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AIM AND SCOPE

World Journal of Experimental Medicine (*World J Exp Med*, *WJEM*, online ISSN 2220-315X, DOI: 10.5493) is a bimonthly peer-reviewed, online, open-access, journal supported by an editorial board consisting of 104 experts in experimental medicine from 30 countries.

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EDITORS FOR THIS ISSUE

EDITORIAL

Breast cancer and protein biomarkers

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Abstract

Breast cancer is a healthcare concern of women worldwide. Despite procedures being available for diagnosis, prognosis and treatment of breast cancer, researchers are working intensively on the disease in order to improve the life quality of breast cancer patients. At present, there is no single treatment known to bring a definite cure for breast cancer. One of the possible solutions for combating breast cancer is through identification of reliable protein biomarkers that can be effectively used for early detection, prognosis and treatments of the cancer. Therefore, the task of identification of biomarkers for breast cancer has become the focus of many researchers worldwide.

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Key words: Breast cancer; Protein; Biomarkers; Proteomics

INTRODUCTION

Breast cancer is one of the leading causes of death among women[1]. It accounts for approximately 40 000 deaths in the United States annually and still imposes a significant healthcare burden on women worldwide[2].

Cancer is a disorder of cells caused by an unpredictable genetic disorder[3] which leads to growth that is visible as a tumor[4]. It is typically considered as a disease of aging because the chances of developing this disease increase with age[5]. Cancer is characterized by uncontrolled cell proliferation, disruption of apoptosis, sustained angiogenesis and increased cell ability to invade other tissues and metastasize[6,7]. Today, cancer is one of the main causes of global mortality.

A biomarker is a biochemical substrate that indicates a physiological state or development of a disease[8]. It is usually a biological substance found in blood, tissue or other body fluids. Useful biomarkers should have a strong association with the outcome of the disease. Among the common clinical usage of biomarkers are the diagnosis, prognosis, treatment and indicators for the risk of developing the disease[9]. In the context of the disease's treatment, a biomarker whose expression levels change according to treatment can be used to determine the progress of the treatment[10]. The presence of a specific biomarker is often used as an indicator to predict the response of patients to therapy[11]. Nevertheless, before a biomarker can serve its purpose, a thorough evaluation of its reliability needs to be validated.

CANCER BIOMARKERS

Cancer biomarkers can be classified as cellular and humoral markers. A cellular marker is associated with cancer cells and therefore it provides prognostic information for the patient from which a therapeutic plan suit best to the patient can be determined[12,13]. On the other hand, a humoral cancer marker is characterized by its detection in body fluids. It is secreted either by the tumor or during tumor disintegration[13]. A humoral cancer marker is useful in the early detection of cancer,

especially in asymptomatic people with high risk of developing cancer[12].

In terms of the usage of biomarkers, cancer biomarkers can be divided into three main categories, namely diagnostic, prognostic and predictive biomarkers. A diagnostic marker is used to detect the presence of the disease. A prognostic marker is used after the establishment of the disease status to predict the course of the disease and its recurrence and can be used to indicate the aggressiveness of the tumor. A predictive marker is used to predict the likely response of a patient to a drug prior to a treatment so that patients are classified as "responder" or "nonresponder" by the presence or absence of the marker. Such a prediction is important in designing clinical drug trials to define the intended use of the drug[14].

CURRENTLY AVAILABLE BREAST CANCER BIOMARKERS

There are a few potential serum based biomarkers for breast cancer. Nevertheless, only two of the serum based biomarkers were approved by the Food and Drug Administration (FDA) for monitoring and treatment of the advanced or recurrence breast cancer, MUC-1 (CA27.29 and CA15-3) and carcinoembryonic antigen[15,16].

MUC-1 mucins belong to a protein family secreted by the luminal surface of glandular epithelia. The upregulation of MUC-1 mucin was detected in breast cancer patients, particularly in patients' serum[17,18]. Family members of *MUC-1*-gene include *MCA, BRMA CA549, CA27.29* and *CA15-3*. Among which, CA15-3 is reliable in indicating the clinical course of patients with metastatic cancer. The serum level of CA15-3 corresponds to the tumor size. Although CA27.29 was found to be more sensitive than CA15-3, it was less specific than CA15-3[19].

