

**Review****Antioxidant Enzymes and Cancer**Md. Asaduzzaman Khan<sup>1</sup>, Mousumi Tania<sup>1</sup>, Dian-zheng Zhang<sup>1,2</sup>, Han-chun Chen<sup>1\*</sup>

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**ABSTRACT**

Although oxidation is the most common biological and energy producing reaction, oxidative stress is harmful to cell, because the products of oxidation such as free radicals and peroxides damage the cellular components, causing several diseases. Damage in DNA is responsible for cancer formation and progression. However, several enzymes such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glutathione S-transferase etc. act as antioxidants to influence oxidative stress. Polymorphisms in these enzymes are supposed to be associated with DNA damage and subsequently the individual's risk of cancer susceptibility. This review article aims to further elucidate the relationship between antioxidant enzymes and cancers by summarizing the findings of some of the important study concerning expression levels and genetic polymorphisms of antioxidant enzymes in cancer patients.

**Keywords: Superoxide dismutase; Catalase; Glutathione peroxidase; Glutathione-S-Transferase; Cancer****INTRODUCTION**

Oxidation occurs in over one-quarter of the known chemical reactions catalyzed by enzymes in living cells. In many cases, this is accomplished by the transfer of hydrogen atoms or electrons from one molecule to another. Metabolic reactions of this type are the major source of energy for life processes<sup>[1]</sup>. A paradox in metabolism is that although the vast majority of complex life on Earth requires oxygen for its existence, oxygen is a highly reactive molecule that damages living organisms by producing reactive oxygen species including hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), hypo-chlorous acid (HOCl) and free radicals such as the hydroxyl radical ( $\cdot$ OH), the superoxide anion (O<sub>2</sub><sup>-</sup>) and lipid peroxides<sup>[2]</sup>. Directly or indirectly, these chemical species of oxygen can transiently or permanently damage nucleic acids, lipids, and proteins. Oxidative damage to these cellular macromolecules is implicated in the genesis of several

diseases, including cancer<sup>[3,4]</sup>. To protect themselves, body maintains complex systems of multiple types of antioxidants, such as glutathione, vitamin C and vitamin E as well as enzymes such as catalase(CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione-S-transferase (GST)<sup>[1,4]</sup>. These components or enzymes are involved in multiple biochemical reactions to prevent the harmful oxidative damage. Certainly, the genetic polymorphisms of these enzymes and their different expression levels are correlated to the individual's susceptibility to DNA damage and cancer risk.

**Oxidative Damage to DNA and Cancer**

Oxidative stress plays an important role in carcinogenesis because of induction of DNA damage and its effects on intracellular signal transduction pathways<sup>[5]</sup>. Reactive oxygen species (ROS) induce almost all forms of DNA damage, including base modifications, base-free (apurinic and apyrimidinic) sites, strand breakage and DNA- protein cross-links, but the specific spectrum of products depends on the reactive species involved. These types of mutation are

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reported in genes whose dysfunction is involved in the genesis of cancer<sup>[6]</sup>. ROS may also play a key role in cancer development by inducing and maintaining the oncogenic phenotypes of cancers<sup>[7]</sup>. The highly significant correlation between consumption of fats and oils and death rates from leukemia and malignant neoplasia of the breast, ovaries and rectum among persons over 55 years may be a reflection of greater lipid peroxidation<sup>[8]</sup>.

Currently, oxidative stress has been increasingly postulated as a major contributor to carcinogenesis. The assessment of damage in various biological matrices, such as tissues and cells, is vital to understand the mechanisms of carcinogenesis and subsequently devising intervention strategies. Study on genetic polymorphisms, gain or loss of functions of several antioxidant enzymes such as SOD, CAT, GR, GPx and GST has become important way to understand the development of cancer and its therapies<sup>[9]</sup>.

