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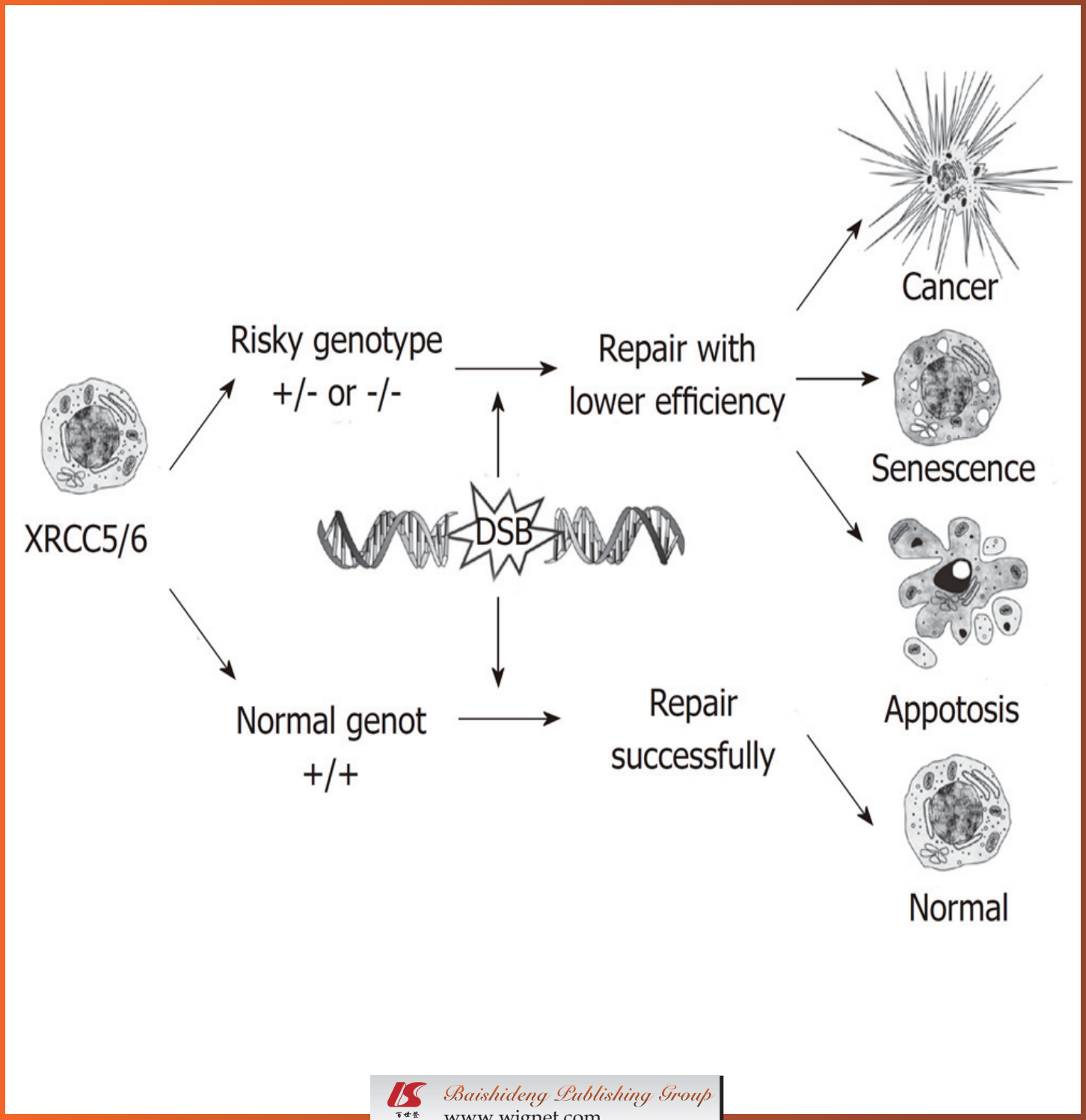

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EDITORIAL

Rationale and techniques of cytoreductive surgery and peritoneal chemohyperthermia

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Abstract

The evolution of loco-regional treatments has occurred in the last two decades and has deeply changed the natural history of primitive and secondary peritoneal surface malignancies. Several phase Ⅱ-Ⅲ studies have proved the effectiveness of the combination of cytoreductive surgery with peritoneal chemohyperthermia. Cytoreductive surgery allows the reduction of the neoplastic mass and increases tumoral chemosensitivity. The development of chemohyperthermia finds its origins in the necessity to exceed the limits of intraperitoneal chemotherapy performed in normothermia. It permits a continuous high concentration gradient of chemotherapeutic drugs between the peritoneal cavity and the plasma compartment to and a more uniform distribution throughout the abdominal cavity compared to systemic administration.

Key words: Hyperthermic intraperitoneal chemotherapy; Peritoneal surface malignancies; Peritoneal carcinomatosis; Cytoreductive surgery; Loco-regional treatments

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INTRODUCTION

Peritoneal surface malignancies (PSM) are a loco-regional neoplastic dissemination that includes peritoneal carcinomatosis (PC), that is the progression of neoplastic diseases from abdominal, pelvic or extra abdominal organs[1-3], pseudomyxoma peritonei (PMP), an uncommon "borderline malignancy" generally arising from a perforated appendiceal epithelial tumor and, finally, primitive tumors of the peritoneum, such as diffuse malignant peritoneal mesothelioma (DMPM). The PC has long been considered a lethal clinical entity[4], with no curative options and a median survival rate of 3-6 mo[5], and it can be present at the moment of the diagnosis of primary cancer or, most frequently, after potentially curative surgery. The evolution of loco-regional treatments options occurred in the last two decades and has deeply changed the natural history of primitive and secondary PSM. In fact, cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has become a promising treatment for patients with peritoneal malignancies thanks to the favorable results in terms of quality of life and outcome[6]. Several studies have proved the effectiveness of the combination of CRS plus HIPEC[7-12]. In fact, this type of approach has been established as the standard therapy for pseudomixoma peritonei with a mean survival rate of 156 mo[13] and a 5-year survival

range from 62.5% to 100% for low grade and from 0 to 65% for high grade disease[14]. In PC from colorectal cancer, the mean survival rate varies considerably from 12 to 32 mo, with 1-year, 2-year, 3-year and, when reported, 5-year survival rates ranging from 65% to 90%, 25% to 60%, 18% to 47%, and 17% to 30% respectively[15]. For patients with a peritoneal diffusion of gastric cancer, the mean survival ranges from 8 to 11 mo and the 5-year survival from 6% to 16%[16,17]. In PC from epithelial ovarian cancer (EOC), the most lethal gynecological malignancy, a median overall and disease free survival of up to 64 mo and 57 mo, respectively[18] with a 5-year survival rate from 39% to 60.7%[9-19] has been reported. Finally, for peritoneal mesothelioma, after aggressive surgery combined with HIPEC, a median survival of 34-92 mo with a 5-year survival rate of 67% has been reported[12,20].