Carcinoembryonic antigen (CEA) is a glycoprotein presence in the serum of cancer patients and can be detected using radioimmunoassay or enzyme-linked immunosorbent assay[20]. CEA does not serve as a good indicator for metastatic breast cancer as the CEA serum level was found elevated in only 15% to 68% of patients[21]. In addition, a high false-positive rate was detected among the normal population, where a false positive rate ranging from 10% to 27% was reported[20], limiting its clinical applications. The main clinical application of CEA is for gastrointestinal cancers, specifically in colorectal malignancy. It is a very useful marker for the early detection of liver metastasis in patients diagnosed with colorectal cancer[22].

Another potential serum based marker is CA-125, a useful serum marker for monitoring ovarian cancer and predicting the patient's response to therapy. Nevertheless, CA-125 had insufficient sensitivity for diagnosis of the disease[23]. In addition, serum CA-125 has been shown to be elevated in various forms of cancer, including ovarian, pancreatic, breast, colon, lung and endometrial carcinoma, making it less specific to any type of cancer[24]. It is commonly agreed that CA-125 has a lack

of both sensitivity and specificity as a marker for early stage disease. However, its specificity can be improved by combining CA-125 with various forms of sonography[14]. Changes in serum protein levels may also indicate the response of patients to chemotherapy in HER2-positive breast cancer patients, where a few serum based proteins, namely alpha-2-macroglobulin, complement 3, hemopexin and serum amyloid P, can be used as indicators for patients' positive response to chemotherapy[25].

Prediction of patients' response to drugs is important for effective cancer treatment. Recently, many predictive biomarkers have been suggested for different types of drug treatment. Estrogen receptor (ER) and progesterone receptor are useful indicators for prediction of breast cancer patients' responses to hormonal therapy in an adjuvant setting and metastatic disease. Heat shock protein 70 showed significant positive correlation for the usage of aromatase inhibitors in hormonal therapy[26]. As for ER-positive breast cancer, truncated BH3 interacting domain death agonist[27] and 14-3-3 proteins, including theta/tau, gamma, epsilon, beta/alpha and seta/delta isoforms, can be used as indicators for patients' responses to neoadjuvant chemotherapy[28]. In the event of triple-negative breast cancer, defined by lack of expression of estrogen, progesterone and human epidermal growth factor receptor 2 (HER-2), heat shock protein 90 has been identified as a critical target for its treatment[29]. On the other hand, FKBP4 and S100A9 were suggested as putative prediction markers in discriminating doxorubicin and docetaxel drug sensitive patients from drug resistant patients[30], while Hsp27 was said to indicate doxorubicin resistance[31]. The response of patients to neoadjuvant paclitaxel/radiation treatment can be evaluated by the overexpression of alpha-defensins and microtubule associated protein 2 to indicate a pathological complete response. In addition, the presence of alpha-defensins and MAP2 were also used to indicate patients' sensitivity to taxane-based treatment[32].

Prognostic biomarkers provide information regarding outcome irrespective of therapy. Amongst the potential prognostic biomarkers for breast cancer are Ki-67 for a primary tumor, cyclins, urokinase plasminogen activator, p53, p21, pro- and anti-apoptotic factors, BRCA1 and BRCA2[33-35].

The discovery of the HER-2/neu oncogene has led to the formulation of an anti-cancer drug for patients with breast cancer[36]. HER-2 belongs to the type I transmembrane tyrosine kinase receptor family. HER-2 is an important regulator for cell growth, differentiation during embryogenesis and for mammary development during puberty. Deregulation of HER-2 signaling in mammary cells promotes breast tumorigenesis[37]. Approximately 25% to 30% of human metastatic breast cancers over-expressed HER-2[38]. Overexpression of HER-2 is a significant predictor of reduced survival and shorter time to relapse[39,40]. This is because these tumors tend to grow faster and are more likely to metastasize than tumors that do not overexpress HER-2. Thus, HER-2 has become an important therapeutic target for

this subtype of breast cancer. When breast cancer is diagnosed, HER-2 status is routinely assessed by either immunohistochemical analysis for HER-2 expression or fluorescent *in situ* hybridization analysis for *HER-2* gene copy[41]. Two HER-2-targeted therapies are approved by the United States FDA for treatment of HER2-overexpressing metastatic breast cancer, namely Trastuzumab (Herceptin) and Lapatinib (Tykerb). The presence of HER-2 overexpression is a predictive factor that may indicate successful use of trastuzumab (Herceptin)[40]. Trastuzumab (Herceptin) is a recombinant humanized monoclonal antibody targeted against the extracellular HER-2 receptor. The initial clinical trials of trastuzumab to be used as a sole agent in HER-2-overexpressing metastatic breast cancer demonstrated a response rate ranging from 12% to 34% for a median duration of 9 months[42].