### Expression of Superoxide Dismutase in Cancer

SOD is a class of enzymes that catalyze the dismutation of superoxide into hydrogen peroxide and oxygen. As such, they are important antioxidant defense in nearly all cells exposed to oxygen. A defect in SOD is experimentally proved to be associated with several types of cancer such as hepatocellular carcinoma. Mice deficient in Cu/Zn-SOD showed no overt abnormalities during development and early adulthood, but had a reduced lifespan and increased incidence of neoplastic changes in the liver, and increased cell proliferation in the presence of persistent oxidative damage to macromolecules likely contributes to hepatocarcinogenesis later in life<sup>[10]</sup>. SOD-2 acts as a downstream mediator of the senescence-associated tumor suppression effect of mac25/insulin-like growth factor binding-protein related protein-1 (IGFBP-rP1) in the suppression of tumor formation and its growth in human breast and prostate epithelial cell lines<sup>[11]</sup>. Diminished SOD was observed in all brain tumor patients compared to control<sup>[12]</sup>. It was implicated that SOD has the potential to induce apoptosis through the generation of H<sub>2</sub>O<sub>2</sub><sup>[13]</sup>. Unfortunately high levels of SOD and H<sub>2</sub>O<sub>2</sub> are also associated with some cancers. Inflammation in the lung contributing high level of Mn-SOD was supposed to lead to increase H<sub>2</sub>O<sub>2</sub> intracellularly and create an intracellular environment favorable to DNA damage and the promotion of cancer<sup>[14]</sup>. However, the orally active SOD derivative prevented tumor progression promoted by inflammation, which is thought to be through the scavenging inflammatory cell-derived superoxide

anion<sup>[15]</sup>. Er et al<sup>[16]</sup> reported the differential expression of SOD in patients with breast cancer in Taiwan. They showed that there was no significant difference in Cu/Zn-SOD expression level between neoplastic and tumor-free breast tissues but a significant increase of Mn-SOD expression level in breast cancer tissues. The authors speculated that up-regulation of Mn-SOD expression induced by oxidative stress or local inflammation may contribute a selective growth advantage to tumor cells compared to their normal counterparts. In a recent study, in laryngeal carcinoma, SOD was found in higher amounts in tumor tissue; however, CAT and GPx were lower<sup>[17]</sup>.

### Expression of Catalase in Cancer

CAT is a very important enzyme of all living organisms which catalyzes the decomposition of hydrogen peroxide to water and oxygen, while the complete mechanism of CAT is not currently known. In 1960, Mason et al<sup>[18]</sup> reported that cancer patients had a 22% lower liver CAT activity than cancer-free people. After few years, human liver CAT was found depressed in the epidermis of patients with advanced cancer<sup>[19]</sup>. Later it was confirmed that hepatic CAT activity is decreased in patients with malignant disease<sup>[20]</sup>.

Decreased CAT activity due to the inflammation in lung was supposed to lead to increase hydrogen peroxide intracellularly and create an intracellular environment favorable to DNA damage and the promotion of cancer<sup>[14]</sup>. Surapaneni and Sadagopan<sup>[21]</sup> suggested that there was higher oxygen free radical production and decreased CAT activity, supporting the oxidative stress in breast cancer. Ahn et al<sup>[22]</sup> evaluated the potential relationship between a functional polymorphism in CAT and breast cancer risk. According to their study, the high-activity CAT CC genotype was associated with an overall 17% reduction in risk of breast cancer compared with having at least one variant allele. The decrease in CAT level and the accumulation of H<sub>2</sub>O<sub>2</sub> are significant events for monocyte/macrophage differentiation by TPA (12-O-tetradecanoylphorbol-13-acetate) and the treatment of U937 cells with CAT inhibited the enhancement of ROS generation induced by TPA, and blocked the TPA-induced differentiation of U937 cells<sup>[23]</sup>. Therapy against breast cancer was also proved effective by increasing CAT activity<sup>[24]</sup>.

### Expression of Glutathione Peroxidase in Cancer

GPx and GR act antioxidatively. Reduced glutathione (GSH) present in most cells, can

chemically detoxify  $H_2O_2$  and forms oxidized glutathione (GSSG), catalyzed by GPx. GR reduces glutathione disulfide (GSSG) to the sulfhydryl form GSH and thus regenerate the antioxidative agent again<sup>[1,25,26]</sup>.

Several studies implicated the association of dysfunctional GPx and GR and cancer risk. Loss of heterozygosity of cytosolic GPx1 gene was implicated in lung cancer patients by Moscow et al<sup>[27]</sup> in 1994. Ratnasinghe et al<sup>[28]</sup> investigated the association between the proline to leucine polymorphism at codon 198 of hGPx1 (human cellular GPx1) and lung cancer risk. They suggested that due to its high prevalence, the hGPx1 variant may contribute significantly to lung cancer risk among the Caucasians but not among the ethnic Chinese who do not exhibit this polymorphism.

