pylori eradication remains to be clarified. Iijima et al. [83] assessed the relationship of the acid secretion pattern to the occurrence site of GC emerging after bacterial eradication in order to estimate the individual cancer risk. The p53 protein frequently was accumulated in non-acid-secreting areas, suggesting that genetic alteration such as TP53 mutation seems to be already present in the residual non-acid-secreting areas that could be the origin site of gastric carcinogenesis even after eradication.

Esophageal and gastric carcinomas show multiple and distinct molecular alterations, which indicate that progression of cancer is a multistep complex process with many different pathways and accumulation of various alterations. Presumably, it is not only one molecular factor that can predict the biological behavior of these cancers, but patterns of TP53 mutations and protein overexpression would appear to be an useful biomarker of tumor progression, prognosis, and prediction of response to treatment of gastroesophageal cancer patients.

5. TP53 Polymorphisms and Risk of Esophageal and Gastric Cancer

The tumor suppressor TP53 pathway plays a crucial role in preventing carcinogenesis, thus single nucleotide polymorphisms (SNPs) of TP53 gene naturally occurring in human
populations are expected to cause measurable perturbation on p53 function [84]. It is known that functional polymorphisms can impact tumor biology and have been implicated in the development and prognosis of several cancers, being highlighted as a potential candidate of the susceptibility for cancer development [85–89]. These genetics variants in TP53 may modulate cancer risk because they are also supposed to influence cell cycle progression, apoptosis, and DNA repair [90].

At least 85 SNPs are described on TP53 [25]. However, the most investigated polymorphism in this gene is a nonsynonymous single base pair change in a proline-rich domain located in exon 4 codon 72 (TP53 Arg72Pro, rs 1042522), which consists in a substitution of cytosine (C) for guanine (G) and results in the substitution of arginine (Arg72—CGC) by proline (Pro72—CCC) [91].

The Arg72Pro polymorphism shows differences in its biochemical or biological functions [92, 93]. This change in amino acid sequence may alter the ability of p53 to bind to response elements in target genes and thus induce gene transcription, its interaction with p73 and its targeting of the proteasome. In addition, alter recognition motifs for posttranslational modifications or p53 stability, and still the susceptibility to degradation by human papillomavirus E6 protein [94, 95]. It may also modulate the apoptosis at differing rates [94] and modify sensitivity to chemotherapeutic agents [96]. The Pro72 variant exhibits decreased apoptotic potential than the Arg72 variant [87, 91, 93, 97], indicating that the two polymorphic variants of TP53 are functionally distinct, which may influence the cancer risk or treatment [88, 97].

Some studies have reported the identification of Arg72Pro polymorphism and its role in many kinds of cancers such as cervical [98], lung [99–102], breast [103–108], colorectal [109, 110], esophageal [111–113], and gastric [114].

Even if TP53 gene is highly polymorphic, the TP53 codon 72 polymorphism is the only whose role has been extensively studied in relation to esophageal and gastric cancer and the results have been inconsistent (Table 1). Some studies in esophageal and gastric cancer of different populations have evidenced association of the Pro72 variant with cancer risk, while others with the Arg72 variant.

5.1. Association with Esophageal Cancer. In the last decades, several studies had been focused in the association between Arg72Pro polymorphism and esophageal cancer (EC) susceptibility, but the results are still conflicting and heterogeneous [88, 111–113, 115–119, 121, 132].

Some studies showed that in EC, the Pro allele was associated to protection [93] or that the Arg allele was associated with increased risk of EC [112], but others found the opposite, that Arg allele was associated to protection [88], or that the Pro allele was associated with increased risk of this disease [46, 87, 111, 113, 117, 120, 121]. Moreover, maintaining this functional change had been associated not only with increased risk, but also with earlier age of onset, reduced response to chemotherapy, and early recurrence in a variety of cancers [85, 87]. However, other studies did not find any association between Arg72Pro polymorphism and susceptibility to ESCC [118, 132], either to EA, age of onset and stage of disease at the time of the diagnosis detection [74].

