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TOPIC HIGHLIGHT

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Potential prognostic, diagnostic and therapeutic markers for human gastric cancer

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Abstract

The high incidence of gastric cancer (GC) and its consequent mortality rate severely threaten human health. GC is frequently not diagnosed until a relatively advanced stage. Surgery is the only potentially curative treatment. Thus, early screening and diagnosis are critical for improving prognoses in patients with GC. Gastroscopy with biopsy is an appropriate method capable of aiding the diagnosis of specific early GC tumor types; however, the stress caused by this method together with it being excessively expensive makes it difficult to use it as a routine method for screening for GC on a population basis. The currently used tumor marker assays for detecting GC are simple and rapid, but their use is limited by their low sensitivity and specificity. In recent years, several markers have been identified and tested for their clinical relevance in the management of GC. Here, we review the serum-based tumor markers for GC and their clinical significance, focusing on discoveries from microarray/proteomics research. We also review tissue-based GC tumor markers and their clinical application, focusing on discoveries from immunohistochemical research. This review provides a brief description of various tumor markers for the purposes of diagnosis, prognosis and therapeutics, and we include markers already in clinical practice and various forthcoming biomarkers.

Key words: Tumor marker; Prognosis; Gastric cancer; Serum-based; Tissue-based

Core tip: Serum-based gastric cancer tumor markers and their clinical significance or application are discussed. Serum-based carcinoembryonic antigen, carbohydrate antigen 19-9 and carbohydrate antigen 72-4 and tissue-based human epidermal growth factor receptor 2/Neu are potential tumor markers for various types of gastrointestinal cancer. This review provides a brief description of various tumor markers for the purposes of diagnosis, prognosis and therapeutics, and we include markers already in clinical practice and various forthcoming biomarkers. Hopefully, based on the markers, we will generate accurate diagnoses, prognoses and select the most appropriate therapy.

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INTRODUCTION

Gastric cancer (GC) is the second most common cancer worldwide and the sixth leading cause of tumor-associated death in Taiwan. However, the pathogenic mechanisms underlying GC tumorigenesis remain unknown[1]. Surgery continues to be the only curative treatment for GC. In a recent study, more than 30% of surgical patients who presented with GC were too advanced for curative resections. To improve the low survival outcome and assist in the earlier diagnosis of specific tumor types, new prognostic and/or therapeutic tumor markers are required[2]. Indeed, the identification of novel tumor markers presents a new approach for the early screening of populations and for GC therapy.

In this review, we focus primarily on gastric adenocarcinomas. Based on Lauren's classification, "intestinal-differentiated" (I-GC) and "diffuse-undifferentiated" (D-GC) are two histomorphologic GC subtypes[3,4]. Although these subtypes show related histomorphologic lesions, the tumor cells may contrast in their aggressiveness or response to chemotherapy[5]. The molecular actions involved in the progression of GC are multipart and involve multiple genes and steps that operate sequentially or in concert[4]. Several risk factors for GC, including *Helicobacter pylori* (*H. pylori*) infection, genetic alterations, and chromosomal instability, have been reported[6-8]. The identification of various tumor markers has also added to our basic knowledge of molecular and cellular mechanisms of GC tumorigenesis and progression[8]. The majority of tumor markers are effective prognostic tools that are used to identify groups of patients at risk of relapse or metastasis or to monitor cancer survivors following treatment[9]. However, suitable tumor markers to expose the molecular mechanisms of GC or monitor disease development are critical.

Cancer may increase tumor markers in blood or body tissues. There are numerous and varying tumor markers for specific disease processes, which are used to aid in the diagnosis of cancer. An increase in a particular biomarker may indicate cancer. However, there may also be other underlying causes. Tumor markers may be produced directly by cancer cells or by non-cancer cells responding to the tumor. In summary, the diagnostic assay should include gastroscopy with biopsy. Thus, tumor markers are not optimal for screening for GC on a population basis, and as diagnostic assays, they show poor sensitivity and specificity. Assays based on multiple tumor markers will provide more exact results[10]. Thus far, assays based on multiple tumor markers are helpful only as prognostic indicators in patients with GC to monitor cancer survivors following treatment[11-15]. Recently, many studies have been performed using microarrays/proteomics, and they have reported new markers with potential clinical significance in patients with GC. In this paper, we review the progress in serum-based tumor markers associated with GC, focusing on discoveries from microarray/proteomics research[16-20]. The most widely investigated serum-based tumor markers for GC are listed in Table 1.

CARCINOEMBRYONIC ANTIGEN

Carcinoembryonic antigen (CEA) is a cell-surface-anchored protein involved in cell-cell adhesions. CEA serves as a functional receptor for colon cancer E-selectin and L-selectin ligands, which may be critical for the metastatic spreading of colon cancer cells[21,22]. Serum from individuals with colon cancer often shows higher levels of CEA than that from healthy controls. CEA from serum is primarily used as a biomarker to monitor colon cancer treatment, to identify recurrences following surgical resection and to stage or localize cancer spread[23].

CEA levels may also be raised in other cancer types and in some non-neoplastic conditions. Several factors may influence increases in CEA. It is associated with tumor grade, lymph node metastasis, distant metastasis and tumor stage, suggesting that as the tumor progresses, CEA levels increase[24].

Anti-CEA antibodies are also frequently used in IHC to identify cells expressing CEA in tissue samples. In adults, CEA is expressed only in cancer cells, primarily adenocarcinomas. It can therefore be used to distinguish between this and other similar types of cancers. Because even anti-CEA antibodies tend to show some degree of cross-reactivity, false positive results are observed, and this assay is typically used in combination with other tests[25].

CARBOHYDRATE ANTIGEN 19-9

In 1981, carbohydrate antigen 19-9 (CA19-9) (also called the Lewis antigen) was first discovered in the serum of individuals with colon or pancreatic cancer. However, CA19-9 is used primarily in the management of pancreatic cancer. CA19-9 may be increased in many types of gastrointestinal cancer[26].

CARBOHYDRATE ANTIGEN 72-4

Carbohydrate antigen 72.4 (CA72.4) is a mucin-like glycoprotein found on the surface of many cancer cells[27]. CA72.4-Ab assay shows good specificity for GC and is used to identify GC relapses and for follow-up after treatment[28].

CYTOKERATIN SUBUNIT 19 FRAGMENT, TISSUE POLYPEPTIDE ANTIGENAND TISSUE POLYPEPTIDE-SPECIFIC ANTIGEN

Cytokeratin subunit 19 fragment (Cyfra21.1) is potentially useful for monitoring lung carcinoma. It is a member of the keratin family. The keratins are intermediate filament proteins responsible for the structural integrity of epithelial cells and are grouped into cytokeratins and hair keratins. Cyfra21.1 has been suggested to play a role in lung, colon, stomach, pancreas, breast, and prostate cancers. Cyfra21.1 is the most sensitive tumor marker for non-squamous cell lung cancer. Because Cyfra21.1 detects

Table 1 Serum-based tumor markers in gastric cancer

Biological category	Biomarker (Gene name)	Cutoff level /Expression levels in human GC serum	Clinical significance	Associated tumor types	Ref.
Oncofetal antigen	*CEA*	5 μg/L	Prognosis GC progression monitoring	Gastrointestinal cancer Cervix cancer Lung cancer Ovary cancer Breast cancer Urinary tract cancer	[24,25]
Glycoprotein antigen	*CA19.9*	37 kU/L	Prognosis GC progression monitoring	Mainly pancreatic cancer but also colorectal cancer other types of gastrointestinal cancer	[26]
	CA72.4	6 kU/L	Prognosis GC progression monitoring	Ovary cancer Breast cancer Colon cancer Pancreatic cancer	[27]
Cytokeratins	*Cyfra21.1*	Variable	Prognosis	Many types of carcinoma Some types of sarcoma	[29]
	TPA	Variable	Prognosis	Carcinoma	[30]
	TPS	Variable	Prognosis	Adult epithelial tumours	[30]
Hormone	*B* subunit of *h*CG	4 μg/L	Prognosis	Seminoma Choriocarcinoma Germ cell tumors Choriocarcinoma Islet cell tumor Testicular cancer	[31]
Cell proliferation	*Reg Ⅳ*	Overexpression	Prognosis	Gastrointestinal malignancies	[33,34]
	Granulin	Overexpression	Prognosis	Gastrointestinal malignancies	[35,36]
Signaling protein	*14-3-3 protein*	Downexpression	Prognosis	Epithelial cancer Lung cancer Breast cancer Bladder cancer Liver cancer Oral cancer Head-and-neck squamous cell cancer	[40-42]
	DKK-1	Overexpression	Prognosis	Prostate cancer Breast cancer Colon cancer Esophageal cancer Lung cancer Multiple myeloma (MM)	[43-49]
Inflammatory	*SAA*	Overexpression	Prognosis	Lung cancer Kidney cancer Colon cancer Prostate cancer Liver cancer	[50,52,53]
Cell apoptosis	*MG7-Ag*	Overexpression	Prognosis	Gastrointestinal cancer	[55,56]
Enzyme	*PG*	Overexpression	Prognosis	Gastrointestinal cancer	[57]

CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4; Cyfra21.1: Cytokeratin subunit 19 fragment; TPA: Tissue polypeptide antigen; TPS: Tissue polypeptide-specific antigen; β-hCG: β-subunit of human chorionic gonadotropin; Reg Ⅳ: Regenerating gene Ⅳ; Dkk-1: Dickkopf-1; SAA: Serum Amyloid A; MG7-Ag: Gastric cancer associated antigen; PG: Pepsinogens.

only fragments of cytokeratin 19, the test shows higher specificity than tissue polypeptide antigen (TPA) and is an independent prognostic factor[29].