Early detection of breast cancer increases the survival rate of patients[43]. However, early symptoms of breast cancer are sometimes absent or not recognized. It is often detected in the advanced stage and is untreatable when the cancer is diagnosed[16]. Thus, a reliable biomarker is needed to rule out breast cancer in the early state. Unfortunately, currently available tumor markers lack the specificity and sensitivity to be used in early detection of breast cancer[13,16].

PROTEOMIC APPROACH FOR BIOMARKER IDENTIFICATION

Protein profiling studies on different types of cancer have been carried out by researchers throughout the world. The 2D-PAGE coupled with mass spectrometry, isotope coded affinity tags, multidimensional protein identification technology, protein array technology and surface enhanced laser-desorption ionization-time of flight are among the common technologies applied in proteomic study[44-46]. The proteome of a cell contains all of the gene products that represent the functional output of the cell[47]. This makes proteomics a promising tool for characterizing cells and tissues of interest and for biomarker discovery[48].

It has been estimated that only 2% of human diseases result from single gene defects. As for the remaining 98% of human diseases, epigenetic and environment factors need to be considered as they affect both etiology and severity of the disease[49]. Therefore, cancer biomarker discovery targeting protein expressions has become popular as proteomic approaches characterize both modified and unmodified proteins involved in cancer progression. In recent years, the emerging sciences of genomics and proteomics have revealed the identity of proteins that can potentially serve as cancer biomarkers. Unfortunately, very few of these biomarkers are reliable clinically for prognosis or diagnosis of the disease and even fewer have been validated and approved for clinical usage[50,51].

The proteomics of normal breast and cancerous tissue was first reported by Wulfkuhle *et al*[52]. The authors revealed 57 differentially expressed proteins between normal and cancerous tissues, including VDAC, transgelin, Hsp 27, GRP78 and cathepsin. Following this study, Somiari *et al*[45] reported the identification of annexin V, HSP 90, carbonic dehydrase, protein disulfide isomerase, gelsolin and fibrinogen beta chain. Luo *et al*[53] added to the list of differentially expressed proteins, including manganese SOD, biliverdin reductase B, carbonic anhydrase I and annexin I, binding protein 4, cofilin 1, profiling 1 and uracil DNA glycosylase. On the other hand, Deng *et al*[54] reported the potential of alpha-1-antitrypsin, EF-1-beta, cathepsin D, translationally controlled tumour protein, SMT3A and PSMA1 as candidate biomarkers for patients with breast cancer. Besides these studies, there are many recent reports on the identification of biomarkers in breast cancer[26-30]. Although the potential use of most reported biomarkers for breast cancer has been scientifically proven, they need to be clinically validated.

HETEROGENEITY BETWEEN PATIENTS

It is a challenge to identify a common biomarker that fits all patients. Many different factors are involved in the development of cancer. They include age, race, family history, personal history of cancer, presence of viruses, mutations in cell regulation genes and tumor suppressing genes, exposure to carcinogens, lack of physical activity and diet[55,56]. All these factors will cause heterogeneity in protein expression between patients. Therefore, individualized medicine has become a popular trend for treating cancer in Western countries. Nevertheless, in developing countries, such a treatment will be too expensive for most patients. In the author's laboratory, we have received surgically removed tissues from patients with breast and colon cancer. In general, Malaysia is a country populated by three main ethnic groups, namely Malays, Chinese and Indian. Although the environment and lifestyle factors are relatively similar between the ethnic groups, they originated from different parts of the world, with the Malays and Chinese mainly from China-Mongolia regions and the Indians mainly from south India. We have shown in our studies[47] that the Malays and Chinese have relatively similar protein profiles, while Indians are very different. Therefore, the usability of each protein biomarker to be commonly used for a cancer per se among Malaysian patients was not reliable, but when an ethnic-specific biomarker was identified for each ethnic group, their significance greatly increased. Consequently, we have suggested the possibility of ethnic specific drug-targeted therapy, which may be more affordable to patients from developing or under developed countries where health insurance is not well established.