RATIONALE OF CYTOREDUCTIVE SURGERY

This therapeutic approach, so complex that it requires a specifically dedicated multidisciplinary team, is based on a rationale and techniques by now well codified. On one hand, CRS allows reduction of the neoplastic mass and, on the other hand, by means of induction of the cell-growth phase, the elimination of the chemoresistant clones and the improvement of the antiblastic perfusion, increasing tumoral chemosensitivity[21,22]. The concept of CRS, different from that more widespread of debulking surgery, forecasts the complete removal of the neoplastic implants with the possibility of leaving residual disease with a maximum cut-off value of 2.5 mm, the optimal target for the employment of HIPEC[23]. For this reason and to evaluate the entity of cytoreduction, we utilized the "Completeness of Cytoreduction Score" (CC score) proposed by Sugarbaker[24]: CC-0: no disease; CC-1: residual disease with size < 2.5 mm; CC-2: residual disease with size included from 2.5 mm to 2.5 cm: CC-3: residual disease with size > 2.5 cm or confluence of many tumoral nodules. While CC-0 and CC-1 are deemed optimal results thanks to the "chemical cytoreduction" performed, CC-2 and CC-3 are defined as incomplete cytoreduction. An accurate surgical technique must be combined with a deep knowledge of the modalities of tumoral dissemination inside the peritoneum. In fact, the dissemination of the PSM occurs by parietal and visceral surfaces and, in particular, in the areas where the digestive tract (rectum-sigma, ileocecal valve and gastric antrum) is fixed to the retroperitoneum and peristalsis is less active. This consideration justifies the fact that a complete cytoreduction can also require multivisceral resections.

RATIONALE OF CHEMOHYPERTHERMIA

The development of chemohyperthermia finds its origins in the necessity to exceed the limits of intraperitoneal chemotherapy performed in normothermia, represented by the low penetration of cytotoxic drugs in the context of the neoplastic tissue[25] and by their lack of homogenous distribution caused by the postoperative adhesions. The essential condition for intraperitoneal treatment is the direct instillation of cytotoxic drugs in the peritoneal cavity, leading to an increase in the contact between chemotherapeutic and peritoneum surfaces due to the peritoneal-plasma barrier[26]. In fact, drugs with a high molecular weight containing hydrophilic groups show a slow rate of movement from the peritoneal cavity into the plasma (peritoneal clearance). This consequently leads to a continuous high concentration gradient of chemotherapeutic drugs between the peritoneal cavity and the plasma compartment, with a more uniform distribution of them throughout the abdominal cavity compared to systemic administration. An additional advantage of intraperitoneal chemotherapy administration is that the blood drainage of the peritoneal surface occurs via the portal vein to the liver, providing a detoxifying first-pass effect and an increased exposure of potential hepatic micrometastases to cytotoxic drugs. Certain drugs are also transported through the lymphatics to the systemic circulation and consequently higher drug concentrations in the lymph than in the plasma are achieved. Also, the association of hyperthermia is based on a strict scientific rationale. In fact, the heat, besides having a recognized direct cytotoxic effect, presents a synergistic activity with some chemotherapeutic agents, allowing the following advantages[27]: a greater intracellular accumulation of drugs, a reduction of the repair of CDDP-DNA complexes, a reduction of intracellular drugs detoxification, a reduction of cellular proliferation, an increase of the apoptotic fraction and a greater tissue penetration. Such mechanisms are further amplified by the chaotic structure of the tumoral vascularity that, being in charge of a reduction of the pH and the glucose and oxygen concentrations, leads to a more sensitive microenvironment to the chemohyperthermic action in respect to healthy tissues[28-30].

TECHNIQUE

The surgical act requires an accurate phase of preparation: on the operating table, the patient must be placed in the lithotomy position with the legs abducted at 90° and with the buttock folds advanced to the borders of the operating table, a position that affords a wide access to the perineum. The operating table must be able to preserve a good thermal equilibrium or else it is best practice to utilize a cooling-heating blanket on the patient. Moreover, in the preparation of the patient it is important to insert a bladder catheter with three ways that allows hydrodistention of the bladder during the dissection of the pelvic peritoneum, an essential condition to perform this difficult time. A careful abdominal examination is performed through a laparotomy from the xyphoid to the pubic area, making use of a Thompson or Codman self-retaining retractor. The peritonectomy is performed by an electrosurgical scalpel with a spherical electrode of 2-3 mm (ball-tip electrosurgical hand piece) because the peri-