The TPA tumor marker comprises a molecular complex of cytokeratins 8, 18, and 19. It is used in the diagnosis and staging of bronchogenic cancer. TPA assays represent first-generation cytokeratin tumor marker tests.

Although tissue polypeptide-specific antigen has been reported to be a potentially useful serum marker in adult epithelial tumors, few reports have been published on childhood malignancies. Currently, there is no widely used marker for Wilms' tumor[30].

β-SUBUNIT OF HUMAN CHORIONIC GONADOTROPIN

β-subunit of human chorionic gonadotropin (β-hCG) is a hormone formed by the syncytiotrophoblast, a component of the fertilized egg, following conception. Following grafting, the syncytiotrophoblast gives rise to the placenta. Some tumors produce β-hCG; thus, elevated levels in individuals who are not pregnant may indicate cancer. However, whether β-hCG production promotes carcinogenesis remains unknown.

β-hCG may be used as a tumor marker as its β sub-

unit is secreted by some tumors. Based on this reason, a positive result in males indicates testicular cancer. Combined with α-fetoprotein, β-hCG is a good tumor marker for monitoring of tumors of germ cells[31].

REGENERATING GENE Ⅳ

Regenerating gene Ⅳ (*Reg Ⅳ*) belongs to the regenerating family of secreted C-lectin proteins[32]. Reg proteins are expressed normally in the gastrointestinal tract and are induced in inflammatory bowel disease and in some gastrointestinal malignancies. They show multiple functions including enhancing tissue regeneration, proliferation and are anti-apoptotic[33]. Reg Ⅳ is expressed at low levels in a subgroup of primary tumors and is moderately or highly expressed in a majority of hormone refractory and metastatic tumors[34].

GRANULIN

Granulins are a family of secreted, glycosylated peptides that are cleaved from a single precursor. Both the peptides and the intact granulins regulate cell growth. However, different members of the granulin family may act as inhibitors, activators, or show dual roles in cell growth. The granulin family is important for normal development, wound healing, and in tumorigenesis[35]. In addition, the human liver contributes to the development of liver cancer by secreting a granulin-like growth hormone[36].

14-3-3 PROTEINS

14-3-3 proteins, which belong to a family of regulatory proteins, are able to bind a multitude of signaling proteins of various functions, such as kinases, phosphatases, and transmembrane receptors. More than 200 signaling proteins have been reported as being ligands for 14-3-3 proteins[37,38].

Alterations in the expression of several 14-3-3 proteins have been associated with some human cancers. The down-regulation of 14-3-3r has been reported in a multitude of human epithelial cancers. Recently, Urano *et al*[39] showed that breast cancer cells reduced 14-3-3r protein levels by upregulating the protein Efp, a ring-finger-dependent ubiquitin ligase (E3), which targets 14-3-3r for ubiquitin-mediated degradation by the proteosome. MCF7 cells treated with antisense Efp constructs showed increased levels of 14-3-3r, and athymic mice transplanted with these cells showed decreased tumors. Similar trends of cancer-associated downregulation of 14-3-3r have been reported in human lung cancer, vulva squamous neoplasias, bladder cancer, liver cancer, oral cancer, and head-and-neck squamous cell cancer, suggesting a common role for 14-3-3r as a tumor suppressor[40-42].

DICKKOPF-1

Dickkopf-1 (DKK1) inhibits Wnt/β-catenin signaling, which is essential for embryonic head development. DKK1 regulates Wnt signaling by binding to the Wnt coreceptor lipoprotein-related protein-5 (LRP5). Overexpression or down-regulation of *DKK1* gene expression levels has been observed at various stages of tumorigenesis in multiple cancers, such as breast, colorectal, prostate, esophageal, lung cancers, and multiple myeloma (MM). Thus, DKK1 play dual roles as an oncogene or tumor suppressor. Serum from individuals with breast cancer and bone metastases showed significantly higher DKK1 levels compared with healthy individuals. In addition, human primary lung and esophageal cancers, lung cancer cell lines, and esophageal cancer cell lines show increased DKK1 expression. However, DKK1 protein expression was also down-regulated in colon cancer and melanoma[43-49]. Qian *et al*[44] reported that DKK1 protein expression was detected in the majority of MM cell lines and clinical MM samples.

SERUM AMYLOID A PROTEIN

Serum amyloid A (SAA) proteins combined with the high-density lipoprotein (HDL) complex belong to a family of apolipoproteins that are secreted during the acute phase of inflammation[50]. There are three isoforms of SAA. SAA (SAA1 and SAA2) levels are consistently increased in the liver during acute inflammation, and SAA3 is induced in various distinct tissues[50,51].

SAA are not specific for any type of cancer and are expected to be elevated in other malignant diseases and in inflammatory diseases[52,53]. Cho *et al* observed that SAA had previously been reported to increase in several different cancers including kidney, colon, prostate cancers, leukemias and lymphomas. However, these proteins are released into the blood from the liver. These findings suggest that these proteins may not be of much clinical significance in our future efforts to more effectively diagnose and monitor cancer[50].

GASTRIC CANCER ASSOCIATED ANTIGEN (MG7-AG)

Akashi *et al*[54] produced a MG7-Ag monoclonal antibody to use for GC screening. Using the immuno-polymerase chain reaction (Immuno-PCR) assay, the authors observed that MG7-Ag had the highest sensitivity and specificity for detecting GC. They tested serum MG7-Ag levels and found that the rate of MG7-Ag positivity was 82.8% for GC in 198 GC patients and 44.4% for colonic cancer. However, the Immuno-PCR assay is too complicated and expensive for screening the high-risk population in Linqu county. Therefore, they used an ELISA to detect MG7-Ag expression in serum from patients with GC or other carcinomas. They also used IHC to test MG7-Ag expression in GC tissues[55,56].

PEPSINOGENS

There are three genes that encode human pepsinogen A.

A fourth human gene encodes gastricsin, also known as pepsinogen C, a digestive enzyme. Gastricsin is an aspartic proteinase that belongs to the A1 peptidase family and is produced in the stomach; it constitutes a major component of the gastric mucosa. Gastricsin is secreted into the serum and is synthesized as an inactive zymogen that includes a highly basic prosegment. Gastricsin is converted into its active mature form at low pH by serial cleavage of the prosegment, performed by the enzyme. Polymorphisms in gastricsin are associated with susceptibility to GC. Serum levels of the enzyme have been identified as tumor markers for specific GCs and *H. pylori*-associated gastritis[57].

Tumor markers may also be detected using IHC. Although IHC remains the most reliable and cheapest method, several efforts have been made to identify and test novel tumor markers to achieve the prognosis goals. In recent years, many proteins have been identified and validated for their clinical significance in the management of GC. The most widely investigated tissue-based tumor markers for GC and the most correlated clinical parameters are listed in Table 2.

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2/NEU

Human epidermal growth factor receptor 2/neu (HER2/neu) is a well-known oncogene. HER2/neu belongs to a member of the epidermal growth factor receptor family and plasma membrane-bound receptor tyrosine kinases. Overexpression of this oncogene has been shown to play an important role in the tumorigenesis of aggressive types of breast cancer. Thus, the protein has become an important tumor marker and target of therapy for over 30% of patients with breast cancer. It is positively associated with increased breast cancer recurrence and poor prognosis. Overexpression of HER2/neu has also been reported in ovarian, stomach, uterine and endometrial cancers. Dimerization results in the autophosphorylation of tyrosine residues within the cytoplasmic domain of the receptors and initiates a variety of signaling pathways.

IHC is used to measure levels of HER2/neu protein in samples. Fluorescence *in situ* hybridization (FISH) assays may also be used to measure whether HER2/neu gene amplification has occurred. The extracellular domain of HER2 may be shed from the surface of tumor cells and enter the circulation. Testing serum for HER2 using enzyme-linked immunosorbent assay (ELISA) offers a method for determining HER2 levels. Changes in serum HER2 concentrations may be useful in predicting response to trastazumab treatment[58-63].

VASCULAR ENDOTHELIAL GROWTH FACTOR

Vascular endothelial growth factor (VEGF) is an angiogenic factor. It is a signaling protein secreted by many solid tumors. VEGF overexpression has been reported in many human cancer cells including breast, colon, gastric, liver and lung cancers. It is also expressed in stromal cells, particularly at sites of relative hypoxia. VEGF enhances endothelial cell proliferation and migration and induces endothelial cell angiogenesis. VEGF is also called vascular permeability factor. Thus, VEGF increases vascular permeability to plasma and its proteins, a typical requirement of tumor microvasculature. IHC and ELISA are popular methods used to examine expression patterns of VEGF in serum and tissues from cancer patients[64-68].

HUMAN ETHER-À-GO-GO-RELATED GENE

Human ether-à-go-go-related gene (hERG1) belongs to the K^+ channel family, which may regulate cell apoptosis and proliferation. Overexpression of this protein has been observed in several tumors, such as primary human endometrial, gastric and colorectal cancers. *hERG1* gene expression has been used as a specific tumor marker in colon cancer, and it regulates the invasion of tumor cells[69].

KRUEPPEL-LIKE FACTOR 5 (KLF5/IKLF/BTEB2)

KLF5/IKLF/BTEB2 is a member of the Kruppel-like transcription factor family. Several members of the KLF family have been implicated in the development of human cancers[70]. KLF5 repeatedly shows genetic deletions and decreased expression in human prostate and breast cancers[71,72]. KLF5 also plays a suppressive role in tumor growth in colon cancer. However, overexpression of KLF5 activated fibroblast cell growth and tumorigenesis. KLF5 has also been reported to affect H-Ras, Wnt-1, platelet-derived growth factor A chain (PDGF), cyclin D1, PPARg and ERBB2 oncogenes[73]. Moreover, several growth factors, such as PMA, sphingosine-1-phosphate, and β-FGF, induce the expression of KLF5. Furthermore, KLF5 has been reported to promote angiogenesis in a knock-out mouse model. In a bladder cancer cell line, KLF5 was reported to inhibit cell growth. These findings suggest that the actual role of KLF5 in tumorigenesis remains unknown[74].