Piao et al. [120], in South Korea population, observed the Arg72Pro polymorphism was associated with an increased risk of EC and also found that smoking status changed the association between the Arg72Pro polymorphism and the risk of this cancer, so that the Odds Ratio of the Arg/Pro genotype was higher in ever-smokers than in never-smokers. Another study had indicated significant association between this polymorphism and smoking with risk of development of ESCC being the highest risk in smokers carrying Pro/Pro genotypes [111]. In addition, a study in a Chinese mainland population found that the Pro/Pro genotype was significantly associated with an increased risk of ESCC and the association was especially noteworthy in women and in younger patients [113].

Besides, Cescon et al. [87] showed that, among all EC patients treated with standard therapy, the Pro/Pro genotype was associated with shorter overall survival and progression, independent of standard clinical prognostic features, thus the authors suggest that TP53 could help the prediction of prognosis in EC, identifying high-risk patient's subgroups that might benefit themselves from new therapeutic strategies. Some recent meta-analyses have focused on Arg72Pro polymorphism on EC risk. For example, Jiang et al. [88] verified a significantly reduced risk of EC associated with TP53 genotypes (Arg/Arg + Arg/Pro versus Pro/Pro) and their analysis was restricted to well-designed studies. Moreover, the Arg allele was significantly associated with decreased EC risk. Other meta-analysis showed that the Arg72Pro was associated with an increased risk of EC (Pro/Arg + Pro/Pro versus Arg/Arg) and the authors have observed no heterogeneity between the studies [133]. However, when the authors performed a stratified analysis by ethnicity, the increased risk of EC associated with Arg72Pro polymorphism (Pro/Arg + Pro/Pro versus Arg/Arg) was more evident in Asian group, thus their results suggest that Arg72Pro polymorphism may contribute to EC development, especially in Asians.

Despite of various studies assessing the functional TP53 Arg72Pro polymorphism in relation to EC susceptibility, the results remain conflicting probably due to methodological errors such as selection bias, inappropriate specimens used for genotyping, or limited statistical power [88] and also ethnicity. Therefore, additional well-designed large studies still are required for the validation of this association.

5.2. Association with Gastric Cancer. Similarly to studies of association with EC, the relationship between the Arg72Pro polymorphism, and GC susceptibility is also controversial. Studies performed in southern China [122] and in Venezuela [134] suggest that Arg allele-carriers could be associated with the development of GC. In contrast, studies in Korea reported that Pro/Pro genotype was associated with increased risk of this neoplasm [95, 126]. While in a Chinese
Table 1: Frequency distribution of TP53 codon 72 polymorphism genotype and association with risk of the gastric and esophageal cancers in the worldwide.

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Country (Ethnicity)</th>
<th>Case/Control (n)</th>
<th>Genotype frequency case/Control (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arg/Arg</td>
<td>Arg/Pro</td>
</tr>
<tr>
<td>Esophagus</td>
<td>China (Asians)</td>
<td>758/1420</td>
<td>26.2/29.9</td>
<td>44.9/51.5</td>
</tr>
<tr>
<td>China (Asians)</td>
<td>435/550</td>
<td>85.7/49.6</td>
<td>4.4/35.8</td>
<td>9.9/14.6</td>
</tr>
<tr>
<td>China (Asians)</td>
<td>673/694</td>
<td>24.2/28.1</td>
<td>45.5/52.7</td>
<td>30.3/19.2</td>
</tr>
<tr>
<td>China (Asians)</td>
<td>62/50</td>
<td>43.0/20.0</td>
<td>34.0/52.0</td>
<td>23.0/28.0</td>
</tr>
<tr>
<td>China (Asians)</td>
<td>120/232</td>
<td>24.0/29.0</td>
<td>50.0/52.0</td>
<td>27.0/18.0</td>
</tr>
<tr>
<td>China (Asians)</td>
<td>218/415</td>
<td>20.1/30.1</td>
<td>43.6/45.8</td>
<td>36.3/24.2</td>
</tr>
<tr>
<td>Japan (Asians)</td>
<td>102/241</td>
<td>36.3/37.7</td>
<td>30.0/44.4</td>
<td>13.7/18.0</td>
</tr>
<tr>
<td>South Africa (Africans)</td>
<td>73/115</td>
<td>36.0/32.0</td>
<td>56.0/54.0</td>
<td>7.0/14.0</td>
</tr>
<tr>
<td>South Korea (Asians)</td>
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population, Ke-Xiang et al. [123] showed that Arg/Pro + Pro/Pro genotypes increased risk of GC. Corroborating these data, a recent meta-analysis suggests that the Pro/Pro genotype was associated with several types of cancer, including GC [93].

