Novelty Journals

ISSN 2394-7330

International Journal of Novel Research in Healthcare and Nursing
Vol. 5, Issue 2, pp: (25-30), Month: May - August 2018, Available at: www.noveltyjournals.com

Association of P53 with Esophageal Carcinoma: Review

[1]Sabin Yadav, [2]Rui Xin Lin, [3]Qiao Shi Xing, [4]Shu Li Yang

[1]Department of General Surgery, the Second Hospital of Jilin University, No. 218 of Ziqiang St., Changchun, Jilin Province, 130041, China.
[2,3]Department of Hepatobiliary and Pancreatic Surgery, the Second Hospital of Jilin University, No. 218 of Ziqiang St., Changchun, Jilin Province, 130041, China.
[4]Department of Obstetrics and Gynecology, the Second Hospital of Jilin University, No. 218 of Ziqiang St., Changchun, Jilin Province, 130041, China.

Abstract: **P53, also known as tumor suppressor is guard or gatekeeper of the cell and genome. It protects the cells from any type of stress by DNA repair or apoptosis or cell cycle arrest thus maintaining normal homeostasis. But in certain circumstances, there occurs overexpression or mutation of P53, resulting in disruption on normal cellular mechanism and disturbance of homeostasis causing the cells to grow unexpectedly. Overexpression of P53 is mostly encountered in advanced stage of tumors. Among the mutant verities, missense mutation is commonly encountered. Esophageal carcinoma is one of them which results from either overexpression or due to mutation of P53. Serum P53 antibody can be detected from patients with esophageal carcinoma. P53 directed therapy has shown good results in patients with esophageal carcinoma. So P53 represents an important biomarker and thus has clear association with esophageal carcinoma.**

Keywords: **Esophageal carcinoma, P53, P53 over expression, P53 mutation.**

1. INTRODUCTION

Cancer, as a highly complex disorder involves genomic changes, immunological, hormonal, environmental factors as well as other diseases. It is well known that cancer sera contain antibodies that react with groups of autologous cellular antigens called tumor-associated antigens (TAAs). These antigens may be cellular proteins, such as p53, p62, p90 and p16, whose default regulation and or overexpression can lead to tumorigenesis [1].

Esophageal cancer ranks as the eighth most common cancer in the world. Being a disease of high mortality, it is the sixth most common cause of cancer related death worldwide [2]. Esophageal caners are of two important histological types: esophageal squamous cell carcinoma and esophageal adenocarcinoma. Esophageal squamous cell carcinoma may occur as a result of achalasia. Achalasia causes food retention as well as stasis and leads to esophagitis. These factors in turn cause esophageal dilatation a term called mega-esophagus, which increases the chance to develop squamous cell carcinoma by 3-8%. Esophageal adenocarcinoma may occur as a result of Barrett's esophagus in which intestinal metaplasia occurs.

Esophageal squamous cell carcinoma is predominant worldwide but incidence of esophageal adenocarcinoma is increasing now a days. The incidence of esophageal carcinoma varies geographically as well as ethnically [3,5]. The incidence is high in Northern China and also in Northern Iran, moderately high in Japan, South Asia as well as South Africa and low in western Africa [2,3]. Esophageal squamous cell carcinoma is the main type in the areas of high incidence [4]. Environmental carcinogens, dietary factors, nutritional deficiencies especially antioxidants, thermal radiation, hot beverages, betel chewing, smoking, alcohol as well as fermented foods are the causes for different histology as well as geographical variation according to the life style [2,3,5]. During the initial stage of the disease patients are usually asymptomatic, so they are usually undetected till the disease becomes difficult to cure. Because of the late detection

(advanced stage), the prognosis is usually poor for squamous cell carcinoma of esophagus [6,7]. Genetic factors also play a role in the development of esophageal carcinoma which is supported by the fact that only a small number of population who are exposed to the risk factors, develop the disease as well as the fact that the descendants of patients having esophageal carcinoma have higher tumor susceptibility than those who does not have family history of esophageal cancer [8,9].

P53 is a protein normally found in cells, which is also known as gatekeeper of the cell or genome because it regulates the cellular response in presence of cellular stress. In response to various stimuli like DNA damage, oxidative cellular stress, oncogene activation, heat shock, hypoxia; P53 functions as cellular response by apoptosis, DNA repair, cell cycle arrest or autophagy [10,11,13]. It is also known as tumor suppressor gene and is located at chromosome 17q13.1 [12,15]. P53 protein is present at low level in normal condition or in the absence of stress because of the balance between its transcription and degradation. This balance is of much importance because excessive P53 can damage the cells but low-level can let the cancers to grow [13]. For the stress response pathway to work properly target gene must be transcripted by P53 but P53 can also work independent of transcription [10,11].