SPECIAL AT-RICH SEQUENCE-BINDING PROTEIN-1

Special at-rich sequence-binding protein-1 (SATB1) is an AT-rich sequence-binding protein 1 and gene regulator. It functions as a genome organizer. SATB1 is highly expressed in many types of human cancers including breast, gastric, colon and bladder carcinomas. It enables tumor growth and metastasis by altering the expression of a large number of genes[75-78].

C-MYC2

c-Myc protein is a transcription factor that activates and represses the expression of many genes. In addition,

Table 2 Tissue-based tumor markers in gastric cancer

Biological category	Biomarker (Gene name)	Parameters	Clinical significance	Associated tumor types	Ref.
Receptor	*HER2/neu*	Lauren histotype Lymph node metastasis	Prognosis Therapeutic response	Ovarian cancer Stomach cancer Uterine cancer Endometrial cancer Breast cancer Esophageal cancer	[58-63]
	VEGF	Lauren histotype Tumor progression	Prognosis Therapeutic response	Breast cancer. Colon cancer Gastric cancer Liver cancer Lung cancer	[64-68]
Ion channel	*hERG1*	Lauren histotype Grading Stage	Prognosis	Endometrial cancer Gastric cancer Colorectal cancer	[69]
Transcription factor	*KLF5/IKLF/BTEB2*	Grading Stage Lymph node status	Prognosis	Bladder cancer Prostate cancer Breast cancer Colon cancer	[71,72]
	SATB1	Lymph node metastasis Distant metastasis Stage	Prognosis	Breast cancer Gastric cancer Colon cancer Bladder cancer	[75-78]
	c-myc2	Lymph node metastasis	Prognosis	Cervix cancer Colon cancer Breast cancer Lung cancer Stomach cancer	[80]
Enzyme	*CA IX*	Lymph node metastasis	Prognosis	Kidney cancer Colon cancer Cervical cancer	[81-83]
	MMP-2	Stage Survival	Prognosis	Ovarian cancer Colon cancer Breast cancer Bladder cancer Gastric cancer	[79,80,84,85]
	HDAC	Lymph node metastasis Survival	Prognosis	Renal cancer Colorectal cancer Gastric cancer Breast cancer Pancreatic cancer Liver cancer Lung cancer Prostate cancer Hodgkin's lymphoma	[86-92]
	COX-2	Lymph node metastasis Survival	Prognosis	Breast cancer Intestinal tract cancer	[93,94]
	SLPI	Depth of invasion Serosal invasion Lymph node metastasis Stage	Prognosis	Ovan cancer Cervical cancer Gastric cancer	[96,97]
	GLO1	Depth of invasion Serosal invasion Lymph node metastasis Stage	Prognosis	Colon cancer Breast cancer Prostate cancer Gastric cancer Melanoma cancer	[99-103]
Cell growth	*Ki-67*	Lymph node metastasis	Prognosis	Prostate cancer Brain cancer Breast cancer Nephroblastoma	[104]
	TGF-β	Stage	Prognosis	Breast cancer Gastric cancer	[105,106]
Signal Protein/cell adhesion	*PKP3*	Stage	Prognosis	Gastric cancer Lung cancer	[109,110]
	E-cadherin	Invasion Grading Lauren histotype	Prognosis	Esophagus cancer Ovary cancer Stomach cancer	[111]

	TSP-1	Stage	Prognosis	Breast cancer Melanoma cancer Lung cancer Gastric cancer	[112-115]
	SPARC	Depth of invasion Serosal invasion Lymph node metastasis Distant metastasis	Prognosis	Breast cancer Melanoma cancer Gastric cancer Oesophageal cancer Glioma cancer	[118-120]
Regulate cell death (apoptosis)	*Bcl-2*	Lymph node metastasis	Prognosis	Melanoma cancer Breast cancer Prostate cancer Chronic lymphocytic Leukemia lung cancer	[121]
	Bcl-6	Lymph node metastasis	Prognosis	Gastric cancer Pancreas cancer Colon cancer Bladder cancer	[122]
	Bax	No data	Prognosis	Gastric cancer Colon cancer	[123-125]
Cytokine	*CXCL1/CXCR2*	Lymph node metastasis	Prognosis	Gastric cancer Colon cancer	[128]
Vesicular transport	*ARF1*	Depth of invasion Serosal invasion Lymph node metastasis Distant metastasis Stage	Prognosis	Gastric cancer	[129]

HER2/neu: Human epidermal growth factor receptor 2/neu; VEGF: Vascular endothelial growth factor; hERG1: Human Ether-à-go-go-Related Gene; KLF5/IKLF/BTEB2: Krueppel-like factor 5; SATB1: Special AT-rich sequence-binding protein-1; CA IX: Carbonic anhydrase 9; MMP-2: Matrix metalloproteinase-2; HDAC: Histone deacetylases; SLP1: Antiprotease secretory leukocyte protease inhibitor; GLO1: Glyoxalase I; TGF-β: Transforming growth factor beta; PKP3: Plakophilin-3; TSP-1: Thrombospondin 1; SPARC: Secreted protein and rich in cysteine; Bcl-2: B-cell lymphoma 2; Bcl-6: B-cell lymphoma 6; Bax: Bcl-2-associated X protein; CXCL1: Chemokine (C-X-C motif) ligand 1; CXCR2: CXC chemokine receptors 2; ARF1: ADP-ribosylation factor 1.

c-myc has three isoforms and is extremely influential in controlling DNA replication[79].

The MAPK/ERK pathway may activate c-myc, and c-myc activation results in many cellular effects including cell proliferation, apoptosis, differentiation and stem cell self-renewal. c-Myc is a very robust proto-oncogene, and it is very often upregulated in many cancers. c-Myc is correlated with recurrence and may be a potential prognostic factor. High levels of c-myc2 were correlated with lymph node metastasis and poor prognosis in cancers of the cervix, colon, breast, lung and stomach[80].

CARBONIC ANHYDRASE 9

Carbonic anhydrases (CAs) are a large family of zinc metalloenzymes that catalyze the reversible hydration of carbon dioxide. They are involved in some biological reactions, such as respiration, calcification, acid-base balance, bone resorption, and the formation of aqueous humor, cerebrospinal fluid (CSF), saliva, and gastric acid. CA9 is a transmembrane protein and a tumor-associated carbonic anhydrase isoenzyme. It is increased in renal cancers and hypoxic solid tumors. It is also involved in cell proliferation and tumorigenesis.

Drug compounds targeted to CA9 are in preclinical development for the treatment of kidney, colon, and cervical cancers. CA9 is one of the markers of tumor hypoxia. Moreover, recent studies assaying CA9 levels and various clinicopathological outcomes indicated that CA9 expression may also be a valuable prognostic factor of overall survival. Antibodies targeted against CA9 may be used to show hypoxic regions in many solid tumors[81-83].

MATRIX METALLOPROTEINASE-2

Matrix metalloproteinase-2 (MMP-2) is a collagenase that assists tumor growth and invasion by digesting the extracellular matrix surrounding the tissue. MMP-2 is considered a possible tumor marker for ovarian, colon, breast, bladder and gastric cancers[79,80,84,85].

HISTONE DEACETYLASES

Histone deacetylases (HDACs) promote the removal of acetyl groups from acetylated residues to release an acetate molecule. Lysine acetylation typically occurs in a number of non-histone proteins.

Mutation and/or aberrant expression of various HDACs have often been observed in cancer, making them important therapeutic targets for many human cancers. Several studies have indicated that overexpression of HDACs is present in renal, colorectal, gastric, breast, pancreatic, liver, lung and prostate cancers and in classical Hodgkin's lymphoma and that they are associated with poor prognoses[86-92].

CYCLOOXYGENASE-2

Cyclooxygenase (COX)-2 is an enzyme responsible for

inflammation and pain. COX-2 appears to be associated with cancers and irregular growths in the intestinal tract[93]. COX inhibitors have been shown to reduce the occurrence of cancers. COX-2 inhibitors are currently being studied for the treatment of breast cancer[94].

ANTIPROTEASE SECRETORY LEUKOCYTE PROTEASE INHIBITOR

Secretory leukocyte protease inhibitor (SLPI) neutralizes elastase, tryptase, and cathepsin G[95]. Several studies have indicated that SLPI may be involved in tumorigenesis[96]. Abundant expression of SLPI was noted in several cancers including ovarian, cervical and gastric cancers[97].

GLYOXALASE I

Glyoxalase I (GLO1) is an essential component in pathways leading to the detoxification of methylglyoxal (MG). Over-expression of GLO1 has been reported in several cancers, such as colon, breast, prostate, gastric cancers and melanoma[98-103].

KI-67

Ki-67 is a nuclear protein that is a cellular marker of cell proliferation. It always correlates with cell proliferation. During interphase, Ki-67 may be exclusively detected within the cell nucleus, and when the cell enters mitosis, the majority of Ki-67 relocates to the surface of the chromosomes. Ki-67 is present during all active phases of the cell cycle (G_1, S, G_2, and mitosis), but is absent in resting cells (G_0). Thus, Ki-67 is a good marker for determining cell growth rate. Ki-67-positive tumor cells are often correlated with advanced tumors including carcinomas of the prostate, brain, breast and nephroblastomas. With respect to these tumors, survival and tumor recurrence have been positively correlated with Ki-67 IHC staining[104].