toneal and visceral resections executed with traditional techniques can scatter a great number of tumoral emboli around inside the abdominal cavity. Furthermore, with the standard dissection it is difficult to obtain a peritoneal surface without cancer cells because only the excision performed with the electrosurgical scalpel leaves a margin of necrosis without vital malignant cells. The electrical burn of the neoplastic and healthy tissue at the level of the resection edges not only reduces the probability of residual disease but also the blood loss. The high-voltage electrosurgical scalpel used on pure cut or spray must be placed on the interface between the peritoneum that must be removed and the healthy tissue. During this type of dissection that leads to tissue carbonization, it is necessary to use a smoke evacuator in order to maintain an optimal vision of the operating field. The aspirator is located 2-3 cm to the dissection field every time that the electrosurgical scalpel is utilized. Cytoreductive surgery is performed through a sequence of manoeuvres well codified[31] that are carried out according to the extent of disease: resection of the greater omentum, right parietal peritonectomy ± resection of right colon; left upper side and left parietal peritonectomy ± splenectomy; right upper side peritonectomy, Glisson's capsule resection, Morrison pouch peritonectomy; lesser omentum resection, hepatic ileus cytoreduction ± cholecystectomy ± total or partial stomach resection; pelvic peritonectomy ± sigmoid resection ± hysterectomy and bilateral annexectomy; other bowel resections and/or tumoral mass resection; bowel anastomosis. Chemohyperthermia begins at the end of cytoreductive surgery with the placement of four or five drains in the abdominal cavity. We use five drains, two for the infusion of liquid, placed in the right subdiaphragmatic region and in pelvic pouch respectively and three for the effusion of liquid, placed in the left subdiaphragmatic region, in the subhepatic space and in the shallow pelvis respectively. Continuous thermal monitoring is performed by six thermometric probes placed at the level of the upper and lower abdomen, in inflow and outflow and at the level of the rectum and esophagus respectively. There are many procedures for intraperitoneal administration of hyperthermic chemotherapy but those most utilized are the closed and open abdomen techniques. In the first option, the skin edges of the abdominal incision are temporarily closed by a continuous suture[32], while in the second one, the skin edges of the laparotomy are covered by a patch of plastic material and a smoke evacuator is placed under the plastic sheet to clear chemotherapy particles that may be liberated during the procedure[33]. After that, the drains are connected to an extracorporeal circuit and in the open abdominal technique the surgeon performs a manual manipulation of the intra-abdominal contents to assure a homogeneous distribution of both chemotherapeutic agents and heat. Hence, the phase of replenishment of the circuit, defined priming, starts with the liquid chosen, on which optimal composition there is still no consensus. The possibilities most utilized are peritoneal dialysis solution[32], saline solution[34] and a solution composed of a ratio of 2 to 1 by Normosol R to pH 7.4 and a plasma volume expander[35]. The volume of liquid used must be sufficiently copious to guarantee a constant and homogeneous heat in the whole peritoneal cavity, without inducing excessive abdominal distension and thermodilution. For a suitable circuit to work, a volume of about 3-4 L is sufficient for the open abdomen technique while, for the closed abdomen technique, a volume of about 6 L[36] is necessary. Therefore, the heating phase of the perfusion begins, using inflow temperature of approximately 44-46 ℃ until a intraperitoneal temperature oscillating from 41 to 43 ℃ is reached when the chemotherapeutic agents are administered (Figure 1). The most commonly used drugs, in mono or poli-chemotherapy, are docetaxel[34], oxaliplatin[12], cisplatin, doxorubicin and mytomicin C[37]. We use cisplatin (25 mg/m² per liter) associated with mytomicin C (3.3 mg/m² per liter) for 60 min in the treatment of colic and gastric carcinomatosis and pseudomyxoma peritonei and cisplatin (43 mg/L) plus doxorubicin (15.25 mg/L) for 90 min in the treatment of the ovarian carcinomatosis and peritoneal mesothelioma. The heated perfusate containing the chemotherapeutic agents is administered in the peritoneal cavity with a medium flow of 600-1000 L/min. At the end of the perfusion, the liquid is quickly drained and, after careful control of the abdominal cavity with particular attention to the possible "suction lesions" of the small intestine, the surgeon proceeds to the definitive closure of the abdominal wall.

In succession, we report the results that we have obtained at our department (unpublished data). The 1-, 3- and 5-year overall survival rate were 96%, 44% and 5% respectively, with a median survival of 33 mo for the whole sample (Figure 2A); for the gastrointestinal sample, the 1-, 3- and 4-year overall survival rate were 100%, 34% and 17% respectively, with a median survival of 30 mo (Figure 2B) and, finally, for the ovarian sample, the 1-, 3- and 5 year overall survival rate were 86%, 57% and 12% respectively with a median survival of 38 mo (Figure 2C).

FUTURE PERSPECTIVES

The peritoneal surface remains an important failure site for patients with abdominal, pelvic or extra abdominal malignancies. During the last two decades, novel therapeutic approaches combining CRS with HIPEC have emerged for peritoneal carcinomatosis patients. This has resulted in remarkable clinical successes in contrast with prior failures. However, there is still a lack of uniformity in the methodology in the interaction and the results between the various operative techniques and intraperitoneal chemotherapies regimens used by various international study groups. In fact, for this reason, a recent international conference was convened and a consensus statement on the appropriate use of CRS and HIPEC was developed and adopted by the Peritoneal Surface Malignancy Group in an attempt to standardize the several procedures for this treatment[37]. However, we

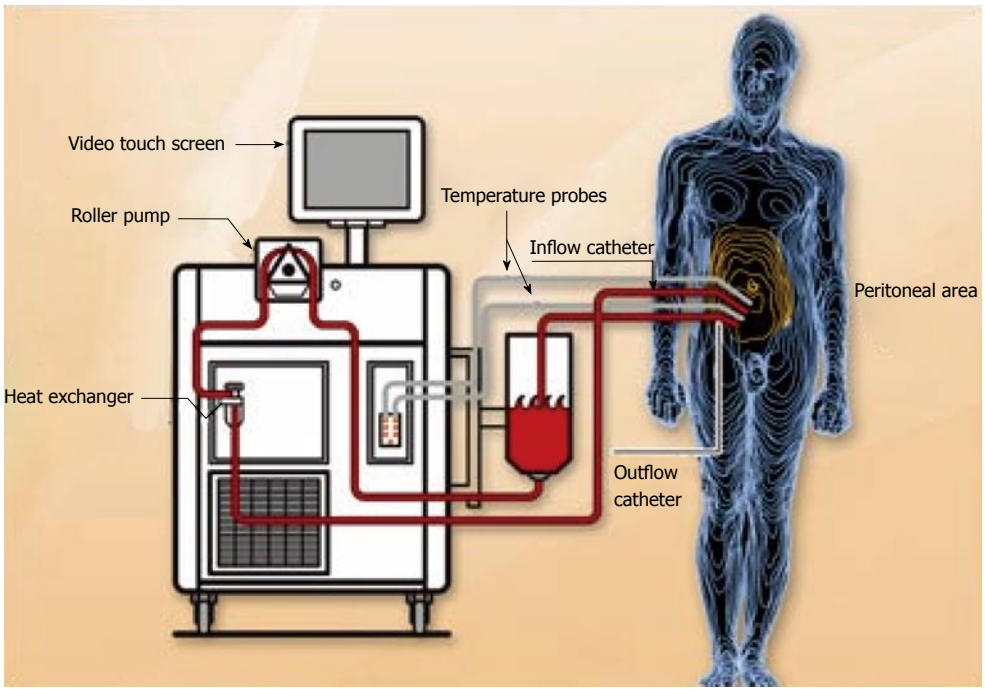

Figure 1 Pattern of hyperthermic intraperitoneal chemotherapy. From the site: www. healthinfoispower.wordpress.com.