In contrast, other recent meta-analysis with 21 case-control studies did not associate the Arg72Pro polymorphism with the risk of GC. However, when subgroups were assessed according to anatomical site, it was found that Pro/Pro genotype was significantly associated with increased risk of cardia GC [89]. Others case-control studies performed in Asian [122, 124, 127, 132, 135] and Mexico [136] showed a higher frequency of Pro allele in cardia GC [124, 135] and of Arg allele in noncardia GC [122, 127, 136]. On the other hand, studies performed in United Kingdom revealed an increase in the frequency of the Arg allele in patients with cardia GC [131, 137], suggesting an effect of ethnic group beyond of location region in the stomach.

Corroborating these findings, recent meta-analyses about the distributions of the two polymorphic variants of TP53 codon 72 and their effect on the risk of GC indicated that the anatomical site of tumor and ethnicity may contribute to the differences in the risk of gastric tumorigenesis [89]. The meta-analyses study by Zhou et al. [114] performed among eight studies in Asians and four in Caucasians showed that cardia GC had a significantly higher frequency of Pro/Pro genotype among Asians.

Another variable that should also be considered in the studies on association of the Arg72Pro polymorphism is the histological type of the GC. Whereas some authors found no relationship [126, 127, 129, 138], studies performed in China [139] and Korea [95] observed that the Pro allele carriers had a higher risk of developing the intestinal-type GC and others studies performed in Japan [125] and United States [130] found that this polymorphic allele was associated with an increased risk of developing the diffuse-type GC. The exact biological mechanism underlying the association between Arg72Pro polymorphism with the histological type is still unclear [95]. However, it has been suggested that the intestinal-type predominates in high-risk geographic areas such as East Asia, and it is related to the prevalence of H. pylori infection among the elderly, whereas the diffuse-type is found more uniformly worldwide and is apparently unrelated to H. pylori prevalence [140].

Although the potential effects of Arg72Pro polymorphism and their interactions with location, histology, ethnicity, and environmental exposures on GC risk have been assessed in several studies in different population worldwide, their exact effect are still unknown. The genetic susceptibility to gastric carcinogenesis related to TP53 polymorphisms may be attributed to several factors, including the accumulation and interaction of SNPs [124, 129], gene-environmental interactions [93], age [128, 131], H. pylori infection [123], bile or acid reflux, and smoking [137].
In general, these data suggest that the TP53 polymorphism alone is insufficient to explain its effect on risk of cancer, but together with others genetic polymorphisms and environmental factors may modulate the individual risk of developing cancer.

6. Conclusions

In this study we focused on the participation of genetic alterations of TP53 gene, such as mutational inactivation, LOH, SNPs, and expression of mutant form of p53 protein in the esophageal and gastric carcinogenesis. The studies emphasize the fundamental role of molecular alterations of “the guardian of the genome” in these neoplasms, with serious consequences for the deregulation of the cell cycle, loss of proapoptotic function and reduced sensitivity for anticancer drugs. Considering the involvement of TP53 alterations both in early stages as in tumor progression, it is an important biomarker for the diagnosis, tumor progression, and poor prognosis associated with lymph nodes metastasis.

Recent studies have demonstrated another pathway of participation of the TP53 gene in carcinogenesis, through the regulation of miRNAs. TP53 regulates the transcription expression and the maturation of a group of miRNAs. On the other hand, miRNAs can regulate the activity and function of TP53 through its direct repression or its regulators in cells. Thus these findings have demonstrated that miRNAs are important components in the TP53 network [141].

Despite major advances and growing number of publications on the role of TP53 tumor suppressor gene in carcinogenesis, still several other functions has emerged as cell metabolism, stem cells renewal and the occurrence of p53 isoform variants that may alter the function of wild-type p53. Therefore, p53 and other members of its family as p63 and p73 act in an intricate regulatory network controlling the expression of hundreds of target genes that regulate the cell cycle for the maintenance of genetic stability and preventing cancer formation.

Authors’ Contribution

The authors M. Succi and M. A. Proença had the same contribution in the realization of the manuscript.

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References


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