TRANSFORMING GROWTH FACTOR-β

Transforming growth factor-β (TGF-β) regulates cellular proliferation, differentiation and apoptosis. TGF-β is a multifunctional cytokine, and increased or decreased production has been linked to many cancers including breast cancer and GC[105].

TGF-β is a pluripotent cytokine with diverse effects on normal physiology and a role in both normal mammary gland development and the progression of breast cancer. During early stages of cancer, TGF-β acts as a tumor suppressor, whereas in later stages, when tumor cells become resistant to growth inhibition by TGF-β, it acts as a tumor promoter. Thus, TGF-β as a tumor marker is useful primarily during the follow-up of cancer patients and particularly in monitoring advanced disease[106].

PLAKOPHILIN-3

Plakophilin-3 (PKP3) is a member of the armadillo (ARM)/plakophilin families. ARM-related proteins physically localize to cell desmosomes and nuclei and are involved in linking cadherins to intermediate filaments in the cytoskeleton. PKP3 may play a role as in cellular desmosome-dependent adhesion and signaling pathways[107,108]. Several publications have reported that genetic aberrations in members of the ARM-protein family including plakoglobin (PKGB), h-catenin (CTNNB1), and adenomatous polyposis coli (APC) promote tumor progression. However, with regard to the role(s) of the subfamily member PKP3 during carcinogenesis, evidence shows that PKP3 is a potential prognostic marker and that it shows clinicopathological correlation with lung cancer and GC[109,110].

E-CADHERIN

E-cadherin is a calcium-regulated transmembrane cell-cell adhesion protein that is expressed in most normal epithelial tissues. Selective loss of E-cadherin can cause dedifferentiation and invasiveness in human carcinomas, suggesting that E-cadherin may play a role as a tumor suppressor. Reduced expression of E-cadherin has been observed in aggressive tumors of the esophagus, ovary, and stomach[111].

THROMBOSPONDIN 1

Thrombospondin 1 (TSP-1) is an extracellular matrix glycoprotein that regulates cell adhesion, cell motility, angiogenesis, and cell growth. TSP1 is down-regulated in many tumors including breast, melanoma, lung and gastric cancers[112-115].

SECRETED PROTEIN AND RICH IN CYSTEINE

Secreted protein and rich in cysteine (SPARC) is a member of the matricellular protein family. SPARC may regulate cell-matrix interactions and cell function without participating in the structural scaffold of the extracellular matrix[116,117]. Recently, SPARC over-expression has been reported in breast, melanoma, gastric, esophageal cancers and gliomas[118-120].

B-CELL LYMPHOMA 2/B-CELL LYMPHOMA 6/BCL-2-ASSOCIATED X PROTEIN

B-cell lymphoma 2 (Bcl-2) is a member of the Bcl-2 family of regulator proteins that either induce or inhibit cell apoptosis. Bcl-2 is an important anti-apoptotic oncoprotein. Mutation of the *Bcl-2* gene causes cancers including

melanoma, chronic lymphocytic leukemia, breast, gastric, prostate, and lung cancers[121]. Bcl-2 is a commonly used IHC marker, and it has been used in the classification of lymphoid processes and the identification of specific epithelial tumors.

Bcl-6 is also a biomarker of gastric, pancreas, colon and bladder cancers[122].

Bcl-2-associated X protein (BAX) is a member of the *Bcl-2* gene family. BAX is a pro-apoptotic factor based on its binding to Bcl-2. It is also a prognostic marker of colon and bladder cancers[123-125].

CXCL1/CXCR2

CXCL1 is thought to be a chemo-attractant for neutrophils and lymphocytes[126,127]. However, it was observed that neutrophil infiltration into tumors was dependent on CXCR2 signaling. Moreover, the expression of CXCL1/CXCR2 was significantly associated with GC progression. This evidence is consistent with the previous observation the CXCL1/CXCR2 signaling pathway was important in the metastasis of several cancers including breast, gastric and colon cancers[128].

ADP-RIBOSYLATION FACTOR 1

ADP-ribosylation factor 1 (ARF1) is a member of the small GTPase family. ARF1 is involved in many cellular processes including cell differentiation, proliferation, necrosis, apoptosis, and inter- and intracellular signaling[129].

CONCLUSION

There are no current excellent tumor indices or tumor markers for GC. However, it is very important to use many tumor markers in different types of cancer to screen, diagnose and stage the cancer, for evaluation of prognosis and for monitoring of recurrence following treatment. However, determining the significance of the markers and assessing and interpreting them requires an accumulation of expertise and experience. These processes cannot work when based on a single tumor marker. From the viewpoint of the clinic, it is critical to examine the performance of the marker using imaging, to select a tumor marker assay and to consider the variety of non-specific factors that may have caused the increase in the biomarker. Finally, this knowledge may lead to more accurate diagnoses and prognoses, may enable the selection of optimal and appropriate therapies and also may enable assessments of the effectiveness of treatments, with or without postoperative tracking of recurrence. Thus, tumor markers are only references; they are used by the physician for examining the cancer and cannot diagnose the disease themselves.

REFERENCES

1 **Wang CS**, Hsieh CC, Chao TC, Jan YY, Jeng LB, Hwang TL, Chen MF, Chen PC, Chen JS, Hsueh S. Resectable gastric cancer: operative mortality and survival analysis. *Chang Gung Med J* 2002; **25**: 216-227 [PMID: 12079155]

2 **Marrelli D**, Roviello F, De Stefano A, Farnetani M, Garosi L, Messano A, Pinto E. Prognostic significance of CEA, CA 19-9 and CA 72-4 preoperative serum levels in gastric carcinoma. *Oncology* 1999; **57**: 55-62 [PMID: 10394126]

3 **Laurén P**. Histogenesis of intestinal and diffuse types of gastric carcinoma. *Scand J Gastroenterol Suppl* 1991; **180**: 160-164 [PMID: 2042032 DOI: 10.3109/00365529109093194]

4 **Tahara E**. Molecular mechanism of stomach carcinogenesis. *J Cancer Res Clin Oncol* 1993; **119**: 265-272 [PMID: 8440743 DOI: 10.1007/BF01212724]

5 **Cervantes A**, Rodríguez Braun E, Pérez Fidalgo A, Chirivella González I. Molecular biology of gastric cancer. *Clin Transl Oncol* 2007; **9**: 208-215 [PMID: 17462972 DOI: 10.1007/s12094-007-0041-4]

6 **Barreto-Zuñiga R**, Maruyama M, Kato Y, Aizu K, Ohta H, Takekoshi T, Bernal SF. Significance of Helicobacter pylori infection as a risk factor in gastric cancer: serological and histological studies. *J Gastroenterol* 1997; **32**: 289-294 [PMID: 9213239 DOI: 10.1007/BF02934482]

7 **Kim KM**, Kwon MS, Hong SJ, Min KO, Seo EJ, Lee KY, Choi SW, Rhyu MG. Genetic classification of intestinal-type and diffuse-type gastric cancers based on chromosomal loss and microsatellite instability. *Virchows Arch* 2003; **443**: 491-500 [PMID: 12920592 DOI: 10.1007/s00428-003-0840-0]

8 **Yasui W**, Oue N, Kuniyasu H, Ito R, Tahara E, Yokozaki H. Molecular diagnosis of gastric cancer: present and future. *Gastric Cancer* 2001; **4**: 113-121 [PMID: 11760076 DOI: 10.1007/PL00011733]

9 **Allgayer H**, Heiss MM, Schildberg FW. Prognostic factors in gastric cancer. *Br J Surg* 1997; **84**: 1651-1664 [PMID: 9448610 DOI: 10.1002/bjs.1800841206]

10 **Pesch B**, Taeger D, Johnen G, Gawrych K, Bonberg N, Schwentner C, Wellhäußer H, Kluckert M, Leng G, Nasterlack M, Lotan Y, Stenzl A, Brüning T. Screening for bladder cancer with urinary tumor markers in chemical workers with exposure to aromatic amines. *Int Arch Occup Environ Health* 2014; **87**: 715-724 [PMID: 24129706 DOI: 10.1007/s00420-013-0916-3]

11 **Dilege E**, Mihmanli M, Demir U, Ozer K, Bostanci O, Kaya C, Aksakal O, Sakiz D. Prognostic value of preoperative CEA and CA 19-9 levels in resectable gastric cancer. *Hepatogastroenterology* 2010; **57**: 674-677 [PMID: 20698248 DOI: 10.1007/s12325-008-0100-4]

12 **Duraker N**, Celik AN. The prognostic significance of preoperative serum CA 19-9 in patients with resectable gastric carcinoma: comparison with CEA. *J Surg Oncol* 2001; **76**: 266-271 [PMID: 11320518 DOI: 10.1002/jso.1044]

13 **Emoto S**, Ishigami H, Yamashita H, Yamaguchi H, Kaisaki S, Kitayama J. Clinical significance of CA125 and CA72-4 in gastric cancer with peritoneal dissemination. *Gastric Cancer* 2012; **15**: 154-161 [PMID: 21892754 DOI: 10.1007/s10120-011-0091-8]

14 **Li Y**, Yang Y, Lu M, Shen L. Predictive value of serum CEA, CA19-9 and CA72.4 in early diagnosis of recurrence after radical resection of gastric cancer. *Hepatogastroenterology* 2011; **58**: 2166-2170 [PMID: 22024091 DOI: 10.5754/hge11753]

15 **Ychou M**, Duffour J, Kramar A, Gourgou S, Grenier J. Clinical significance and prognostic value of CA72-4 compared with CEA and CA19-9 in patients with gastric cancer. *Dis Markers* 2000; **16**: 105-110 [PMID: 11381189 DOI: 10.1155/2000/595492]