The role of allelic variation within the gene for GPx1 in the risk or etiology of breast cancer was investigated by Hu and Diamond<sup>[29]</sup>. By analyzing the frequency of a polymorphism within the GPx1 gene resulting in a leucine or proline at codon 198, it was determined that the leucine-containing allele was more frequently associated with breast cancer than the proline-containing allele.

Many studies have shown that selenium increases hGPx1 expression and activity<sup>[30,31]</sup>. It is generally assumed that selenium increases the antioxidant capacity of a cell, consequently reducing intracellular oxidative stress. The association between prospectively collected serum selenium and lung cancer has been reported in some studies. Most of these studies found that selenium concentration was slightly lower in the lung cancer cases than that in controls<sup>[28,32,33]</sup>. Epidemiological data have also supported a protective effect for selenium in humans with regard to the prevention of prostate cancer<sup>[34,35]</sup>.

### Expression of Glutathione S-transferase in Cancer

Another series of glutathione related important enzyme family is GST. GST family catalyzes the conjugation of reduced glutathione via a sulfhydryl group to electrophilic centers on a wide variety of substrates. This activity detoxifies endogenous compounds such as peroxidized lipids<sup>[36]</sup>.

GSTM1 has been extensively studied as a cancer risk factor. Houlstone<sup>[37]</sup> reported that GSTM1 status has no effect on the risk of lung cancer. Also, the results of another study indicated that GSTM1 genetic polymorphisms are not associated with breast cancer risk, even in an environment low in antioxidant defenses<sup>[38]</sup>. The GSTM1 null genotype has also been reported as showing no association with breast cancer by Curran et al<sup>[39]</sup>. Smith et al<sup>[40]</sup> found no association

of GSTZ1 variant and reported that GSTZ1 does not appear to play a significant role in the development of sporadic breast cancer. However, the GSTM1 null genotype was reported as showing significant association in breast cancer risk by Park et al<sup>[41]</sup>. A potential effect of the GSTP1 Ile105Val polymorphism genotype on smoking and the risk of prostate cancer was reported by Mao et al<sup>[42]</sup>. Nomani et al<sup>[43]</sup> suggested GST measurement as a marker in colorectal cancer, as they found plasma GSTs activity significantly higher in colorectal cancer patients than those obtained from normal individuals. According to Prabhu and Bhat<sup>[44]</sup>, alterations in serum total GST level may have a role in cancer progression.

### Expression of All Antioxidant Enzymes Is Not Similar in Different Cancers

In some studies, alterations of different antioxidant enzymes have been also proved to be associated with cancer. The serum levels of SOD, GPx and CAT and vitamin C and E were significantly declined in patients with multiple myeloma whereas malondialdehyde levels were elevated as compared with controls studied recently<sup>[45]</sup>. A comparative study of the systemic antioxidant activities in red blood cell lysate from subjects with non-small cell lung carcinoma (NSCLC) and healthy control subjects was conducted<sup>[46]</sup>. In this study, in subjects with lung cancer, there was similar CAT activity, lower SOD activity and higher GPx activity compared with controls.

A significant decrease in CAT and Cu/Zn-SOD activity in adenocarcinoma was proved while Mn-SOD activity was increased<sup>[47]</sup>. But lower activities of all enzymes i.e., GPx, CAT and Cu/Zn-SOD were found in erythrocytes of prostate cancer patients<sup>[48]</sup>. A significant alteration in SOD, CAT, GPx, GR activity in blood of prostate cancer patients was also revealed in another study<sup>[49]</sup>. The SOD and CAT levels were found significantly reduced in tissue samples of oral squamous cell carcinoma (OSCC) patients than that in the control group while in the erythrocytes, CAT level was significantly reduced and the SOD level was higher in OSCC group in comparison with the healthy controls<sup>[50]</sup>.

Rajaraman et al<sup>[51]</sup> studied nine single nucleotide polymorphisms from seven genes involved in oxidative stress responders including CAT, GPx1, NOS3, PON1, SOD1, SOD2, and SOD3 and observed increased risk of glioma and meningioma with the C variant of SOD3 rs699473. There was also indication of increased acoustic neuroma risk with the SOD2 rs4880 C(Ala) variant and decreased acoustic neuroma risk with the CAT rs1001179 T allele variant

suggesting that common variants in the SOD2, SOD3, and CAT genes may influence brain tumor risk.