When, cell damage due to any type of stress is minimal, then P53 stimulates transient cell cycle arrest either in G1 or G2 phase allowing repair of damage and again begins normal cell cycle. But when the damage is excessive or irreparable then P53 triggers apoptosis, which is a primary cause of tumor suppression. These different results are due to activation of different P53 target genes [11,13].

P53 and DNA REPAIR:

P53 has the ability to repair DNA after cellular stress. Transcriptional regulation along with direct interaction with mediators occurs in the presence of P53 to help repair damaged DNA. The cells that lack P53, do not have the ability to repair DNA properly, rather they do repair by nucleotide excision [14].

P53 and APOPTOSIS:

Apoptosis is an important tumor suppressor mechanism. Apoptosis is triggered by P53 when the damage to the cell is excessive and irreparable [11]. These are mediated through two apoptotic pathways. In extrinsic pathway, the expression of APO-1/Fas receptor as well as TRAIL receptor are increased by nuclear P53 where as caspase 8 and 3 are activated by cytoplasmic P53. In intrinsic pathway, the expression of pro-apoptotic proteins PIDD and BH3 only proteins are increased by nuclear P53 resulting in increased MMP, cytochrome C release as well as activation of caspase 9 and 8 whereas cytoplasmic P53 forms a complex with BCL-2/BCL-XL and releases pro-apoptotic proteins BAX an BAK. All these leads to apoptosis [15,16].

P53 and CELL CYCLE ARREST:

Cell cycle arrest is an important mechanism by which P53 suppresses tumor growth. After DNA damage, P53 arrests cell at G1/S transition by the expression of cycline dependent kinase (CDK) P21. Like G1 arrest P53 is also involved in G2/M arrest. In G2 arrest P53 is involved in maintenance but not in initiation of the arrest. This is true for cells with wild type P53 but not for mutant P53 [14]. So tumor can grow in cells with mutant P53. Cell senescence is another mechanism for cell cycle arrest, preventing tumor growth. In senescence, growth is arrested with a DNA content of G1 phase. After growth arrest, even in the presence of growth conditions, initiation of DNA replication is failed which is caused by cell cycle inhibitors and this is permanent [17].

P53 and TUMEROGENESIS:

This important protein P53 is inactivated or mutated in many tumors leading to low or no expression. This inactivation of p53 expression may play a role early in tumor formation and tumor progression [13,15,18]. P53 can be inactivated at protein level by binding to viral proteins or by p53 degradation or nuclear exclusion etc. [12,13].

Advance stage of tumors may have P53 overexpression. Overexpression of P53 occurs in those tumors, which contains genetically wild type TP53 gene with inert protein [12,19,20]. The difference between mutated and overexpressed P53 is that many of the mutant p53 forms lose their tumor suppressive function and have mainly-negative activities. They also gain onco-genic properties that are independent of wild-type p53. The main type of mutations in P53 is missense mutation,

which forms mutant P53 that cannot suppress tumor formation. Frequencies of TP53 mutation ranges from 10% (hematopoietic malignancies) to 50-70% (ovarian, head/neck, gastrointestinal malignancies). P53 mutations can be divided into two classes. First are mutations, which are mainly involved in DNA binding and second are mutations that cause conformational or local changes. The main mutations noted in development of human tumors are of first type [20]. Mutant P53 that leads to tumor progression causes chromosomal instability along with inhibition of DNA repair pathways and also leads to invasiveness of the tumor. It also inhibits the function of other family members of P53 [21].

P53 and ESOPHAGEAL CARCINOMA:

There are many researches regarding P53 with esophageal carcinoma. From those researches it is clear that P53 is an important protein and TP53 an important gene in the context of esophageal carcinoma.

Some researches are based on animal model and some are on human tissues. Researches on mice showed the accumulation of wild type P53 in mice with adenocarcinoma of esophagus but it was negative for squamous cell carcinoma of esophagus. Loss of P53 function resulted in increased cell cycle progression, genetic instability and malignancy [22, 23]. Somatic alteration in exon 6 of P53 gene have been found in more than 50% of cases of esophageal squamous cell carcinoma patients [24]. In one study, immunohistochemistry study demonstrated that P53 was overexpressed in 64% of cases (72% cases with adenocarcinoma and 67% of cases with squamous carcinoma of esophagus). Excessive TP53 mutation was noted in smokers with esophagus squamous cell carcinoma. P53 gene mutation was noted in 36-80% of cases with esophageal cancer [25, 26]. One Japanese study demonstrated P53 gene mutation in 47.4% of patients with esophageal carcinoma. Another study from South America reported Tp53 mutation in 63% of cases of squamous cell carcinoma of esophagus [27,28].