16 **Lu HB**, Zhou JH, Ma YY, Lu HL, Tang YL, Zhang QY, Zhao CH. Five serum proteins identified using SELDI-TOF-MS as potential biomarkers of gastric cancer. *Jpn J Clin Oncol* 2010; **40**: 336-342 [PMID: 20089528 DOI: 10.1093/jjco/hyp175]

17 **Liu W**, Gao X, Cai Q, Li J, Zhu Z, Li C, Yao X, Yang Q, Xiang M, Yan M, Zhu Z. Identification of novel serum biomarkers for gastric cancer by magnetic bead. *Front Biosci* (Elite Ed)

2010; **2**: 961-971 [PMID: 20515767 DOI: 10.2741/E155]
18 **Umemura H**, Togawa A, Sogawa K, Satoh M, Mogushi K, Nishimura M, Matsushita K, Tanaka H, Takizawa H, Kodera Y, Nomura F. Identification of a high molecular weight kininogen fragment as a marker for early gastric cancer by serum proteome analysis. *J Gastroenterol* 2011; **46**: 577-585 [PMID: 21298293 DOI: 10.1007/s00535-010-0369-3]
19 **Ahn HS**, Shin YS, Park PJ, Kang KN, Kim Y, Lee HJ, Yang HK, Kim CW. Serum biomarker panels for the diagnosis of gastric adenocarcinoma. *Br J Cancer* 2012; **106**: 733-739 [PMID: 22240791 DOI: 10.1038/bjc.2011.592]
20 **Zhang Z**, Li M, Zhang G, Fang P, Yao H, Xiao Z, Chen Z. Identification of human gastric carcinoma biomarkers by differential protein expression analysis using 18O labeling and nanoLC-MS/MS coupled with laser capture microdissection. *Med Oncol* 2010; **27**: 296-303 [PMID: 19330469 DOI: 10.1007/s12032-009-9208-x]
21 **Thomas SN**, Zhu F, Schnaar RL, Alves CS, Konstantopoulos K. Carcinoembryonic antigen and CD44 variant isoforms cooperate to mediate colon carcinoma cell adhesion to E- and L-selectin in shear flow. *J Biol Chem* 2008; **283**: 15647-15655 [PMID: 18375392 DOI: 10.1074/jbc.M800543200]
22 **Konstantopoulos K**, Thomas SN. Cancer cells in transit: the vascular interactions of tumor cells. *Annu Rev Biomed Eng* 2009; **11**: 177-202 [PMID: 19413512 DOI: 10.1146/annurev-bioeng-061008-124949]
23 **Thomas SN**, Tong Z, Stebe KJ, Konstantopoulos K. Identification, characterization and utilization of tumor cell selectin ligands in the design of colon cancer diagnostics. *Biorheology* 2009; **46**: 207-225 [PMID: 19581728 DOI: 10.3233/BIR-2009-0534]
24 **Maestranzi S**, Przemioslo R, Mitchell H, Sherwood RA. The effect of benign and malignant liver disease on the tumour markers CA19-9 and CEA. *Ann Clin Biochem* 1998; **35** (Pt 1): 99-103 [PMID: 9463746 DOI: 10.1177/000456329803500113]
25 **Duffy MJ**, van Dalen A, Haglund C, Hansson L, Klapdor R, Lamerz R, Nilsson O, Sturgeon C, Topolcan O. Clinical utility of biochemical markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines. *Eur J Cancer* 2003; **39**: 718-727 [PMID: 12651195 DOI: 10.1016/S0959-8049(02)00811-0]
26 **Koprowski H**, Herlyn M, Steplewski Z, Sears HF. Specific antigen in serum of patients with colon carcinoma. *Science* 1981; **212**: 53-55 [PMID: 6163212 DOI: 10.1126/science.6163212]
27 **Louhimo J**, Alfthan H, Stenman UH, Haglund C. Serum HCG beta and CA 72-4 are stronger prognostic factors than CEA, CA 19-9 and CA 242 in pancreatic cancer. *Oncology* 2004; **66**: 126-131 [PMID: 15138364 DOI: 10.1159/000077438]
28 **Louhimo J**, Kokkola A, Alfthan H, Stenman UH, Haglund C. Preoperative hCGbeta and CA 72-4 are prognostic factors in gastric cancer. *Int J Cancer* 2004; **111**: 929-933 [PMID: 15300805 DOI: 10.1002/ijc.20321]
29 **Kanazawa H**, Yoshikawa T, Yamada M, Shoji S, Fujii T, Kudoh S, Hirata K, Yoshikawa J. CYFRA 21-1, a cytokeratin subunit 19 fragment, in bronchoalveolar lavage fluid from patients with interstitial lung disease. *Clin Sci* (Lond) 1998; **94**: 531-535 [PMID: 9682677 DOI: 10.1042/cs0940531]
30 **D'Alessandro R**, Roselli M, Ferroni P, Mariotti S, Spila A, Aloe S, Carone MD, Abbolito MR, Carlini S, Perri P, Ricciotti A, Botti C, Conti F, Vici P, Chiappetta NR, Cognetti F, Buonomo O, Guadagni F. Serum tissue polypeptide specific antigen (TPS): a complementary tumor marker to CA 15-3 in the management of breast cancer. *Breast Cancer Res Treat* 2001; **68**: 9-19 [PMID: 11678313 DOI: 10.1023/A:1017903724176]
31 **Gregory JJ**, Finlay JL. Alpha-fetoprotein and beta-human chorionic gonadotropin: their clinical significance as tumour markers. *Drugs* 1999; **57**: 463-467 [PMID: 10235686 DOI: 10.2165/00003495-199957040-00001]
32 **Hartupee JC**, Zhang H, Bonaldo MF, Soares MB, Dieckgraefe BK. Isolation and characterization of a cDNA encoding a novel member of the human regenerating protein family: Reg IV. *Biochim Biophys Acta* 2001; **1518**: 287-293 [PMID: 11311942 DOI: 10.1016/S0167-4781(00)00284-0]
33 **Macadam RC**, Sarela AI, Farmery SM, Robinson PA, Markham AF, Guillou PJ. Death from early colorectal cancer is predicted by the presence of transcripts of the REG gene family. *Br J Cancer* 2000; **83**: 188-195 [PMID: 10901369 DOI: 10.1054/bjoc.2000.1227]
34 **Gu Z**, Rubin MA, Yang Y, Deprimo SE, Zhao H, Horvath S, Brooks JD, Loda M, Reiter RE. Reg IV: a promising marker of hormone refractory metastatic prostate cancer. *Clin Cancer Res* 2005; **11**: 2237-2243 [PMID: 15788672 DOI: 10.1158/1078-0432.CCR-04-0356]
35 **Baker M**, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boeve B, Feldman H, Hutton M. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature* 2006; **442**: 916-919 [PMID: 16862116 DOI: 10.1038/nature05016]
36 **Smout MJ**, Laha T, Mulvenna J, Sripa B, Suttiprapa S, Jones A, Brindley PJ, Loukas A. A granulin-like growth factor secreted by the carcinogenic liver fluke, Opisthorchis viverrini, promotes proliferation of host cells. *PLoS Pathog* 2009; **5**: e1000611 [PMID: 19816559 DOI: 10.1371/journal.ppat.1000611]
37 **Obsil T**, Ghirlando R, Klein DC, Ganguly S, Dyda F. Crystal structure of the 14-3-3zeta: serotonin N-acetyltransferase complex. a role for scaffolding in enzyme regulation. *Cell* 2001; **105**: 257-267 [PMID: 11336675 DOI: 10.1016/S0092-8674(01)00316-6]
38 **Cann KL**, Hicks GG. Regulation of the cellular DNA double-strand break response. *Biochem Cell Biol* 2007; **85**: 663-674 [PMID: 18059525 DOI: 10.1139/O07-135]
39 **Urano T**, Saito T, Tsukui T, Fujita M, Hosoi T, Muramatsu M, Ouchi Y, Inoue S. Efp targets 14-3-3 sigma for proteolysis and promotes breast tumour growth. *Nature* 2002; **417**: 871-875 [PMID: 12075357 DOI: 10.1038/nature00826]
40 **Moreira JM**, Gromov P, Celis JE. Expression of the tumor suppressor protein 14-3-3 sigma is down-regulated in invasive transitional cell carcinomas of the urinary bladder undergoing epithelial-to-mesenchymal transition. *Mol Cell Proteomics* 2004; **3**: 410-419 [PMID: 14736829 DOI: 10.1074/mcp.M300134-MCP200]
41 **Iwata N**, Yamamoto H, Sasaki S, Itoh F, Suzuki H, Kikuchi T, Kaneto H, Iku S, Ozeki I, Karino Y, Satoh T, Toyota J, Satoh M, Endo T, Imai K. Frequent hypermethylation of CpG islands and loss of expression of the 14-3-3 sigma gene in human hepatocellular carcinoma. *Oncogene* 2000; **19**: 5298-5302 [PMID: 11077447 DOI: 10.1038/sj.onc.1203898]
42 **Gasco M**, Sullivan A, Repellin C, Brooks L, Farrell PJ, Tidy JA, Dunne B, Gusterson B, Evans DJ, Crook T. Coincident inactivation of 14-3-3sigma and p16INK4a is an early event in vulval squamous neoplasia. *Oncogene* 2002; **21**: 1876-1881 [PMID: 11896620 DOI: 10.1038/sj.onc.1205256]
43 **Forget MA**, Turcotte S, Beauseigle D, Godin-Ethier J, Pelletier S, Martin J, Tanguay S, Lapointe R. The Wnt pathway regulator DKK1 is preferentially expressed in hormone-resistant breast tumours and in some common cancer types. *Br J Cancer* 2007; **96**: 646-653 [PMID: 17245340 DOI: 10.1038/sj.bjc.6603579]
44 **Qian J**, Xie J, Hong S, Yang J, Zhang L, Han X, Wang M, Zhan F, Shaughnessy JD, Epstein J, Kwak LW, Yi Q. Dickkopf-1 (DKK1) is a widely expressed and potent tumor-associated antigen in multiple myeloma. *Blood* 2007; **110**: 1587-1594 [PMID: 17515399 DOI: 10.1182/blood-2007-03-082529]