Whole blood CAT and SOD activities were found in reduced level with increased plasmatic thiobarbituric acid reactive substances (TBARS) in acute lymphoblastic leukemia (ALL) patients, indicating a possible link between decreased antioxidants and increased cell alterations due to oxidative damage, supporting the idea that there is a persistence of oxidative stress in ALL<sup>[52]</sup>.

The expressions of CAT and SOD were significantly lower in cancer tissue than that in normal bladder tissue but GPx expression was not significantly different. CAT and SOD expression was also significantly lower in invasive transitional cell carcinomas than that in superficial transitional cell carcinomas but again GPx expression was not significantly different indicating that down-regulation of the antioxidant enzyme system, as indicated by the expression of CAT and SOD, appears to be related to carcinogenesis and progression in bladder cancer<sup>[53]</sup>. It was showed that total SOD activity was increased, CAT activity decreased and glutathione and GPx were similar in lung tumors compared with tumor-free lung tissues. Alterations in antioxidant activities were attributable to increased Mn-SOD and decreased CAT protein and mRNA expression in tumors. Immunohistochemical localization of CAT in the lung revealed decreased or no expression in the tumor cells, although healthy adjacent airway epithelial cells were strongly positive for CAT. Parallel changes in antioxidant activities, protein, and mRNA expression were noted in lung carcinoma cell line A549 cells when exposed to cytokines (tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , and interferon- $\gamma$ ). Thus, inflammation in the lung may contribute to high levels of Mn-SOD and decreased CAT, which together may lead to increased H<sub>2</sub>O<sub>2</sub> intracellularly and create an intracellular environment favorable to DNA damage and the promotion of cancer<sup>[14]</sup>.

### Antioxidant Enzymes against Cancer

The well established role of antioxidant enzymes against cancer is to prevent oxidative DNA damage. However, some newly understood mechanisms also exist. For example, over-expression of CAT has been found to delay G<sub>0</sub>/G<sub>1</sub> to S-phase transition during cell cycle progression in mouse aortic endothelial cells<sup>[54]</sup>. CAT transduction made CD4<sup>+</sup> T cells less sensitive to H<sub>2</sub>O<sub>2</sub>-induced loss-of-function, measured by their cytokine production and ability to expand *in vitro* following anti-CD3 stimulation and may also enhanced the resistance to oxidative stress-induced cell death after co-culture with activated granulocytes and exposure to oxidized lipid 4-hydroxynonenal or H<sub>2</sub>O<sub>2</sub>.

Expression of CAT by cytomegalovirus (CMV)-specific CD8<sup>+</sup> T cells saves cells from cell death and improved their capacity to recognize CMV peptide-loaded target cells when exposed to H<sub>2</sub>O<sub>2</sub>. This study indicated that CAT-transduced T cells are more efficacious for the immunotherapy of patients with advanced cancer or chronic viral infections<sup>[55]</sup>.

Much more attempts have been taken by the researchers in cancer therapies. Some attempts include antioxidant therapies among which some were successfully acted against cancer. In a study using animal model, gene therapy with either GPx or Mn-SOD alone slowed tumor growth by 51% and 54% respectively, while the combination of these two suppressed tumor growth by 81% and increased animal survival<sup>[56]</sup>.

Resveratrol is now proved suppressive of colorectal cancer in rats by preventing oxidative stress. Experimental results<sup>[9]</sup> showed that supplementation with resveratrol (entire-period) treatment regimen significantly increased the enzymatic (SOD, CAT, GR, GPx and GST) and non-enzymatic (reduced glutathione, vitamin C, vitamin E and beta-carotene) antioxidant status with a corresponding decrease in the extent of lipid peroxidation markers.

Taurine increases the expressions of SOD, GPx and CAT genes and thus effective against melanoma<sup>[57]</sup>. The anticancer activity of Ginkgo biloba extract is supposed to be due to the increasing activity of antioxidant enzymes, including SOD and CAT<sup>[58]</sup>.

These findings encourage the researchers to do future works with antioxidant enzyme therapy and related studies to control cancer.

### CONCLUSION

Over the last decades, a considerable number of studies have been done to find out the correlation between cancer susceptibility and the polymorphisms or different expression levels of antioxidant enzymes. Most of the works confirmed the relationship in both similar and different ways. As cancer is one of the most complicated diseases and its pathogenic mechanism is diverse, new studies about genetic polymorphisms and expression levels of several antioxidative enzymes will open new possibilities to understand the pathogenesis of cancers and therapies.