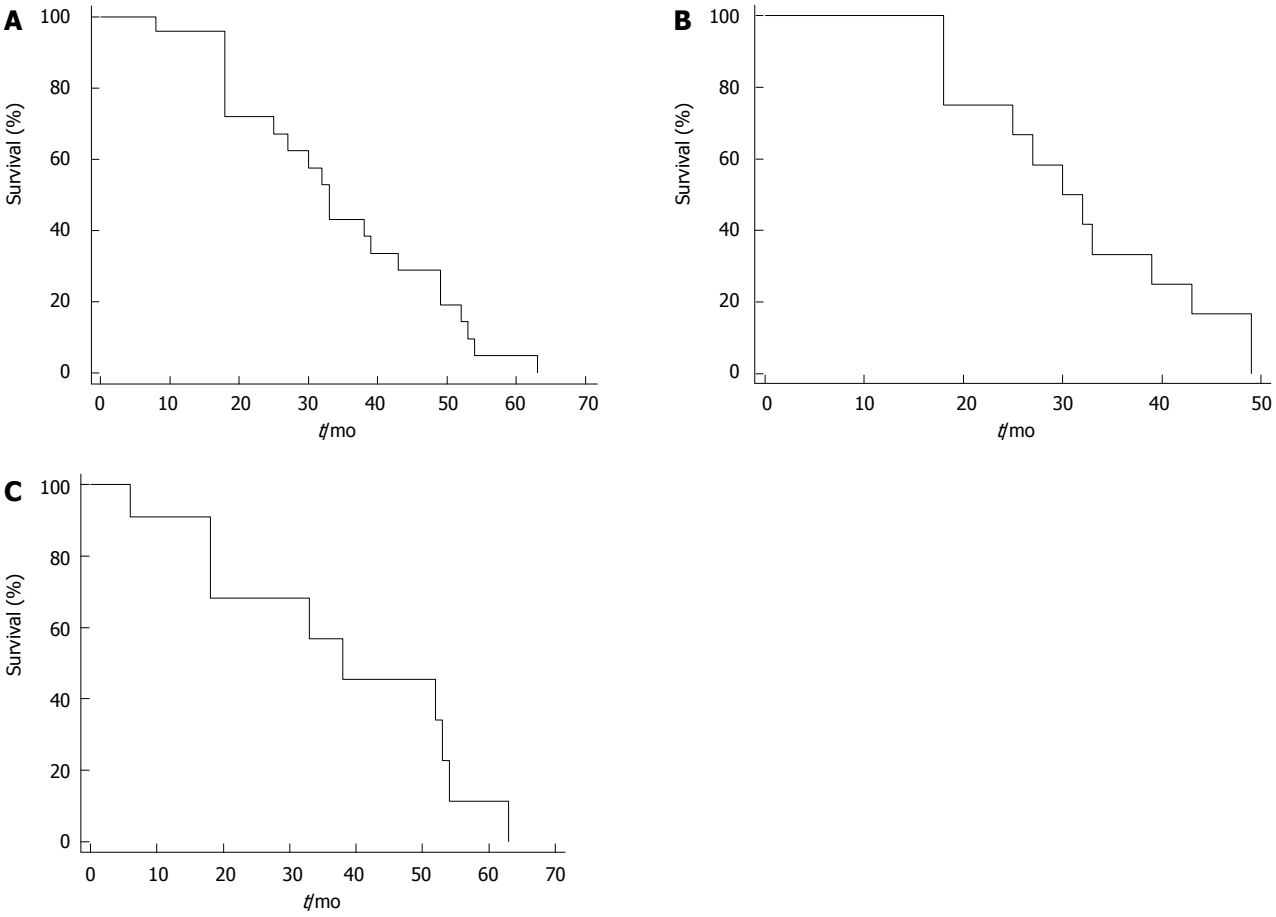

Figure 2 Kaplan-Meier curves. A: Survival probability of patients submitted to cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy; B: Survival probability of gastrointestinal sample; C: Survival probability of ovarian sample.

maintain that is necessary to perform several RCTs to standardize the technique (open or close abdomen), the chemotherapy regimens, the length of time of HIPEC, the temperature, the flow of the heated perfusate and so on. Furthermore, we maintain that other RCTs should be performed in the future concerning the role of the HIPEC after complete cytoreductive surgery in patients with colorectal cancer (CRS plus HIPEC *vs* CRS both followed by best systemic therapy), the role of upfront CRS plus HIPEC for long-term survival in selected patients with advanced stage EOC and finally, the role of upfront CRS plus HIPEC for long-term survival in patients with gastric cancer stage Ⅲ-Ⅳ.

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REVIEW

Predictive role of *XRCC5*/*XRCC6* genotypes in digestive system cancers

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Abstract

Cancers are a worldwide concern; oral, esophageal and gastrointestinal cancers represent important causes of cancer-related mortality and contribute to a significant burden of human health. The DNA repair systems are the genome caretakers, playing a critical role in the initiation and progression of cancers. However, the association between the genomic variations of DNA repair genes and cancer susceptibility is not well understood. This review focuses on the polymorphic genotypes of the non-homologous end-joining DNA repair system, highlighting the role of two genes of this pathway, *XRCC5* and *XRCC6*, in the susceptibility to digestive system cancers and discussing their potential contributions to personalized medicine.

Key words: XRCC5; XRCC6; Polymorphism; Oral cancer; Esophageal cancer; Gastrointestinal cancer; Colorectal cancer

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INTRODUCTION

The human genome is maintained mainly by DNA repair pathways which can sense all kinds of DNA damage and repair them. In the recent literature, six main DNA repair pathways are identified and studied *via* their individual functional assays: (1) direct reversal repair; (2) nucleotide excision repair; (3) base excision repair; (4)homologous repair (HR); (5) non-homologous end-joining (NHEJ); and (6) mismatch repair. Normally, if these repair pathways fail to repair the DNA damage during the cell cycle arrest caused by DNA abnormality, the cell itself can sense the defects as a "threat" and trigger the cell to undergo apoptosis. However, when the DNA damage is not repaired or turned to the induction of cell apoptosis and terminating the unhealthy cell, the DNA defects will be left and propagated to its offspring cells. Under the latter circumstances, cancer will develop step by step. The decreasing of genomic stability in most cancer types and the identification of cancer predisposition syndromes linked to the defects of DNA repair pathways support the concept that DNA repair genes may play critical roles in opposing cancer initiation and progression[1-3].