45 **Hall CL**, Bafico A, Dai J, Aaronson SA, Keller ET. Prostate cancer cells promote osteoblastic bone metastases through Wnts. *Cancer Res* 2005; **65**: 7554-7560 [PMID: 16140917 DOI: 10.1158/0008-5472.CAN-05-1317]

46 **Thudi NK**, Martin CK, Nadella MV, Fernandez SA, Werbeck JL, Pinzone JJ, Rosol TJ. Zoledronic acid decreased osteolysis but not bone metastasis in a nude mouse model of canine prostate cancer with mixed bone lesions. *Prostate* 2008; **68**: 1116-1125 [PMID: 18461562 DOI: 10.1002/pros.20776]

47 **Schwaninger R**, Rentsch CA, Wetterwald A, van der Horst G, van Bezooijen RL, van der Pluijm G, Löwik CW, Ackermann K, Pyerin W, Hamdy FC, Thalmann GN, Cecchini MG. Lack of noggin expression by cancer cells is a determinant of the osteoblast response in bone metastases. *Am J Pathol* 2007; **170**: 160-175 [PMID: 17200191 DOI: 10.2353/ajpath.2007.051276]

48 **Voorzanger-Rousselot N**, Goehrig D, Journe F, Doriath V, Body JJ, Clézardin P, Garnero P. Increased Dickkopf-1 expression in breast cancer bone metastases. *Br J Cancer* 2007; **97**: 964-970 [PMID: 17876334 DOI: 10.1038/sj.bjc.6603959]

49 **Yamabuki T**, Takano A, Hayama S, Ishikawa N, Kato T, Miyamoto M, Ito T, Ito H, Miyagi Y, Nakayama H, Fujita M, Hosokawa M, Tsuchiya E, Kohno N, Kondo S, Nakamura Y, Daigo Y. Dikkopf-1 as a novel serologic and prognostic biomarker for lung and esophageal carcinomas. *Cancer Res* 2007; **67**: 2517-2525 [PMID: 17363569 DOI: 10.1158/0008-5472.CAN-06-3369]

50 **Uhlar CM**, Whitehead AS. Serum amyloid A, the major vertebrate acute-phase reactant. *Eur J Biochem* 1999; **265**: 501-523 [PMID: 10504381 DOI: 10.1046/j.1432-1327.1999.00657.x]

51 **de Beer MC**, de Beer FC, Gerardot CJ, Cecil DR, Webb NR, Goodson ML, Kindy MS. Structure of the mouse Saa4 gene and its linkage to the serum amyloid A gene family. *Genomics* 1996; **34**: 139-142 [PMID: 8661036 DOI: 10.1006/geno.1996.0253]

52 **Diamandis EP**. Analysis of serum proteomic patterns for early cancer diagnosis: drawing attention to potential problems. *J Natl Cancer Inst* 2004; **96**: 353-356 [PMID: 14996856 DOI: 10.1093/jnci/djh056]

53 **Diamandis EP**. Point: Proteomic patterns in biological fluids: do they represent the future of cancer diagnostics? *Clin Chem* 2003; **49**: 1272-1275 [PMID: 12881441 DOI: 10.1373/49.8.1272]

54 **Akashi H**, Hinoda Y, Itoh F, Adachi M, Endo T, Imai K. A novel gastric-cancer-associated mucin antigen defined by a monoclonal antibody A3D4. *Int J Cancer* 1997; **73**: 795-801 [PMID: 9399654 DOI: 10.1002/(SICI)1097-0215(19971210)73:6<795::AID-IJC4>3.0.CO;2-Y]

55 **Ren J**, Chen Z, Juan SJ, Yong XY, Pan BR, Fan DM. Detection of circulating gastric carcinoma-associated antigen MG7-Ag in human sera using an established single determinant immuno-polymerase chain reaction technique. *Cancer* 2000; **88**: 280-285 [PMID: 10640958 DOI: 10.1002/(SICI)1097-0142(20000115)88:2<280::AID-CNCR6>3.0.CO;2-7]

56 **Fan D**, Zhang X, Chen X, Mou Z, Hu J, Zhou S, Ding J, Wu K. Bird's-eye view on gastric cancer research of the past 25 years. *J Gastroenterol Hepatol* 2005; **20**: 360-365 [PMID: 15740477 DOI: 10.1111/j.1440-1746.2005.03797.x]

57 **Pals G**, Azuma T, Mohandas TK, Bell GI, Bacon J, Samloff IM, Walz DA, Barr PJ, Taggart RT. Human pepsinogen C (progastricsin) polymorphism: evidence for a single locus located at 6p21.1-pter. *Genomics* 1989; **4**: 137-148 [PMID: 2567697 DOI: 10.1016/0888-7543(89)90292-9]

58 **Mitri Z**, Constantine T, O'Regan R. The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy. *Chemother Res Pract* 2012; **2012**: 743193 [PMID: 23320171 DOI: 10.1155/2012/743193]

59 **Olayioye MA**. Update on HER-2 as a target for cancer therapy: intracellular signaling pathways of ErbB2/HER-2 and family members. *Breast Cancer Res* 2001; **3**: 385-389 [PMID: 11737890 DOI: 10.1186/bcr327]

60 **Burstein HJ**. The distinctive nature of HER2-positive breast cancers. *N Engl J Med* 2005; **353**: 1652-1654 [PMID: 16236735 DOI: 10.1056/NEJMp058197]

61 **Tan M**, Yu D. Molecular mechanisms of erbB2-mediated breast cancer chemoresistance. *Adv Exp Med Biol* 2007; **608**: 119-129 [PMID: 17993237 DOI: 10.1007/978-0-387-74039-3_9]

62 **Santin AD**, Bellone S, Roman JJ, McKenney JK, Pecorelli S. Trastuzumab treatment in patients with advanced or recurrent endometrial carcinoma overexpressing HER2/neu. *Int J Gynaecol Obstet* 2008; **102**: 128-131 [PMID: 18555254 DOI: 10.1016/j.ijgo.2008.04.008]

63 **Kaufmann R**, Müller P, Hildenbrand G, Hausmann M, Cremer C. Analysis of Her2/neu membrane protein clusters in different types of breast cancer cells using localization microscopy. *J Microsc* 2011; **242**: 46-54 [PMID: 21118230 DOI: 10.1111/j.1365-2818.2010.03436.x]

64 **Shah DK**, Menon KM, Cabrera LM, Vahratian A, Kavoussi SK, Lebovic DI. Thiazolidinediones decrease vascular endothelial growth factor (VEGF) production by human luteinized granulosa cells in vitro. *Fertil Steril* 2010; **93**: 2042-2047 [PMID: 19342033 DOI: 10.1016/j.fertnstert.2009.02.059]

65 **Nagy JA**, Feng D, Vasile E, Wong WH, Shih SC, Dvorak AM, Dvorak HF. Permeability properties of tumor surrogate blood vessels induced by VEGF-A. *Lab Invest* 2006; **86**: 767-780 [PMID: 16732297 DOI: 10.1038/labinvest.3700436]

66 **Murat A**, Migliavacca E, Hussain SF, Heimberger AB, Desbaillets I, Hamou MF, Rüegg C, Stupp R, Delorenzi M, Hegi ME. Modulation of angiogenic and inflammatory response in glioblastoma by hypoxia. *PLoS One* 2009; **4**: e5947 [PMID: 19536297 DOI: 10.1371/journal.pone.0005947]

67 **Pinto MP**, Badtke MM, Dudevoir ML, Harrell JC, Jacobsen BM, Horwitz KB. Vascular endothelial growth factor secreted by activated stroma enhances angiogenesis and hormone-independent growth of estrogen receptor-positive breast cancer. *Cancer Res* 2010; **70**: 2655-2664 [PMID: 20332242 DOI: 10.1158/0008-5472.CAN-09-4373]

68 **Wang S**, Li X, Parra M, Verdin E, Bassel-Duby R, Olson EN. Control of endothelial cell proliferation and migration by VEGF signaling to histone deacetylase 7. *Proc Natl Acad Sci USA* 2008; **105**: 7738-7743 [PMID: 18509061 DOI: 10.1073/pnas.0802857105]

69 **Ding XW**, Yang WB, Gao S, Wang W, Li Z, Hu WM, Li JJ, Luo HS. Prognostic significance of hERG1 expression in gastric cancer. *Dig Dis Sci* 2010; **55**: 1004-1010 [PMID: 19495974 DOI: 10.1007/s10620-009-0834-0]

70 **Chen X**, Johns DC, Geiman DE, Marban E, Dang DT, Hamlin G, Sun R, Yang VW. Krüppel-like factor 4 (gut-enriched Krüppel-like factor) inhibits cell proliferation by blocking G1/S progression of the cell cycle. *J Biol Chem* 2001; **276**: 30423-30428 [PMID: 11390382 DOI: 10.1074/jbc.M101194200]

71 **Chen C**, Bhalala HV, Qiao H, Dong JT. A possible tumor suppressor role of the KLF5 transcription factor in human breast cancer. *Oncogene* 2002; **21**: 6567-6572 [PMID: 12242654 DOI: 10.1038/sj.onc.1205817]