### REFERENCES

- [1] Champe PC, Harvey RA, Ferrier DR. Intermediary metabolism. Champe PC, Lippincott's Illustrated Reviews: Biochemistry. 4th edition[M]. Lippincott

- Williams & Wilkins. Philadelphia, USA. 2007; p: 69-82, 148.
- [2] Valko M, Leibfritz D, Moncol J, et al. Free radicals and antioxidants in normal physiological functions and human disease[J]. *Int J Biochem Cell Biol* 2007; 39: 44-84.
- [3] Mayne ST. Antioxidant nutrients and chronic disease: use of biomarkers of exposure and oxidative stress status in epidemiologic research[J]. *J Nutr* 2003; 133: 933S-40S.
- [4] Bagchi K, Puri S. Free radicals and antioxidants in health and disease[J]. *Eastern Mediterranean Health Journal* 1998; 4: 350-60.
- [5] Frederiks WM, Bosch KS, Hoeben KA, et al. Renal cell carcinoma and oxidative stress: The lack of peroxisomes[J]. *Acta Histochem* 2009; Jun 3 [Epub ahead of print]
- [6] Hussain SP, Raja K, Amstad PA, et al. Increased p53 mutation load in nontumorous human liver of Wilson disease and hemochromatosis: oxyradical overload diseases[J]. *Proc Natl Acad Sci USA* 2000; 97: 12770-5.
- [7] Gargouri B, Lassoued S, Ayadi W, et al. Lipid peroxidation and antioxidant system in the tumor and in the blood of patients with nasopharyngeal carcinoma[J]. *Biol Trace Elem Res* 2009; 132: 27-34.
- [8] Kulbacka J, Saczko J, Chwiłkowska A. Oxidative stress in cells damage processes[J]. *Pol Merkur Lekarski* 2009; 27: 44-7.
- [9] Sengottuvelan M, Deeptha K, Nalini N. Resveratrol ameliorates DNA damage, prooxidant and antioxidant imbalance in 1,2-dimethylhydrazine induced rat colon carcinogenesis[J]. *Chem Biol Interact* 2009; 181: 193-201.
- [10] Elchuri S, Oberley TD, Qi W, et al. CuZnSOD deficiency leads to persistent and widespread oxidative damage and hepatocarcinogenesis later in life[J]. *Oncogene* 2005; 24: 367-80.
- [11] Plymate SR, Haugk KH, Sprenger CC, et al. Increased manganese superoxide dismutase (SOD-2) is part of the mechanism for prostate tumor suppression by Mac25/insulin-like growth factor binding-protein-related protein-1[J]. *Oncogene* 2003; 22: 1024-34.
- [12] Aggarwal S, Subberwal M, Kumar S, et al. Brain tumor and role of beta-carotene, a-tocopherol, superoxide dismutase and glutathione peroxidases[J]. *J Cancer Res Ther* 2006; 2: 24-7.
- [13] de Haan JB, Cristiano F, Iannello R, et al. Elevation in the ratio of Cu/Zn-superoxide dismutase to glutathione peroxidase activity induces features of cellular senescence and this effect is mediated by hydrogen peroxide[J]. *Hum Mol Genet* 1996; 5: 283-92.