One of the most deleterious DNA damaging types is

the double strand break (DSB), which should be repaired in eukaryotes by the two major pathways mentioned above: HR and NHEJ. HR is a template guided, error-free pathway predominantly operating in the S and G2 phases of the cell cycle and involves RAD51, RAD51B/C/D, XRCC2/3, and p53, RPA, BRCA1/2, BLM and MUS81[4]. NHEJ, on the other hand, is a potentially less accurate form of DSB repair, in which the two termini of the broken DNA molecule are processed to form compatible ends that are directly joined. In most cases, NHEJ results in the loss of a few nucleotides at the broken ends, making this pathway error-prone. This article discusses the role of XRCC5/XRCC6 (also known as Ku80/Ku70) hetero-dimers in NHEJ; NHEJ is considered to be the major repair pathway of DSBs in eukaryotic cells during the cell cycle[5]. NHEJ involves the XRCC5/XRCC6, XRCC7 (DNA-dependent protein kinase catalytic subunit; DNA-PKcs), Artemis, XLF, XRCC4, DNA ligase 4, ATM, p53 and MDM2 proteins[6,7]. NHEJ deficiencies can lead to increased genomic instability[8,9] and cause increased tumorigenesis[10-13]. However, the exact roles of these genes and their protein products, such as XRCC5 or XRCC6, in each type of cancer are not well investigated or revealed. The model for DSB repair *via* NHEJ and the proteins involved are shown in Figure 1.

XRCC5 and XRCC6 usually form the heterodimer Ku. They are probably the first proteins that bind to the DNA ends of a DSB and the XRCC5/6-DNA complex recruits and activates XRCC7[14,15]. XRCC5/6 dimer and XRCC7 are proposed to act in the synapsis process[14,15]. *XRCC5* and *XRCC6* knockout mice are growth retarded, radiosensitive and are severely immuno-deficient[16,17]. B-cell development is arrested at an early stage due to a profound deficiency in V(D)J recombination, which is commonly employed by vertebrates to generate diversity as an adaptive immune response[16,17]. Although the XRCC5- or XRCC6-deficient mice are viable, their cells have defects in DNA end joining, which manifest as irradiation sensitivity, growth defects, premature senescence and inability to perform end-joining during V(D)J recombination. All these defects may also happen during human embryonic development. A human cell is statistically insulted by hundreds of thousands exogenous and endogenous DNA damage per day, and if the cell does not repair DSB well, the accumulated genomic instability leads the cell to apoptosis and causes the embryonic lethality of the subject. Therefore, there is no doubt that XRCC5 and XRCC6 are very critical in both genomic stability and human carcinogenesis.

Since the *NHEJ* genes play critical and specific roles during the overall process of repairing the DSBs, if any of them fails to finish its job correctly and immediately, the NHEJ capacity will become lower and the overall genomic instability will become higher. It is therefore tempting to speculate that defects in the NHEJ pathway may be associated with the susceptibility of human cancers. Given this, it is puzzling that no direct genetic evidence has been found to link the defective *NHEJ* genes with cancers. Among them, only mutations in two have been found to predispose carriers to a higher rate of genetic diseases, DNA ligase 4 and Artemis, which are associated with Nijmegen breakage syndrome-like syndrome and severe combined immunodeficiency, respectively[18,19]. One explanation is that any severe defects (null mutants) in NHEJ-related genes would result in great genomic instability and might be incompatible with life, thus no cancer cases can be observed in our population. The crucial and irreplaceable roles of these *NHEJ* gene products may also increase the difficulty of approaching their physiological functions via single gene knockout mice models. For this reason, for these high-penetrance NHEJ genes, only subtle defects arising from low-penetrance alleles (e.g., hypomorphic mutant or polymorphic variant) would escape the cell cycle checkpoint surveillance and allow the cell to survive and to accumulate enough unrepaired genomic alterations required for tumor formation[20,21]. Currently, it is a worldwide trend to approach the subtle variations among subjects by the single nucleotide polymorphism (SNP) technique and investigate their association with human diseases.

The aim of this article is to summarize and evaluate the associations between the SNPs of *XRCC5/XRCC6* genes with the susceptibility to four digestive system cancers, including oral, esophageal, gastric and colorectal cancers. Among the digestive cancers, gastric, liver, and esophageal cancers have continued to be among the top five cancers during the past three decades. More interestingly, colorectal cancer is more and more serious in Asia, especially in China Mainland and Taiwan. However, knowledge about the genomic effects on their incidence, prognosis and responses to chemotherapy or radiotherapy is still lacking. In pancreas cancer, genomic studies are lacking due to the difficulty of collection of enough samples. Although the rapid development of genome-wide association studies and bioinformatics indeed do a great favor in revealing the secret of the human genome in cancer, the knowledge of cancer genomics is still far from satisfying and in need of further studies. Therefore, we hope this article can provide some useful markers in oncology for early detection, prevention and anticancer interventions. To this aim, we have summarized the literature in the second section for oral (2.1), esophageal (2.2), gastric (2.3) and colorectal (2.4) cancers and discussed the contribution of these findings to personalized medicine and therapy in the third section.

XRCC5/*XRCC6* POLYMORPHIC STUDIES IN DIGESTIVE SYSTEM CANCERS

Oral cancer

Oral cancer specifically refers to a subgroup of head and neck malignancies that develop at the lips, tongue, salivary glands, gingiva, mouth floor, oropharynx, buccal surfaces and other intra-oral locations. The World Health Organization has estimated oral cancer to be the eighth most common cancer worldwide. As with other upper aerodigestive tract cancers, five-year survival rates for oral cavity