72 **Chen C**, Bhalala HV, Vessella RL, Dong JT. KLF5 is frequently deleted and down-regulated but rarely mutated in prostate cancer. *Prostate* 2003; **55**: 81-88 [PMID: 12661032 DOI: 10.1002/pros.10205]

73 **Bateman NW**, Tan D, Pestell RG, Black JD, Black AR. Intestinal tumor progression is associated with altered function of KLF5. *J Biol Chem* 2004; **279**: 12093-12101 [PMID: 14726538 DOI: 10.1074/jbc.M311532200]

74 **Chen C**, Benjamin MS, Sun X, Otto KB, Guo P, Dong XY, Bao Y, Zhou Z, Cheng X, Simons JW, Dong JT. KLF5 promotes cell proliferation and tumorigenesis through gene regulation and the TSU-Pr1 human bladder cancer cell line. *Int J Cancer* 2006; **118**: 1346-1355 [PMID: 16184550 DOI: 10.1002/ijc.21533]

75 **Pavan Kumar P**, Purbey PK, Sinha CK, Notani D, Limaye A,

Jayani RS, Galande S. Phosphorylation of SATB1, a global gene regulator, acts as a molecular switch regulating its transcriptional activity in vivo. *Mol Cell* 2006; **22**: 231-243 [PMID: 16630892 DOI: 10.1016/j.molcel.2006.03.010]

76 **Galande S**, Purbey PK, Notani D, Kumar PP. The third dimension of gene regulation: organization of dynamic chromatin loopscape by SATB1. *Curr Opin Genet Dev* 2007; **17**: 408-414 [PMID: 17913490 DOI: 10.1016/j.gde.2007.08.003]

77 **Yasui D**, Miyano M, Cai S, Varga-Weisz P, Kohwi-Shigematsu T. SATB1 targets chromatin remodelling to regulate genes over long distances. *Nature* 2002; **419**: 641-645 [PMID: 12374985 DOI: 10.1038/nature01084]

78 **Lu X**, Cheng C, Zhu S, Yang Y, Zheng L, Wang G, Shu X, Wu K, Liu K, Tong Q. SATB1 is an independent prognostic marker for gastric cancer in a Chinese population. *Oncol Rep* 2010; **24**: 981-987 [PMID: 20811679 DOI: 10.3892/or_00000945]

79 **Cotterman R**, Jin VX, Krig SR, Lemen JM, Wey A, Farnham PJ, Knoepfler PS. N-Myc regulates a widespread euchromatic program in the human genome partially independent of its role as a classical transcription factor. *Cancer Res* 2008; **68**: 9654-9662 [PMID: 19047142 DOI: 10.1158/0008-5472.CAN-08-1961]

80 **Ross JS**, Ali SM, Wang K, Palmer G, Yelensky R, Lipson D, Miller VA, Zajchowski D, Shawver LK, Stephens PJ. Comprehensive genomic profiling of epithelial ovarian cancer by next generation sequencing-based diagnostic assay reveals new routes to targeted therapies. *Gynecol Oncol* 2013; **130**: 554-559 [PMID: 23791828 DOI: 10.1016/j.ygyno.2013.06.019]

81 **Opavský R**, Pastoreková S, Zelník V, Gibadulinová A, Stanbridge EJ, Závada J, Kettmann R, Pastorek J. Human MN/CA9 gene, a novel member of the carbonic anhydrase family: structure and exon to protein domain relationships. *Genomics* 1996; **33**: 480-487 [PMID: 8661007 DOI: 10.1006/geno.1996.0223]

82 **Nakagawa Y**, Uemura H, Hirao Y, Yoshida K, Saga S, Yoshikawa K. Radiation hybrid mapping of the human MN/CA9 locus to chromosome band 9p12-p13. *Genomics* 1998; **53**: 118-119 [PMID: 9787087 DOI: 10.1006/geno.1998.5483]

83 **Kirkpatrick JP**, Rabbani ZN, Bentley RC, Hardee ME, Karol S, Meyer J, Oosterwijk E, Havrilesky L, Secord AA, Vujaskovic Z, Dewhirst MW, Jones EL. Elevated CAIX Expression is Associated with an Increased Risk of Distant Failure in Early-Stage Cervical Cancer. *Biomark Insights* 2008; **3**: 45-55 [PMID: 19578493 DOI: 10.1016/j.ijrobp.2005.07.364]

84 **Dominguez-Sola D**, Ying CY, Grandori C, Ruggiero L, Chen B, Li M, Galloway DA, Gu W, Gautier J, Dalla-Favera R. Non-transcriptional control of DNA replication by c-Myc. *Nature* 2007; **448**: 445-451 [PMID: 17597761 DOI: 10.1038/nature05953]

85 **Nie Z**, Hu G, Wei G, Cui K, Yamane A, Resch W, Wang R, Green DR, Tessarollo L, Casellas R, Zhao K, Levens D. c-Myc is a universal amplifier of expressed genes in lymphocytes and embryonic stem cells. *Cell* 2012; **151**: 68-79 [PMID: 23021216 DOI: 10.1016/j.cell.2012.08.033]

86 **Peng L**, Seto E. Deacetylation of nonhistone proteins by HDACs and the implications in cancer. *Handb Exp Pharmacol* 2011; **206**: 39-56 [PMID: 21879445 DOI: 10.1007/978-3-642-21631-2_3]

87 **Choi YW**, Bae SM, Kim YW, Lee HN, Kim YW, Park TC, Ro DY, Shin JC, Shin SJ, Seo JS, Ahn WS. Gene expression profiles in squamous cell cervical carcinoma using array-based comparative genomic hybridization analysis. *Int J Gynecol Cancer* 2007; **17**: 687-696 [PMID: 17504382 DOI: 10.1111/j.1525-1438.2007.00834.x]

88 **Minamiya Y**, Ono T, Saito H, Takahashi N, Ito M, Mitsui M, Motoyama S, Ogawa J. Expression of histone deacetylase 1 correlates with a poor prognosis in patients with adenocarcinoma of the lung. *Lung Cancer* 2011; **74**: 300-304 [PMID: 21466904 DOI: 10.1016/j.lungcan.2011.02.019]

89 **Zhang Z**, Yamashita H, Toyama T, Sugiura H, Ando Y, Mita K, Hamaguchi M, Hara Y, Kobayashi S, Iwase H. Quantitation of HDAC1 mRNA expression in invasive carcinoma of the breast*. *Breast Cancer Res Treat* 2005; **94**: 11-16 [PMID: 16172792 DOI: 10.1007/s10549-005-6001-1]

90 **Adams H**, Fritzsche FR, Dirnhofer S, Kristiansen G, Tzankov A. Class I histone deacetylases 1, 2 and 3 are highly expressed in classical Hodgkin's lymphoma. *Expert Opin Ther Targets* 2010; **14**: 577-584 [PMID: 20415600 DOI: 10.1517/14728221003796609]

91 **Fritzsche FR**, Weichert W, Röske A, Gekeler V, Beckers T, Stephan C, Jung K, Scholman K, Denkert C, Dietel M, Kristiansen G. Class I histone deacetylases 1, 2 and 3 are highly expressed in renal cell cancer. *BMC Cancer* 2008; **8**: 381 [PMID: 19099586 DOI: 10.1186/1471-2407-8-381]

92 **Weichert W**, Röske A, Niesporek S, Noske A, Buckendahl AC, Dietel M, Gekeler V, Boehm M, Beckers T, Denkert C. Class I histone deacetylase expression has independent prognostic impact in human colorectal cancer: specific role of class I histone deacetylases in vitro and in vivo. *Clin Cancer Res* 2008; **14**: 1669-1677 [PMID: 18347167 DOI: 10.1158/1078-0432.CCR-07-0990]

93 **Cao L**, Hu X, Zhang Y, Sun XT. Omental milky spots in screening gastric cancer stem cells. *Neoplasma* 2011; **58**: 20-26 [PMID: 21067262 DOI: 10.4149/neo_2011_01_20]

94 **Behrns KE**. Gastric remnant cancer: Is elimination of the bug the answer?: Comment on "Screening of Helicobacter pylori infection after gastrectomy for cancer or peptic ulcer". *Arch Surg* 2010; **145**: 967 [PMID: 20968122 DOI: 10.1001/archsurg.2010.212]

95 **Song Xy**, Zeng L, Jin W, Thompson J, Mizel DE, Lei K, Billinghurst RC, Poole AR, Wahl SM. Secretory leukocyte protease inhibitor suppresses the inflammation and joint damage of bacterial cell wall-induced arthritis. *J Exp Med* 1999; **190**: 535-542 [PMID: 10449524 DOI: 10.1084/jem.190.4.535]

96 **Bouchard D**, Morisset D, Bourbonnais Y, Tremblay GM. Proteins with whey-acidic-protein motifs and cancer. *Lancet Oncol* 2006; **7**: 167-174 [PMID: 16455481 DOI: 10.1016/S1470-2045(06)70579-4]

97 **Devoogdt N**, Revets H, Ghassabeh GH, De Baetselier P. Secretory leukocyte protease inhibitor in cancer development. *Ann N Y Acad Sci* 2004; **1028**: 380-389 [PMID: 15650263 DOI: 10.1196/annals.1322.044]

98 **Thornalley PJ**. Advances in glyoxalase research. Glyoxalase expression in malignancy, anti-proliferative effects of methylglyoxal, glyoxalase I inhibitor diesters and S-D-lactoylglutathione, and methylglyoxal-modified protein binding and endocytosis by the advanced glycation endproduct receptor. *Crit Rev Oncol Hematol* 1995; **20**: 99-128 [PMID: 7576201 DOI: 10.1016/1040-8428(94)00149-N]