- [14] Chung-man Ho J, Zheng S, Comhair SA, et al. Differential expression of manganese superoxide dismutase and catalase in lung cancer[J]. *Cancer Res* 2001; 61: 8578-85.
- [15] Okada F, Shionoya H, Kobayashi M. Prevention of inflammation-mediated acquisition of metastatic properties of benign mouse fibrosarcoma cells by administration of an orally available superoxide dismutase[J]. *Br J Cancer* 2006; 94: 854-62.
- [16] Er TK, Hou MF, Tsa EM, et al. Differential expression of manganese containing superoxide dismutase in patients with breast cancer in taiwan[J]. *Ann Clin Lab Sci* 2004; 34: 159-64.
- [17] Kacakci A, Aslan I, Toplan S, et al. Significance of the counteracting oxidative and antioxidative systems in the pathogenesis of laryngeal carcinoma[J]. *J Otolaryngol Head Neck Surg* 2009; 38: 172-7.
- [18] Mason EE, Chin TF, Li YW, et al. Cancer and human liver catalase[J]. *Cancer Res* 1960; 20: 1474-81.
- [19] Falkson G, Dejager ME. Catalase activity in the epidermis of patients with advanced cancer[J]. *Nature* 1964; 202: 203-4.
- [20] De Craemer D, Pauwels M, Hautekeete M, et al. Alterations of hepatocellular peroxisomes in patients with cancer. Catalase cytochemistry and morphometry [J]. *Cancer* 1993; 71: 3851-8.
- [21] Surapaneni KM, Sadagopan C. Status of Lipid peroxidation and antioxidant enzymes in patients with carcinoma of breast[J]. *J Med Sci Res* 2007; 1: 21-4.
- [22] Ahn J, Gammon MD, Santella RM, et al. Associations between breast cancer risk and the catalase genotype, fruit and vegetable consumption, and supplement use[J]. *Am J Epidemiol* 2005; 162: 943-52.
- [23] Yamamoto T, Sakaguchi N, Hachiya M, et al. Role of catalase in monocytic differentiation of U937 cells by TPA: hydrogen peroxide as a second messenger[J]. *Leukemia* 2009; 23: 761-9.
- [24] Petit E, Courtin A, Kloosterboer HJ, et al. Progestins induce catalase activities in breast cancer cells through PRB isoform: correlation with cell growth inhibition[J]. *J Steroid Biochem Mol Biol* 2009; 115(3-5): 153-60.
- [25] Mannervik B. The enzymes of glutathione metabolism: an overview[J]. *Biochem Soc Trans* 1987; 15: 717-8.
- [26] Meister A. Glutathione metabolism and its selective modification[J]. *J Biol Chem* 1988; 263: 17205-8.
- [27] Moscow JA, Schmidt L, Ingram DT, et al. Loss of heterozygosity of the human cytosolic glutathione peroxidase I gene in lung cancer[J]. *Carcinogenesis* 1994; 15: 2769-73.
- [28] Ratnasinghe D, Tangrea JA, Andersen MR, et al. Glutathione peroxidase codon 198 polymorphism variant increases lung cancer risk[J]. *Cancer Res* 2000; 60: 6381-3.
- [29] Hu YJ, Diamond AM. Role of glutathione peroxidase 1 in breast cancer loss of heterozygosity and allelic