Under normal conditions, P53 are usually very low or undetectable but high staining of P53 is due to increased number or less degradation and is usually due to overexpression or mutation of P53 [29].

One study demonstrated that patients with esophageal carcinoma have more chance of positive serum P53 antibody detection. ELISA can detect P53 antibodies, so P53 antibodies can be a valuable marker for screening esophageal carcinoma as well as to know the response of treatment [6]. Other study shows the detection of P53 antibody in 39.1% of cases of esophageal carcinoma but not in healthy persons. This study also explored significant reduction of P53 antibody after radiotherapy and concluded P53 antibody as a useful marker to evaluate the response of treatment as well as prognosis [30].

One recent study serves that, tumor invasion and growth can be halted by removal of the mutant P53 [31]. Yet another study demonstrated that, intra-tumor administration of adenoviral gene therapy (Ad5CMV-p53) caused esophageal cancer cells to be trans-ducted and downstream genes to be activated. Similar type of another study also explored good efficacy in esophageal squamous cell carcinoma patients with P53 gene therapy medicated by adenovirus [32, 33].

Regarding prognosis, one study demonstrated that, P53 gene alteration in esophageal adenocarcinoma detected by immunohistochemistry has no prognostic value. Another study showed that P53 mutated tumor have worst prognosis and anti P53 antibodies to be independent prognostic marker in esophageal carcinoma due to lack of sensitivity [34,35]. Similar type of another study explored that, high level of serum P53 antibody can be assessed before surgery to evaluate the risk and poor prognosis [36]. Another study also demonstrated that neither of the markers such as: P53, p16, p27 are of prognostic value in esophageal carcinoma [37].

As a biomarker, P53 can be used to measure the efficacy of diagnosis and treatment in esophageal carcinoma [15,38]. To improve the effectiveness of currently available therapies used to suppress cancer cells having P53 mutants, restoration of ATM function and destabilization of P53 mutants is necessary [39].

2. CONCLUSION

From the associations that are discussed above, we can easily conclude that, P53 is an important protein and it must be normally expressed in cells to keep proper homeostasis. Failure to do so results in abnormal repair of DNA or abnormal and unprogrammed growth of cells. Esophageal carcinoma is one example to prove this. Esophageal carcinoma has close relation with P53 in every aspect, such as etiology, diagnosis as well as treatment because many of the researches are convincing to prove this. The only place that it lacks adequate association seems to be of prognosis. So many more studies are underway to correlate its association further.

ACKNOWLEDMENTS

The authors thank Anisha Maharjan (anishamaharjan24@gmail.com) for the English language polishing.

REFERENCES

[1] Y. Chai*†, B. Peng†, L. Dai*†, W. Qian†, Y. Zhang* & J.-Y. Zhang†. Autoantibodies Response to MDM2 and p53 in the Immunodiagnosis of Esophageal Squamous Cell Carcinoma. Human Immunology. 2014; doi: 10.1111/ sji.12202

[2] Paramee Thongsuksai, Pleumjit Boonyaphiphat, Puttisak Puttawibul, Wanna Sudhikaran. Specific intronic p53 mutation in esophageal squamous cell carcinoma in Southern Thailand. *World J Gastroenterol*; 2010; 16(42): 5359-5366

[3] Akinori Egashira, Masaru Morita, Yoshihiro Kakeji, Noriaki Sadanaga, Eiji Oki, Takuya Honbo, Mitsuhiko Ohta and Yoshihiko Maehara. *p53* Gene mutations in esophageal squamous cell carcinoma and their relevance to etiology and pathogenesis: Results in Japan and comparisons with other countries. Japanese Cancer Association. 2007; doi: 10.1111/j.1349-7006.2007. 00524.x

[4] Noushin Taghavi, Firouzeh Biramijamal, Masoud Sotoudeh, Omeed Moaven, Hooman Khademi, Mohammad Reza Abbaszadegan, Reza Malekzadeh. Association of p53/p21 expression with cigarette smoking and prognosis in esophageal squamous cell carcinoma patients. *World J Gastroenterol.* 2010; October 21; 16(39): 4958-4967