99 **Zhang D**, Tai LK, Wong LL, Chiu LL, Sethi SK, Koay ES. Proteomic study reveals that proteins involved in metabolic and detoxification pathways are highly expressed in HER-2/neu-positive breast cancer. *Mol Cell Proteomics* 2005; **4**: 1686-1696 [PMID: 16048908 DOI: 10.1074/mcp.M400221-MCP200]

100 **Antognelli C**, Del Buono C, Ludovini V, Gori S, Talesa VN, Crinò L, Barberini F, Rulli A. CYP17, GSTP1, PON1 and GLO1 gene polymorphisms as risk factors for breast cancer: an Italian case-control study. *BMC Cancer* 2009; **9**: 115 [PMID: 19379515 DOI: 10.1186/1471-2407-9-115]

101 **Romanuik TL**, Ueda T, Le N, Haile S, Yong TM, Thomson T, Vessella RL, Sadar MD. Novel biomarkers for prostate cancer including noncoding transcripts. *Am J Pathol* 2009; **175**: 2264-2276 [PMID: 19893039 DOI: 10.2353/ajpath.2009.080868]

102 **Bair WB**, Cabello CM, Uchida K, Bause AS, Wondrak GT. GLO1 overexpression in human malignant melanoma. *Melanoma Res* 2010; **20**: 85-96 [PMID: 20093988 DOI: 10.1097/CMR.0b013e3283364903]

103 **Thornalley PJ**, Rabbani N. Glyoxalase in tumourigenesis and

multidrug resistance. *Semin Cell Dev Biol* 2011; **22**: 318-325 [PMID: 21315826 DOI: 10.1016/j.semcdb.2011.02.006]
104 **Scholzen T**, Gerdes J. The Ki-67 protein: from the known and the unknown. *J Cell Physiol* 2000; **182**: 311-322 [PMID: 10653597 DOI: 10.1002/(SICI)1097-4652(200003)182:3<311::AID-JCP1>3.0.CO;2-9]
105 **Blobe GC**, Schiemann WP, Lodish HF. Role of transforming growth factor beta in human disease. *N Engl J Med* 2000; **342**: 1350-1358 [PMID: 10793168 DOI: 10.1056/NEJM200005043421807]
106 **Reiss M**. TGF-beta and cancer. *Microbes Infect* 1999; **1**: 1327-1347 [PMID: 10611761 DOI: 10.1016/S1286-4579(99)00251-8]
107 **Schmidt A**, Langbein L, Prätzel S, Rode M, Rackwitz HR, Franke WW. Plakophilin 3--a novel cell-type-specific desmosomal plaque protein. *Differentiation* 1999; **64**: 291-306 [PMID: 10374265 DOI: 10.1046/j.1432-0436.1999.6450291.x]
108 **Bonné S**, Gilbert B, Hatzfeld M, Chen X, Green KJ, van Roy F. Defining desmosomal plakophilin-3 interactions. *J Cell Biol* 2003; **161**: 403-416 [PMID: 12707304 DOI: 10.1083/jcb.200303036]
109 **Papagerakis S**, Shabana AH, Depondt J, Gehanno P, Forest N. Immunohistochemical localization of plakophilins (PKP1, PKP2, PKP3, and p0071) in primary oropharyngeal tumors: correlation with clinical parameters. *Hum Pathol* 2003; **34**: 565-572 [PMID: 12827610 DOI: 10.1016/S0046-8177(03)00174-6]
110 **Satoh S**, Daigo Y, Furukawa Y, Kato T, Miwa N, Nishiwaki T, Kawasoe T, Ishiguro H, Fujita M, Tokino T, Sasaki Y, Imaoka S, Murata M, Shimano T, Yamaoka Y, Nakamura Y. AXIN1 mutations in hepatocellular carcinomas, and growth suppression in cancer cells by virus-mediated transfer of AXIN1. *Nat Genet* 2000; **24**: 245-250 [PMID: 10700176 DOI: 10.1038/73448]
111 **Götte M**, Kersting C, Radke I, Kiesel L, Wülfing P. An expression signature of syndecan-1 (CD138), E-cadherin and c-met is associated with factors of angiogenesis and lymphangiogenesis in ductal breast carcinoma in situ. *Breast Cancer Res* 2007; **9**: R8 [PMID: 17244359 DOI: 10.1186/bcr1641]
112 **Zabrenetzky V**, Harris CC, Steeg PS, Roberts DD. Expression of the extracellular matrix molecule thrombospondin inversely correlates with malignant progression in melanoma, lung and breast carcinoma cell lines. *Int J Cancer* 1994; **59**: 191-195 [PMID: 7927918 DOI: 10.1002/ijc.2910590209]
113 **Zajchowski DA**, Band V, Trask DK, Kling D, Connolly JL, Sager R. Suppression of tumor-forming ability and related traits in MCF-7 human breast cancer cells by fusion with immortal mammary epithelial cells. *Proc Natl Acad Sci USA* 1990; **87**: 2314-2318 [PMID: 1690427 DOI: 10.1073/pnas.87.6.2314]
114 **Volpert OV**, Stellmach V, Bouck N. The modulation of thrombospondin and other naturally occurring inhibitors of angiogenesis during tumor progression. *Breast Cancer Res Treat* 1995; **36**: 119-126 [PMID: 8534861 DOI: 10.1007/BF00666034]
115 **Sheibani N**, Frazier WA. Thrombospondin 1 expression in transformed endothelial cells restores a normal phenotype and suppresses their tumorigenesis. *Proc Natl Acad Sci USA* 1995; **92**: 6788-6792 [PMID: 7624320 DOI: 10.1073/pnas.92.15.6788]
116 **Bornstein P**, Sage EH. Matricellular proteins: extracellular modulators of cell function. *Curr Opin Cell Biol* 2002; **14**: 608-616 [PMID: 12231357]
117 **Brekken RA**, Sage EH. SPARC, a matricellular protein: at the crossroads of cell-matrix communication. *Matrix Biol* 2001; **19**: 816-827 [PMID: 11223341]
118 **Briggs J**, Chamboredon S, Castellazzi M, Kerry JA, Bos TJ. Transcriptional upregulation of SPARC, in response to c-Jun overexpression, contributes to increased motility and invasion of MCF7 breast cancer cells. *Oncogene* 2002; **21**: 7077-7091 [PMID: 12370830 DOI: 10.1038/sj.onc.1205857]
119 **Ledda F**, Bravo AI, Adris S, Bover L, Mordoh J, Podhajcer OL. The expression of the secreted protein acidic and rich in cysteine (SPARC) is associated with the neoplastic progression of human melanoma. *J Invest Dermatol* 1997; **108**: 210-214 [PMID: 9008236 DOI: 10.1111/1523-1747.ep12334263]
120 **Wang CS**, Lin KH, Chen SL, Chan YF, Hsueh S. Overexpression of SPARC gene in human gastric carcinoma and its clinic-pathologic significance. *Br J Cancer* 2004; **91**: 1924-1930 [PMID: 15558074 DOI: 10.1038/sj.bjc.6602213]
121 **Otake Y**, Soundararajan S, Sengupta TK, Kio EA, Smith JC, Pineda-Roman M, Stuart RK, Spicer EK, Fernandes DJ. Overexpression of nucleolin in chronic lymphocytic leukemia cells induces stabilization of bcl2 mRNA. *Blood* 2007; **109**: 3069-3075 [PMID: 17179226 DOI: 10.1182/blood-2006-08-043257]
122 **Ye T**, Chen Y, Fang J. DNA methylation biomarkers in serum for gastric cancer screening. *Mini Rev Med Chem* 2010; **10**: 1034-1038 [PMID: 20716059 DOI: 10.2174/1389557511009011034]
123 **Correa P**. Serum pepsinogens in gastric cancer screening. *Dig Dis Sci* 2010; **55**: 2123-2125 [PMID: 20428942 DOI: 10.1007/s10620-010-1248-8]
124 **Nakashima H**, Nagahama R, Yamamoto T, Ohkura Y. Mass screening for gastric cancer: how to select patients for endoscopic examination. *Gastric Cancer* 2010; **13**: 78-83 [PMID: 20602193 DOI: 10.1007/s10120-009-0538-3]
125 **Suzuki H**, Gotoda T, Sasako M, Saito D. Detection of early gastric cancer: misunderstanding the role of mass screening. *Gastric Cancer* 2006; **9**: 315-319 [PMID: 17235635 DOI: 10.1007/s10120-006-0399-y]
126 **Sako A**, Kitayama J, Ishikawa M, Yamashita H, Nagawa H. Impact of immunohistochemically identified lymphatic invasion on nodal metastasis in early gastric cancer. *Gastric Cancer* 2006; **9**: 295-302 [PMID: 17235632 DOI: 10.1007/s10120-006-0396-1]
127 **Oda I**, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262-270 [PMID: 17235627 DOI: 10.1007/s10120-006-0389-0]
128 **Hasuo T**, Semba S, Li D, Omori Y, Shirasaka D, Aoyama N, Yokozaki H. Assessment of microsatellite instability status for the prediction of metachronous recurrence after initial endoscopic submucosal dissection for early gastric cancer. *Br J Cancer* 2007; **96**: 89-94 [PMID: 17179982 DOI: 10.1038/sj.bjc.6603532]
129 **Tsai MM**, Lin PY, Cheng WL, Tsai CY, Chi HC, Chen CY, Tseng YH, Cheng YF, Chen CD, Liang Y, Liao CJ, Wu SM, Lin YH, Chung IH, Wang CS, Lin KH. Overexpression of ADP-ribosylation factor 1 in human gastric carcinoma and its clinicopathological significance. *Cancer Sci* 2012; **103**: 1136-1144 [PMID: 22348287 DOI: 10.1111/j.1349-7006.2012.02243.x]

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