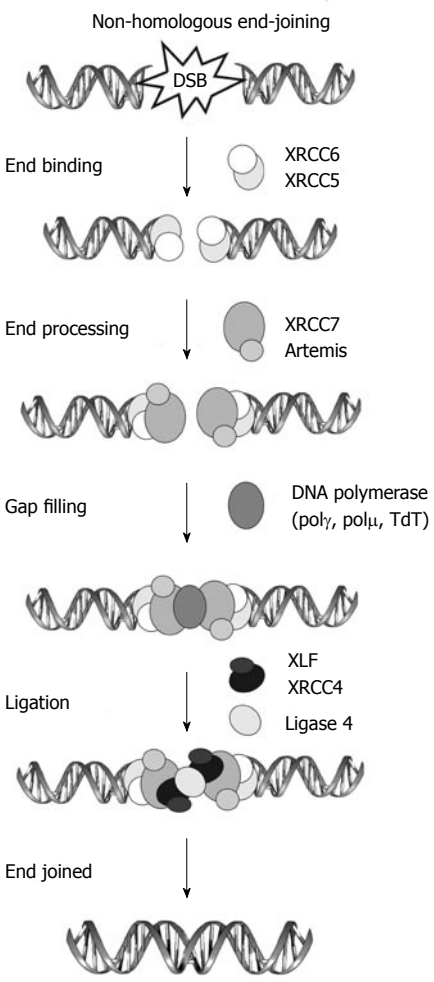

Figure 1 A model for repair of double-strand breaks by non-homologus end-joining.

cancers decrease with delayed diagnosis. Cancers of the oral cavity are thought to progress from premalignant/precancerous lesions, beginning as hyperplastic tissue and developing into invasive squamous cell carcinoma. The most important risk factors for the development of oral cancer in western countries are the consumption of tobacco and alcohol[22,23]. In Asia, chewing betel quid and/or betel nut are responsible for a considerable percentage of oral cancer cases[24,25]. So far, the genomic etiology of oral cancer is of great interest but largely unknown.

In Taiwan, where oral cancer density is the highest in the world, oral cancer is a fatal disease accounting for the fourth highest incidence of malignancy in males and the sixth in females[26]. The relatively high prevalence of oral cancer in Taiwan is mainly because there is a high-risk group of 2.5 million people with the prevalent habits of smoking, alcohol drinking and betel quid chewing. In the literature, there are four papers that investigate the associations of *NHEJ* genes with oral cancer in Taiwan. In 2008, our group found that the C allele of *XRCC6* rs5751129 was a risk marker for oral cancer susceptibility, while those of rs2267437, rs132770 and rs132774 were not[27]. In the next year, we enlarged the investigated population of control/case from 318/318 to 600/600, reporting that *XRCC5* rs828907, but not rs11685387 or rs9288518, was associated with oral cancer susceptibility[28]. People who carried GT and TT genotype at *XRCC5* rs828907 had a 1.6-fold enhanced risk when they also had the habit of betel quid chewing. In addition to *XRCC5* and *XRCC6*, there are two studies that investigated the polymorphic genotypes of *XRCC4* and their association with oral cancer risk in Taiwan[29,30]. These studies reported that the *XRCC4* rs3734091 and rs28360071 genotypes were associated with oral cancer risk. In 2008, a study that investigated Americans with oral premalignant lesions found that there is no association between *XRCC5* rs1051685 genotypes with the susceptibility[31]. The inconsistency can be explained by at least two directions; one, that different populations from different ethnicities were investigated and two, that different SNPs were examined among these studies. The negative findings could not exclude the possibilities that other SNPs of the *XRCC5* may be found to be associated with oral cancer susceptibility. Meanwhile, the positive findings should be verified in an even larger sample size and the functional differences caused by the polymorphic genotypes checked.

Esophageal cancer

Esophageal squamous cell carcinoma (ESCC) is one of the common malignancies with a 5-year survival less than 10%. It is the seventh leading cause of cancer-related deaths in the world[32]. Epidemiologically, it is characterized by a distinctly higher incidence in certain geographical locations, such as China[33]. Smoking tobacco and consuming alcohol are two behavioral factors strongly associated with the risks of both ESCC and esophageal adenocarcinoma[34,35]. ESCC shows a great variation in its geographical distribution and the incidence rates are remarkably higher in distinct high risk areas such as China, Singapore, Iran, France, South Africa, Puerto Rico, Chile, Brazil, northern and eastern Himalayan regions. In 1989, it was thought that the wide geographical variation in the incidence reflects a strong influence of environmental factors[36]. However, recent papers report that the high incidence of ESCC may result primarily from genetic rather than environmental factors which strengthens the importance of continuing to search for the genomic markers for esophageal cancer which are still largely unknown[37-39].

In 2007, Dong and her colleagues recruited 329 esophageal cancer patients and 631 cancer-free controls from China, where esophageal cancer is the fourth leading cause of the cancer death. The risk of esophageal cancer is highly associated with a family history, supporting the concept that genomic effects play an important role in its etiology. Two SNPs of *XRCC5*, C74468A and G74582A (Accession numbers: DQ787434 and DQ787434) were genotyped among the subjects, while no single SNP or combined genotype has been found to be associated with esophageal cancer risk[40]. However, in those subjects with a familial history of esophageal cancer, the C allele of *XRCC5* C74468A seemed to be a protective factor for the incidence[40]. Up to now, there is no report that inves-

tigates the association of *XRCC6* polymorphism with esophageal cancer risk.

Gastric cancer

Gastric cancer is the second most common malignancy and the second most frequent cause of cancer-related death in the world, responsible for approximately 934 000 new diagnoses annually (8.6% of new cancer cases)[41]. Almost two-thirds of cases occurred in Eastern Europe, South America and Asia, with 42% in China alone. In the United States in 2009, an estimated 21 130 new cases (14th most common) of gastric cancer were diagnosed and gastric cancer was responsible for 10 620 deaths (13th most common)[42]. In Europe, gastric cancer ranks as the 5th most prevalent with an estimated 159 900 new cases in 2006 and 118 200 deaths (4th most common cause of cancer-related death)[43].

Now, gastric cancer is still a major health problem worldwide due to its frequency, poor prognosis and limited treatment options. It is often diagnosed in advanced stages and this consequently leads to a poor prognosis. Although the mechanisms of gastric cancer are not yet elucidated, a close relationship between gastric cancer and the provocation, maintenance and modulation of inflammation induced by *Helicobacter pylori* is a well accepted model for gastric carcinogenesis. In addition, high intake of salted, pickled or smoked foods, as well as dried fish and meat and refined carbohydrates significantly increases the risk of developing gastric cancer, while fibers, fresh vegetables and fruit are inversely associated with its risk. However, the genetic factors of gastric cancer are poorly understood.