[5] Marilanda Ferreira Bellini, Aline Cristina Targa Cadamuro, Maysa Succi, Marcela Alcaˆntara Proenc¸a, and Ana Elizabete Silva. Alterations of the TP53 Gene in Gastric and Esophageal Carcinogenesis. Journal of Biomedicine and Biotechnology. 2012; Article ID 891961, doi:10.1155/2012/891961

[6] Zhang J, Xv Z, Wu X, Li K. Potential Diagnostic Value of Serum p53 Antibody for Detecting Esophageal Cancer: A Meta-Analysis. PLoS ONE 7(12): e52896. 2012; doi: 10.1371/journal.pone.0052896

[7] Denise P. Guimaraes, Ivanir M. Oliveira, Emanuela de Moraes, Geisilene R. Paiva, Daniel M. Souza, Christoph Barnas, Daniele B. Olmedo, Carlos E. Pinto, Paulo A. Faria, Claudia Vitoria De Moura Gallo, Isabele A. Small, Carlos G. Ferreira and Pierre Hainaut. Interferon-inducible guanylate binding protein (GBP)-2: A novel p53-regulated tumor marker in esophageal squamous cell carcinomas. Int. J. Cancer. 2009; 124, 272–279

[8] Yaping Zhao, Furu Wang, Shunlin Shan, Yiqi Zhao, Xueming Qiu, Xiangyang Li, Feng Jiao, Jian- guo Wang, Yunxiang Du. Genetic polymorphism of p53, but not GSTP1, is association with suscepti- bility to esophageal cancer risk – A Meta-Analysis. Int. J. Med. Sci. 2010; 7(5):300-308

[9] ZHIWEI CHANG, WEIJIE ZHANG, ZHIJUN CHANG, MIN SONG, YANRU QIN, FUBAO CHANG, HAIYUN GUO and QINGLI WEI. Expression characteristics of *FHIT*, *p53*, *BRCA2* and *MLH1* in families with a history of oesophageal cancer in a region with a high incidence of oesophageal cancer. ONCOLOGY LETTERS 9: 430-436, 2015. DOI: 10.3892/ol.2014.2682

[10] Jan-Philipp Kruse and Wei Gu. Modes of p53 Regulation. Cell. 2009; DOI 10.1016/j.cell.2009.04.050

[11] Yael Aylon and Moshe Oren. Living with p53, Dying of p53. Cell. 2007; DOI 10.1016/j.cell.2007.08.005

[12] Wenjian Yao, Xiuguang Qin, Bo Qi, Jianguo Lu, Ling Guo, Fulei Liu, Shangguo Liu, Baosheng Zhao. Association of p53 expression with prognosis in patients with esophageal squamous cell carcinoma. Int J Clin Exp Pathol 2014;7(10):7158-7163

[13] Sylvanie Surget, Marie P Khoury, Jean-Christophe Bourdon. Uncovering the role of p53 splice variants in human malignancy: a clinical perspective. OncoTargets and Therapy 2014:7 57–68

[14] LUCIANA E. GIONO AND JAMES J. MANFREDI. The P53 Tumor Suppressor Participates in Multiple Cell Cycle Checkpoints. Journal of Cellular Physiology. 2006; 209: 13-20, DOI: 10.1002/jcp.20689

[15] KATE HUANG, LIN CHEN, JILIANG ZHANG, ZHI WU, LINHUA LAN, LU WANG, BIN LU and YONGZHANG LIU. Elevated p53 expression levels correlate with tumor progression and poor prognosis in patients exhibiting esophageal squamous cell carcinoma. ONCOLOGY LETTERS 8: 1441-1446, 2014. DOI: 10.3892/ol.2014.2343

[16] Minfei Su, Yang Mei, and Sangita Sinha. Role of the Crosstalk between Autophagy and Apoptosis in Cancer. Journal of Oncology. Volume 2013, Article ID 102735. http://dx.doi.org/10.1155/2013/102735

[17] Judith Campisi and Fabrizio d'Adda di Fagagna. Cellular senescence: when bad things happen to good cells. NATURE REVIEWS | molecular cell biology. 2007; doi:10.1038/nrm2233

[18] J-C Bourdon. p53 and its isoforms in cancer. British Journal of Cancer. 2007; 97, 277 – 282. doi: 10.1038/sj.bjc.6603886