CHALLENGES FOR IDENTIFICATION OF BIOMARKERS FOR CANCER

A few criteria are required for biomarkers to be effec-

tively used in diagnosis, prognosis or treatment of cancer. First is the specificity of the biomarker to a type of cancer and such biomarker should be uniquely expressed in cancerous tissues only. Furthermore, consistent expression of the protein biomarker in cancer patients will surely increase its reliability as an indicator of the disease. Moreover, the abundant expression of the protein biomarker will ease its detection or its recognition as a target for treatment.

In the author's experience of researching the potential biomarkers for cancer, none of the proteins met the criteria of biomarkers in terms of consistent and unique expression in all cancer patients. Instead, we have detected many common proteins between normal and cancerous tissues that were differentially expressed[57], indicating that the similar types of cell activities were operating between normal and cancerous cells while the rate of operation differs between the two tissues; cancer cell activities repeat more frequently than normal cells, which causes a rapid cell growth that leads to tumor formation. There may be uniquely expressed protein in cancerous tissue but such proteins may express themselves in low quantities, making them not a suitable biomarker for drug-targeted therapy.

CHALLENGES FOR IDENTIFICATION OF BIOMARKERS FOR DRUG-TARGETED THERAPY IN CANCER TREATMENT

Currently, most of the drugs used in chemotherapy are non-targeted, leading to two consequences. Firstly, the quantity of drug used in treatment was generally more than that required to fight cancer because the drug will be circulated in the body without a precise target, leading to the second consequence, the side-effects of the drug on patients who undergo chemotherapy treatment. The solution to this problem is drug-targeted therapy, where the drug will be targeted at the side of tumor so that the amount of drug used can be reduced and therefore the side-effect of chemo treatment can also be minimized. The key answer for drug-targeted therapy is the target itself, which should recognize the tumor and direct the drug to itself. Such a target must not be hidden and, at the same time, it must be easily accessible to drugs.

To date, there are many reports on the potential biomarkers for various types of cancer. Nevertheless, many projects seem to stop at the biomarker identification stage, which may be due to lack of funding or insufficient facilities to carry out the subsequent research. Moreover, innovation of targeted drug therapy is a lengthy process which could possibly take many years of continual research. Multi-factorial aspects on the safety use of the drugs also need to be examined. Such innovation requires large funding, while the revenue is hardly guaranteed as many of the drugs are eliminated even before reaching the second or third stage of a clinical trial. In drug targeted therapy, the drug of interest is

to be tagged on a specific antibody that recognizes the biomarker on the cancer cell. In order to be used as a biomarker in drug targeted therapy, the biomarker is best to be uniquely expressed on the tumor surface at high abundant quantity for easy recognition and access of the drugs. Although such biomarkers may not exist, there are abundantly expressed common proteins on the tumor surface that are differentially expressed, where their expression levels were found much higher in cancerous tissues than normal tissues. These differentially expressed abundant proteins on the surface of cancerous tissues may serve as a good target for recognition when its abundance is much higher than that of the normal tissues.

POSSIBLE SOLUTION BY COLLECTIVE USE OF BIOMARKERS

The use of an individual protein as the sole biomarker for diagnosis, prognosis or treatment for cancer no doubt simplifies the procedure. However, it has been shown in many studies that protein expression variation between patients is the main halting factor of the development of devices as the cost of such development is tremendously high; however, its usability is limited to a small group of patients. One of the possible solutions is the collective use of biomarkers to achieve the desired goal. Through principle component analysis and linear discriminant analysis statistical analysis, we have shown previously[58] that the collective use of biomarkers in cancer has tremendously increased the correct identification of cancerous tissues. The combined use of biomarkers has also been shown to give a better prognosis and increase sensitivity and specificity to predict the response of patients to chemotherapeutic agents[33]. This will also reduce the possibility of a false diagnosis as the reliability of a group of biomarkers is better than the sole use of a single biomarker.

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57   **Liang S**, Singh M, Gam LH. The differential expression of aqueous soluble proteins in breast normal and cancerous tissues in relation to ethnicity of the patients; Chinese, Malay and Indian. *Dis Markers* 2010; **28**: 149-165

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Acknowledgments to reviewers of *World Journal of Experimental Medicine*

MEETINGS

Events Calendar 2012

January 15-20, 2012
Fungal Pathogens: From Basic
Biology to Drug
Santa Fe, NM, United States

January 20-20, 2012
Exploiting Bacteriophages for
Bioscience, Biotechnology and
Medicine
London, United Kingdom

January 22-27, 2012
Biology of Spirochetes
Ventura, CA, United States

February 7-12, 2012
Gene Silencing by Small RNAs
Vancouver, British Columbia,
Canada