Dong *et al*[40] found that in those subjects with a familial history of gastric cancer, the C allele of *XRCC5* C74468A seemed to be a protective factor for the incidence. A similar trend was found in the case of esophageal cancer. Also, in those subjects with a familial history of gastric cancer, the A allele of *XRCC5* G74582A seemed to be a protective factor for the incidence, which was not similar to esophageal cancer. Interestingly, as for esophageal and gastric cancer, there is both the similar (C allele of C74468A) and specific (A allele of G74582A) genomic influences from the same *XRCC5* gene. There is no literature investigating and analyzing the association of XRCC6 polymorphism with esophageal cancer risk.

Colorectal cancer

Colorectal cancer is the third most common malignant cancer worldwide. In 2010, an estimated 142 570 new cases of colorectal cancer (CRC) and 21 100 new cases of gastric adenocarcinoma (GA) will be diagnosed in the United States[44]. Noticeably, colorectal cancer remains a significant cause of morbidity and mortality in the United States, Taiwan and throughout the world[45]. Etiological studies have attributed more than 85% of colorectal cancer to environmental factors[46,47] and, in particular, meat consumption, cigarette smoking and exposure to carcinogenic aromatic amines, such as arylamines and heterocyclic amines[48,49]. These carcinogens are thought of as DNA damage inducers responsible for DNA base damage, DNA single-strand breaks and DSBs[50].

In 2009 in Taiwan, where the highest incidence of colorectal cancer is, it was reported that the *XRCC5* rs828907 polymorphism was associated with increased colorectal cancer, while the *XRCC5* rs11685387 and rs9288518 genotypes have no similar association. In people with individual smoking habits, the genomic effect of the *XRCC5* rs828907 on colorectal cancer risk is even more significant with the T allele which can obviously raise the colorectal risk by 2.54-fold. There was no significant joint effect between these genotypes and alcohol drinking on colorectal risk[51]. It is a pity that diet habits, such as meat, vegetable/fruit and fish/shrimp consumption, cannot be clarified due to the incomplete questionnaire information but they have successfully established the relationship between genomic (*XRCC5* genotype) and environmental (smoking habit) factors for colorectal cancer etiology. To date, there is no literature analyzing the association of *XRCC6* polymorphism with colorectal cancer risk or the joint effects of genomic and environmental factors.

CONTRIBUTION OF XRCC5/XRCC6 BIOMARKERS TO PERSONALIZED MEDICINE

In this article, we have reviewed all the associations of *XRCC5* and *XRCC6* genotypes with the susceptibilities for digestive system cancers in the literature, summarizing the highlights of them concisely (Table 1). Generally speaking, individual cancer susceptibility is determined by three groups of factors: lifestyle/environmental factors, genetic/genomic factors and age/gender factors. Among the three, the effects of lifestyle/environmental and age/gender factors may influence somatic cells as genomic and epigenomic damage, which can be altered during the life span. However, the genomic/genetic factors confer a step-by-step but complicated and multi-pathway development of carcinogenesis. Clinical observations suggest that individuals may exhibit dramatic differences in their responses to therapies and drugs and that these variations could be inherited[52,53]. SNPs could serve as not only as the genomic markers, but also the biomarkers in charge of personal cancer susceptibility. These SNPs in the human genome contribute to wide variations in how individuals respond to clinical medications, either by changing the pharmacokinetics (absorption, distribution, metabolism and elimination) of anticancer drugs or by altering the cellular response to therapeutic agents such as radiotherapy.

As shown in Table 1, cancer molecular epidemiologists are devoted to describing subtle differences among subjects in the distribution of genetic SNPs that affect DNA-repair enzymes, drug-metabolizing enzymes, cell-cycle controlling proteins, oncogenes, tumor suppression genes and cellular transporters of cytotoxic chemotherapy to reveal the overview of carcinogenesis. In this re-

Table 1 Summary of the associations for digestive cancers and the polymorphic genotype of XRCC5 and XRCC6 genes

Cancer	Author	Gene	rs number	Location	Study subjects				
					Ethnic area	Cases	Controls	Statistical significance	Brief description
Oral cancer	Hsu[28]	*XRCC5*	828907	Promoter	Taiwan	600	600	S	Allele C is of higher risk
			11685387	Promoter				NS	
			9288518	Intron 19				NS	
	Bau[27]	*XRCC6*	5751129	Promoter	Taiwan	318	318	S	Allele T is of higher risk, and interacted with betel quid chewing habits
			2267437	Promoter				NS	
			132770	Promoter				NS	
			132774	Intron 3				NS	
Esophageal cancer	Dong[40]	*XRCC5*	Accession number: DQ787434[1]	Intron16	China mainland	329	631	S	Allele A is of higher risk
			Accession number: DQ787434[1]	Intron16				NS	
Gastric cancer	Dong[40]	*XRCC5*	Accession number: DQ787434[1]	Intron16	China mainland	255	631	S	Allele A is of higher risk
			Accession number: DQ787434[1]	Intron16				S	Allele G is of higher risk
Colorectal cancer	Yang[51]	*XRCC5*	828907	Promoter	Taiwan mainland	362	362	S	Allele T is of higher risk, and interacted with smoking habits
			11685387	Promoter				NS	
			9288518	Intron 19				NS	

[1]Accession number was provided instead for the rs number is not available. S: Statistically significant; NS: Not statistically significant.

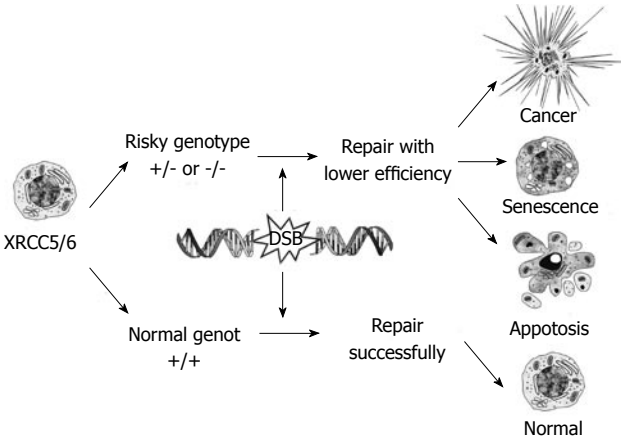

Figure 2 Hypothesis of the XRCC5/XRCC6 genotypic control over the fate of cells.

view, we focus on summarizing the state-of-the-art studies of *XRCC5* and *XRCC6* genes, which are upstream and specifically critical in NHEJ, and their contribution to digestive system cancers. Although currently the hypothesis-free genome-wide association studies (GWAS) are largely applied to studies including cancer research, knowledge about the associations of specific genotypes with specific cancers is still limited and in urgent need. The contributions of the SNPs listed here in Table 1 to other human cancers and cancer-related diseases, and their functional biological meanings to carcinogenesis, all need further investigations. Meanwhile, they may serve as candidate targets pharmacogenomically for the development of personalized anticancer drugs. The hypothesis of how the *XRCC5/XRCC6* genotypes control the fate of cells after DSB insults is shown in Figure 2.