[19] AW Braithwaite and CL Prives. p53: more research and more questions. Cell Death and Differentiation 2006; 13, 877–880. doi: 10.1038/sj.cdd.4401938

[20] Ran Brosh and Varda Rotter. When mutants gain new powers: news from the mutant p53 field. NATURE REVIEWS | CANCER. 2009; **doi**:10.1038/nrc2693

[21] Amanda M Goh, Cynthia R Coffill and David P Lane. The role of mutant p53 in human cancer. *J Pathol* 2011; 223: 116–126 . DOI: 10.1002/path.2784

[22] Naoki Hashimoto. Expression of COX2 and p53 in Rat Esophageal Cancer Induced by Reflux of Duodenal Contents. ISRN Gastroenterology . Volume 2012, Article ID 914824, doi:10.5402/2012/914824

[23] Louise Y.Y.Fong , Yubao Jiang and John L.Farber. Zinc deficiency potentiates induction and progression of lingual and esophageal tumors in p53-deficient mice. Carcinogenesis vol.27 no.7 pp.1489–1496, 2006 doi:10.1093/carcin/bgl012

[24] Imtiyaz Murtaza, Dhuha Mushtaq, Mushtaq A Margoob, Amit Dutt, Nisar Ahmad Wani, Ishfaq Ahmad, Mohan Lal Bhat. A study on p53 gene alterations in esophageal squamous cell carcinoma and their correlation to common dietary risk factors among population of the Kashmir valley. *World J Gastroenterol* 2006 July 7; 12(25): 4033-4037, ISSN 1007-9327

[25] Jonine D. Figueroa, Mary Beth Terry, Marilie D. Gammon, Thomas L. Vaughan, Harvey A. Risch, Fang-Fang Zhang, David E. Kleiner, William P. Bennett, Christine L. Howe, Robert Dubrow, Susan T. Mayne, Joseph F. Fraumeni Jr, and Wong-Ho Chow. Cigarette smoking, body mass index, gastro-esophageal reflux disease, and non-steroidal anti-inflammatory drug use and risk of subtypes of esophageal and gastric cancers by P53 overexpression. *Cancer Causes Control*. 2009; 20(3): 361–368. doi:10.1007/s10552-008-9250-6

[26] LEANDRO TOTTI CAVAZZOLA; ANDRÉ RICARDO PEREIRA DA ROSA; CARLOS CAUDURO SCHIRMER; RICHARD RICACHENEVSKI GURSKI; JOÃO PEDRO BUENO TELLES; FERNANDO MIELKE: MÉDICO; LUÍSE MEURER; MARIA ISABEL ALBANO EDELWEISS; CLEBER DARIO PINTO KRUEL. Immunohistochemical evaluation for P53 and VEGF (Vascular Endothelial Growth Factor) is not prognostic for long term survival in end stage esophageal adenocarcinoma. Rev. Col. Bras. Cir. 2009; 36(1): 024-034

[27] Akinori Egashira, Masaru Morita, Yoshihiro Kakeji, Noriaki Sadanaga, Eiji Oki, Takuya Honbo, Mitsuhiko Ohta and Yoshihiko Maehara. *p53* Gene mutations in esophageal squamous cell carcinoma and their relevance to etiology and pathogenesis: Results in Japan and comparisons with other countries. Cancer science. 2007; doi: 10.1111/j.1349-7006.2007. 00524.x

[28] K. Szyman ska, J.E.Levi, A. Menezes, V.Wu¨nsch-Filho, J. Eluf-Neto, S. Koifman, E. Matos, A.W. Daudt, M.P.Curado, S. Villar, M. Pawlita, T. Waterboer, P. Boffetta, P. Hainaut and P. Brennan. TP53 and EGFR mutations in combination with lifestyle risk factors in tumours of the upper aerodigestive tract from South America. Carcinogenesis. 2010; vol.31 no.6 pp.1054–1059, doi:10.1093/carcin/bgp212

[29] Lianghai Wang, Jing Li, Jun Hou, Man Li, Xiaobin Cui, Shugang Li, Xiaodan Yu, Zhiyu Zhang, Weihua Liang, Jinfang Jiang, Lijuan Pang, Yunzhao Chen, Jin Zhao and Feng Li. p53 expression but not p16 INK4A correlates with human papillomavirus-associated esophageal squamous cell carcinoma in Kazakh population. Wang et al. Infectious Agents and Cancer. 2016; 11:19 DOI 10.1186/s13027-016-0065-x