March 4 -10, 2012
Malaria Experimental Genetics
Hinxton, Cambridge,
United Kingdom

March 12-13, 2012
2nd Annual International
Conference on BioInformatics and
Computational Biology Special
Track: Stem Cell Research
Singapore

March 12-13, 2012
BICB 2012: 2nd Annual International
Conference on BioInformatics and
Computational Biology (updated)
Global Science and Technology
Forum
Thailand

March 18-21, 2012
Annual Conference of the
Association for General and Applied
Microbiology
Tubingen, Germany

March 31-April 3, 2012
22nd European Congress of Clinical
Microbiology and Infectious
Diseases ECCMID
London, United Kingdom

April 2-4, 2012
Electron transfer at the microbe-
mineral interface
Norwich, United Kingdom

April 18, 2012
6th Broadening Microbiology
Horizons in Biomedical Science
Meeting
Stratford-Upon-Avon,
United Kingdom

May 6-12, 2012
4th ASM Conference on Prokaryotic

Cell Biology and Development
Montreal, Canada

May 7-19, 2012
Bioinformatics and comparative
genomes analyses
Napoli, Italy

May 8 - 10, 2012
Exploring Human Host-Microbiome
Interactions in Health and Disease
Cambridge, United Kingdom

May 30-31, 2012
European Lab Automation
Hamburg, Germany

June 3-8, 2012
Anaerobes in Health and Disease;
How to Isolate, Identify and Look
for Resistance in a Cost-Effective
Way
Szeged, Hungary

June 16-21, 2012
Gene transcription in yeast
Girona, Spain

June 21-22, 2012
Swiss Joint Annual Meeting
St. Gallen, Switzerland

July 22-27, 2012
15th International Conference on

Experimental Mechanics
University of Porto
Portugal

July 29-August 2, 2012
XV IS-MPMI Kyoto 2012.
International Congress on Molecular
Plant-Microbe Interactions
Kyoto, Japan

August 18-22, 2012
The 30th World Congress of
Biomedical Laboratory Science
Berlin, Germany

August 25-September 1, 2012
Update on Indications, Interactions
and Complications in the Use of
Pharmaceuticals
Honolulu, Hawaii, United States

September 7-9, 2012
International Congress of Maritime
Medicine
Odessa, Ukraine

October 14-24, 2012
Medical Ethics and Legal Medicine
Miami, Florida, United States

December 1-6, 2012
Qatar Health 2012
Doha, Qatar

GENERAL INFORMATION

World Journal of Experimental Medicine (*World J Exp Med*, *WJEM*, online ISSN 2220-315X, DOI: 10.5493) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 104 experts in experimental medicine from 30 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

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The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJEM* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJEM* is an OA journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJEM* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

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Columns

The columns in the issues of *WJEM* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in experimental medicine; (8) Brief Articles: To briefly report the novel and innovative findings in experimental medicine; (9) Case Report: To report a rare or typical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJEM*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of experimental medicine; and (12) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in experimental medicine.

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing

Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

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Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

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When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

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Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

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Key words
Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/2220-315x/g_info_20100725072755.htm.

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Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any

footnotes. Vertical and italic lines should be omitted.

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Data that are not statistically significant should not be noted. $^aP < 0.05$, $^bP < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of P values, $^cP < 0.05$ and $^dP < 0.01$ are used. A third series of P values can be expressed as $^eP < 0.05$ and $^fP < 0.01$. Other notes in tables or under illustrations should be expressed as ^1F, ^2F, ^3F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

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The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

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Format

Journals

English journal article (list all authors and include the PMID where applicable)

1   **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224   DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2   **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3   **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4   **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377   DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5   **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764   DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6   21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303   DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7   **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325   DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8   **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900   DOI:10.1097/00003086-200208000-00026]

No volume or issue

9   Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10   **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11   **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12   **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13   **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14   **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15   Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16   **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data
Write as mean ± SD or mean ± SE.

Statistical expression
Express t test as t (in italics), F test as F (in italics), chi square test as χ^2 (in Greek), related coefficient as r (in italics), degree of freedom as υ (in Greek), sample number as n (in italics), and probability as P (in italics).

Units
Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc*. Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics
Quantities: t time or temperature, c concentration, A area, l length, m mass, V volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc*.
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc*.
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Guidelines for basic research: http://www.wjgnet.com/2220-315x/g_info_20100725072344.htm

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