Some DNA repair genes in the DNA repair pathways, such as *XRCC4* in NHEJ[54], *MGMT* in direct removal pathway[55,56], *XRCC1* in base excision repair[57], *ERCC1* and *ERCC2* in NER[58,59], *hMSH2* in mismatch repair[57] and *hHR21* in HR[58], are all thought to be anticancer candidate targets. From now on, *XRCC5/XRCC6* may be added to the list above. It should be also noted that anticancer drugs may induce DSBs itself in the feasibility of chemotherapy. On the other hand, co-treatments of DNA-damaging agents and radiation have a central role besides other cancer treatment modalities. The balance between DNA damage and capacity of DNA repair mechanisms determines the final therapeutic outcome. The capacity of cancer cells to complete DNA repair mechanisms is important for therapeutic resistance and has a negative impact upon therapeutic efficacy. Pharmacological inhibition of recently detected targets of DNA repair with several small-molecule compounds, therefore, has the potential to enhance the cytotoxicity of anticancer agents. Futami and his colleagues also discovered that inhibition of the expression of various genes associated with chromosome stabilization induces cancer cell-specific apoptosis and inhibits cell proliferation[60].

In this article, most of the studies are case-control investigations in one or two ethnic groups. The inconsistency of choosing the SNPs and the insufficient sample size limits the multiple comparisons of human populations around the world. Further incorporations among populations and integrations of genotype-phenotype relationship analysis, population-based tissue and blood functional measurements, clinical outcome records, especially those in chemo- and radiotherapy responses, are

in urgent need for international studies on inter-ethnic variations, using these pharmacogenomic biomarkers. The integration of pharmacogenomic, phenotypic and pathological biomarkers, is the main stream in the development of cancer risk prediction, personalized medicine and therapy evaluation.

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Events Calendar 2011

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011, San Francisco, CA, United States

January 27-28, 2011
Falk Workshop, Liver and Immunology, Medical University, Regensburg, Germany

February 17-20, 2011
APASL 2011-The 21st Conference of the Asian Pacific Association for the Study of the Liver, Bangkok, Thailand

February 21-21, 2011
International Conference on Modern Cancer Management-Joint Symposium, Abuja, Nigeria,

February 26-March 1, 2011
Canadian Digestive Diseases Week, Westin Bayshore, Vancouver, British Columbia, Canada

March 11-12, 2011
First Integrative Care for the Future: The future of cancer care, Arnhem, The Netherlands
http://www.integrativecareftfuture.org/

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011, Birmingham, England, United Kingdom

March 24-25, 2011
Advanced Cancer Course "International Clinical Trials Workshop", Punta del Este, Uruguay

April 6-7, 2011
IBS-A Global Perspective, Milwaukee, WI, United States

April 6-8, 2011
Third Latin American Symposium on Gastrointestinal Oncology-Chilean Foundation for Oncology Development Joint Symposium, Vina Del Mar, Chile

April 15-16, 2011
Falk Symposium 177, Endoscopy Live Berlin 2011 Intestinal Disease Meeting, Maritim Hotel Berlin, Stauffenbergstr. 26, 10785 Berlin, Germany

April 20-23, 2011
9th International Gastric Cancer Congress, COEX, World Trade Center, Samseong-dong, Gangnam-gu, Seoul 135-731, South Korea

May 8-12, 2011
ESTRO International Oncology Forum, London, United Kingdom

May 19-22, 2011
1st World Congress on Controversies in the Management of Viral Hepatitis (C-Hep), Palau de Congressos de Catalunya, Barcelona, Spain

May 25–27, 2011
9th CIMT Annual Meeting, Targeting Cancer, Road-Maps for Success, Mainz, Germany

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Sarajevo, Bosnia and Herzegovina

June 3-7, 2011
2011 ASCO Annual Meeting, Chicago, IL, United States

June 18-24, 2011
13th Joint ECCO-AACR-EORTC-ESMO Workshop on "Methods in Clinical Cancer Research", Flims, Switzerland

June 22-25, 2011
ESMO 13th World Congress on Gastrointestinal Cancer, Barcelona, Spain

July 9-10, 2011
Best of ASCO China, Hengzhou, China

July 21-23, 2011
ASCO-JSMO Joint Symposium, Yokohama, Japan

August 25-28, 2011
VII Peruvian Congress SPOM: Toward personalized Oncology-Endorsement, Lima, Peru

September 2-3, 2011
Falk Symposium 178, Diverticular Disease, A Fresh Approach to a Neglected Disease, Martinstr. 29-37, 50667 Cologne, Germany

September 10-14, 2011
ICE 2011-International Congress of Endoscopy, Los Angeles Convention Center, 1201 South Figueroa Street, Los Angeles, CA, United States

September 15-17, 2011
2011 Gastrointestinal Oncology Conference, Sheraton Crystal City, Arlington, VA, United States

September 30-October 1, 2011
Falk Symposium 179, Revisiting IBD Management: Dogmas to be Challenged, Place Rogier 3, 1210 Brussels, Belgium, Germany

October 6-7, 2011
IV InterAmerican Oncology Conference: Current Status and Future of Anti-Cancer Targeted Therapies, Buenos Aires, Argentina

October 14-15, 2011
New Trends in the Medical Treatment of Solid Malignancy-Romanian Society for Medical Oncology Joint Symposium, Bucharest, Romania

October 27-29, 2011
EORTC-NCI-ASCO Annual Meeting on Molecular Markers in Cancer, Brussels, Belgium

November 11-12, 2011
Falk Symposium 180, IBD 2011: Progress and Future for Lifelong Management, 1-12-33 Akasaka, Minato-ku, Tokyo 107-0052, Japan

November 30-December 3, 2011
8th International Cancer Conference "Entering the 21st Century for Cancer Control in Africa"-African Organization for Research and Training in Cancer Joint Symposium, Cairo, Egypt

World Journal of Gastrointestinal Oncology

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Acknowledgments

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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

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Write as mean ± SD or mean ± SE.

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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).

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