- differences in the response to selenium[J]. *Cancer Res* 2003; 63: 3347-51
- [30] Moscow JA, Morrow CS, He R, et al. Structure and function of the 5'-flanking sequence of the human cytosolic selenium-dependent glutathione peroxidase gene (hgp1)[J]. *J Biol Chem* 1992; 267: 5949-58.
- [31] Chada S, Whitney C, Newburger PE. Post-transcriptional regulation of glutathione peroxidase gene expression by selenium in the HL-60 human myeloid cell line[J]. *Blood* 1989; 74: 2535-41.
- [32] Willett WC, Polk BF, Morris JS, et al. Prediagnostic serum selenium and risk of cancer[J]. *Lancet* 1983; 2: 130-4.
- [33] Comstock GW, Alberg AJ, Huang HY, et al. The risk of developing lung cancer associated with antioxidants in the blood: ascorbic acid, carotenoids, alpha-tocopherol, selenium, and total peroxyl radical absorbing capacity[J]. *Cancer Epidemiol Biomarkers Prev* 1997; 6: 907-16
- [34] Yoshizawa K, Willett WC, Morris SJ, et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer[J]. *J Natl Cancer Inst* 1998; 90: 1219-24.
- [35] Brooks JD, Metter EJ, Chan DW, et al. Plasma selenium level before diagnosis and the risk of prostate cancer development[J]. *J Urol* 2001; 166: 2034-8.
- [36] Leaver MJ, George SG. A piscine glutathione S-transferase which efficiently conjugates the end-products of lipid peroxidation[J]. *Marine Environ Res* 1998; 46: 71-4.
- [37] Houlstone RS. Glutathione S-transferase M1 status and lung cancer risk: A meta-analysis[J]. *Cancer Epidemiol Biomark Prev* 1999; 8: 675-82.
- [38] Ambrosone CB, Coles BF, Freudenheim JL, et al. Glutathione-S-transferase (GSTM1) genetic polymorphisms do not affect human breast cancer risk, regardless of dietary antioxidants[J]. *J Nutr* 1999; 129: 565S-8S.
- [39] Curran JE, Weinstein SR, Griffiths LR. Polymorphisms of glutathione S-transferase genes (GSTM1, GSTP1 and GSTT1) and breast cancer susceptibility[J]. *Cancer Lett* 2000; 153: 113-20.
- [40] Smith RA, Curran JE, Weinstein SR, et al. Investigation of glutathione S-transferase zeta and the development of sporadic breast cancer[J]. *Breast Cancer Res* 2001; 3: 409-11.
- [41] Park SK, Yoo KY, Lee SJ, et al. Alcohol consumption, glutathione S-transferase M1 and T1 genetic polymorphisms and breast cancer risk[J]. *Pharmacogenetics* 2000; 10: 301-9.
- [42] Mao GE, Morris G, Lu QY, et al. Glutathione S-transferase P1 Ile105Val polymorphism, cigarette smoking and prostate cancer[J]. *Cancer Detect Prev* 2004; 28: 368-74.
- [43] Nomani H, Ghobadloo SM, Yaghmaei B, et al. Glutathione S-transferases activity in patients with colorectal cancer[J]. *Clin Biochem* 2005; 38: 621-4.
- [44] Prabhu K, Bhat GP. Serum total glutathione-S-transferase levels in oral cancer[J]. *J Cancer Res Ther* 2007; 3: 167-8.
- [45] Sharma A, Tripathi M, Satyam A, et al. Study of antioxidant levels in patients with multiple myeloma[J]. *Leuk Lymphoma* 2009; 50: 809-15.
- [46] Ho JC, Chan-Yeung M, Ho SP, et al. Disturbance of systemic antioxidant profile in nonsmall cell lung carcinoma[J]. *Eur Respir J* 2007; 29: 273-8.
- [47] Monari M, Foschi J, Calabrese C, et al. Implications of antioxidant enzymes in human gastric neoplasms[J]. *Int J Mol Med* 2009; 24: 693-700.
- [48] Arsova-Sarafinovska Z, Eken A, Matevska N, et al. Increased oxidative/nitrosative stress and decreased antioxidant enzyme activities in prostate cancer[J]. *Clin Biochem* 2009; 42: 1228-35.
- [49] Kotrikadze N, Alibegashvili M, Zibzivadze M, et al. Activity and content of antioxidant enzymes in prostate tumors[J]. *Exp Oncol* 2008; 30: 244-7.
- [50] Gokul S, Patil V, Jaiikhani R, et al. Oxidant-antioxidant status in blood and tumor tissue of oral squamous cell carcinoma patients[J]. *Oral Dis* 2009; Jul 27 [Epub ahead of print].
- [51] Rajaraman P, Hutchinson A, Rothman N, et al. Oxidative response gene polymorphisms and risk of adult brain tumors[J]. *Neuro Oncol* 2008; 10: 709-15.
- [52] Battisti V, Maders LD, Bagatini MD, et al. Measurement of oxidative stress and antioxidant status in acute lymphoblastic leukemia patients[J]. *Clin Biochem* 2008; 41: 511-8.
- [53] Jeon SH, Park JH, Chang SG. Expression of antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase) in human bladder cancer[J]. *Korean J Urol* 2007; 48: 921-6.
- [54] Onumah OE, Jules GE, Zhao Y, et al. Overexpression of catalase delays G0/G1- to S-phase transition during cell cycle progression in mouse aortic endothelial cells[J]. *Free Radic Biol Med* 2009; 46: 1658-67.
- [55] Ando T, Mimura K, Johansson CC, et al. Transduction with the antioxidant enzyme catalase protects human t cells against oxidative stress[J]. *J Immunol* 2008; 181: 8382-90.
- [56] Liu J, Hinkhouse MM, Sun W, et al. Redox regulation of pancreatic cancer cell growth: role of glutathione peroxidase in the suppression of the malignant phenotype[J]. *Hum Gene Ther* 2004; 15: 239-50.
- [57] Yu J, Kim AK. Effect of taurine on antioxidant enzyme system in B16F10 melanoma cells[J]. *Adv Exp Med Biol* 2009; 643: 491-9.
- [58] Feng X, Zhang L, Zhu H. Comparative anticancer and antioxidant activities of different ingredients of Ginkgo biloba extract (EGb 761)[J]. *Planta Med* 2009; 75: 792-6.