[30] Hong-Yi Cai, Xiao-Hu Wang, Ying Tian, Li-Ying Gao, Li-Juan Zhang, Zhi-Yan Zhang. Changes of serum p53 antibodies and clinical significance of radiotherapy for esophageal squamous cell carcinoma. *World J Gastroenterology*. 2008; July 7; 14(25): 4082-4086. doi:10.3748/wjg.14.4082

[31] GS Wong, J-S Lee, Y-Y Park, AJ Klein-Szanto, TJ Waldron, E Cukierman, M Herlyn, P Gimotty, H Nakagawa and AK Rustgi. Periostin cooperates with mutant p53 to mediate invasion through the induction of STAT1 signaling in the esophageal tumor microenvironment. Oncogenesis. 2013; 2, e59; doi:10.1038/oncsis.2013.17

[32] Hideaki Shimada, Hisahiro Matsubara, Tooru Shiratori, Takanori Shimizu, Shinichi Miyazaki, Shinichi Okazumi, Yoshihiro Nabeya, Kiyohiko Shuto, Hideki Hayashi, Tooru Tanizawa, Yukio Nakatani, Hiromitsu Nakasa, Mitsukazu Kitada and Takenori Ochiai. Phase I/II adenoviral *p53* gene therapy for chemoradiation resistant advanced esophageal squamous cell carcinoma. Cancer Sci. 2006; doi: 10.1111/j.1349-7006.2006. 0206.x

[33] ISAMU HOSHINO, HISAHIRO MATSUBARA, YASUNORI AKUTSU, TAKANORI NISHIMORI, YASUO YONEYAMA, KENTARO MURAKAMI, HARUHITO SAKATA, KAZUYUKI MATSUSHITA, AKI KOMATSU, RYAN BROOKS and TAKENORI OCHIAI. Role of Histone Deacetylase Inhibitor in Adenovirus-mediated p53 Gene Therapy in Esophageal Cancer. ANTICANCER RESEARCH. 2008; 28: 665-672

[34] C.Sengpiel, I.R.Ko¨nig,D.Rades, F.Noack, M.Duchrow, S.E.Schild, D.Ludwig,andN.Homann. p53 Mutations in Carcinoma of the Esophagus and Gastroesophageal Junction. *Cancer Investigation*. 2009; 27:96–104. DOI: 10.1080/07357900802161047

[35] Pierre Blanchard, Laurent Quero, Vincent Pacault, Marie-Helene Schlageter, Valerie Baruch-Hennequin and Christophe Hennequin. Prognostic significance of anti-p53 and anti-KRas circulating antibodies in esophageal cancer patients treated with chemoradiotherapy. Blanchard et al. BMC Cancer. 2012; 12:119 http://www.biomedcentral.com/1471-2407/12/119

[36] Hideaki Shimada, MD, Yoshihiro Nabeya, MD, Shin-ichi Okazumi, MD, Hisahiro Matsubara, MD, Yutaka Funami, MD, Tooru Shiratori, MD, Hideki Hayashi, MD, Akihiko Takeda, MD, *and* Takenori Ochiai, MD, *Chiba, Japan*. Prognostic significance of serum p53 antibody in patients with esophageal squamous cell carcinoma. Surgery. 2002; *132:41-7*. doi:10.1067/msy.2002.125307

[37] R Langer, B H A Von Rahden, J Nahrig, C Von Weyhern, R Reiter, M Feith, H J Stein, J R Siewert, H Ho¨fler, M Sarbia. Prognostic significance of expression patterns of c-erbB-2, p53, p16 INK4A, p27 KIP1, cyclin D1 and epidermal growth factor receptor in oesophageal adenocarcinoma: a tissue microarray study. J Clin Pathol. 2006; 59:631–634. doi: 10.1136/jcp.2005.034298

[38] Hai-Yan Song, Xiao-Hui Deng, Guo-Yan Yuan, Xin-Fang Hou, Zhen-Dong Zhu, Li Zhou, Ming-Xin Ren. Expression of bcl-2 and p53 in Induction of Esophageal Cancer Cell Apoptosis by ECRG2 in Combination with Cisplatin. *Asian Pac J Cancer Prev*, 2014; 15 (3), 1397-1401. *DOI: http://dx.doi.org/10.7314/APJCP. 2014.15.3.1397*

[39] Dong-ping Liu, Hoseok Song, and Yang Xu. A common Gain of function of p53 cancer mutants in inducing genetic instability. Oncogene. 2010; 29(7): 949–956. doi: 10.1038/onc.2009.376