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Tumor markers and clinical use

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ABSTRACT

In oncology, tumor biomarkers are a critical component of personalized care. Biomarkers include specific cells, molecules, genes and products, proteins, enzymes, and hormones. It has a wide range of uses such as screening, staging, differential diagnosis, risk and prognosis assessment, treatment response, and monitoring disease status. In this review, alpha-fetoprotein, carcinoembryogenic antigen, prostate-specific antigen, cancer antigen 15-3, carbohydrate antigen/cancer antigen 19-9, cancer antigen 125, carbohydrate antigen 50, cancer antigen 72-4, neuron-specific enolase, squamous cell carcinoma antigen, beta 2-microglobulin, and thyroglobulin, and their relation to cancer studies and clinical benefits were discussed.

Keywords: Cancer, molecular oncology, tumor biomarkers.

Biomarkers are biochemical products produced by the tumor or other body tissues in response to the tumor. These products are typically in protein form, and although they can be present in the urine, stool, tumor tissue, or other bodily fluids, they are most often observed in the blood.[1,2] Nowadays, gene mutations in DNA, changes in gene expressions, and metabolomic signatures are also used as genomic markers for malignancies.[3]

The use of tumor markers is subject to certain limitations. These calculated values may suggest a malignant development, but they do not provide a specific cause. Non-cancerous diseases can also cause a rise in tumor markers (Table 1). Furthermore, the predicted rise in cancer-related markers may not be seen in cancer patients.

The ideal tumor marker should be specific to a particular cancer type and sensitive enough to detect even small tumors. However, others have questioned the efficacy of biomarkers due to the lack of tumor markers with these clinically important properties.[4] Although biomarkers are expected to indicate only one type of cancer, some rise in several forms of cancer (Table 1). None of the tumor markers alone are diagnostic.[4] Biomarkers that are useful in benign and malignant conditions are presented (Table 1).

CLINICAL USES OF TUMOR MARKERS

Clinical and pathological tumor markers have a wide variety of clinical uses, including risk and prognosis assessment, screening, selection of a treatment method, determining the reaction to and progress of the treatment during the recovery, and detecting recurrence after surgery (Table 2).[3,12]

Although the level of tumor markers indicates cancer, it is not sufficient alone. Therefore, tumor

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Table 1. Common clinical uses of some tumor markers

Biomarkers	Increase in malignancies	Increase in non-cancerous conditions
AFP (alpha-fetoprotein)	Hepatocellular carcinomas (HCC) Testicles and other germ cell tumors	Cirrhosis, hepatitis, ataxia telangiectasia[1,2,6]
CEA (carcino embryogenic antigen)	Colorectal cancer, breast cancer	Smoking, fibrocystic breast disease, inflammatory bowel diseases pancreatitis, cirrhosis, hepatitis[1,2,7,9]
PSA (prostate-specific antigen)	Prostate cancer	Prostatitis[1,2,6]
Ca15-3	Breast cancer pancreatic cancer, lung cancer, ovarian cancer, colorectal cancer, liver cancer	Endometriosis, pelvic inflammatory diseases, liver disease, pregnancy[2,5,6,7]
Ca19-9	Pancreatic cancer, colorectal cancer, bladder cancer	Pancreatitis, liver cirrhosis, diabetic nephropathy gallbladder obstruction[1,5,6,7,9]
Ca 125	Ovarian cancer, fallopian tube cancer, breast cancer	Endometriosis, pregnancy, congestive heart failure, lupus disease[2,5,6]
Ca50	Pancreas cancer, bile duct tumors-cholangiocarcinoma	Pancreatitis, cholangitis[1,6,7]
Ca 72-4	Gastrointestinal cancer, ovarian cancer	Pancreatitis, cirrhosis, pulmonary diseases, rheumatoid diseases, gynecological diseases etc.[1,2,6,7,9]
NSE (Neuron-specific enolase)	Small cell lung cancer neuroblastoma, thyroid medullary carcinoma, melanoma	Septic shock, pneumonia, nervous system trauma[6,10]
SCC-antigen (squamous cell carcinoma)	Squamous cell carcinoma of the lung, esophageal cancer (esophageal carcinoma, head and neck cancers)	Psoriasis, inflammatory skin diseases (eczema), kidney failure, cirrhosis, pancreatitis, lung diseases[6,7,8,11]
Beta 2-microglobulin	Multiple myeloma (MM), non-hodgkin lymphoma	Diabetic nephropathy[6,7]
Thyreoglobulin	Papillary and follicular thyroid cancer	Hashimoto's disease, thyroiditis, Graves' disease, rheumatoid arthritisz[2]

Table 2. Potential uses for cancer biomarkers[3]

Use	Examples
Screening	Prostate specific antigen (prostate cancer)
Predict response to therapies	KRAS mutation and anti-EGFR antibody (colorectal cancer) HER2 expression and anti-HER2 therapy (breast and gastric cancer)
Determine prognosis of disease	21 gene recurrence score (breast cancer)
Monitor for disease recurrence	CEA (colorectal cancer) AFP, LDH, β-hCG (germ cell tumor)
Monitor for response or progression in metastatic disease	CA15-3 and CEA (breast cancer)
Estimate risk of developing cancer	BRCA1 germline mutation (breast and ovarian cancer)

KRAS: Kirsten Rat Sarcoma Virus gene; EGFR: Epidermal growth factor receptor; HER-2: human epidermal growth factor receptor 2; CEA: Carcinoembryonic antigen; AFP: Alpha-fetoprotein; LDH: Lactate dehydrogenase; β-hCG: Beta-human chorionic gonadotropin; CA 15-3: Carcinoma antigen 15-3; BRCA1: Breast cancer type 1 susceptibility gene.

markers are always used with other examination and diagnosis methods (ultrasonography, computed tomography (CT), positron emission tomography-CT, endoscopy, biopsy).[12]

Genetic tumor markers, which are increasingly important today, offer more effective results than clinical and pathological biomarkers. The patient's response to the treatment and the aggressiveness of the disease can be predicted with the genetic analysis performed together with other assays.[13] In a study, it was stated that 14 genes play an important role in predicting the course of breast and lung cancer.[13] The study analyzed the proteins responsible for the control of genes. As it is known, one of the 10 characteristics of cancer is a genomic imbalance. That is, gene damage impairs gene functions. The primary

factor that causes genomic disorders is the uneven distribution of genetic information to cells during cell proliferation. Centrosomes are the main molecules that allow an equal amount of genetic information to be distributed to cells. Researchers have tried to find genes that direct the functions of centrosomes by performing advanced genetic analysis in tumor tissues.[14]

The study found that the activity of 14 out of 31 genes that control centrosome functions is high in cancer cells. As the defects in chromosomes increase and the more genomic instability there is, the more sensitive the cancer cells become to chemotherapy and radiotherapy.[14] However, the study could not confirm that chromosome abnormalities increased survival in patients who did not receive chemotherapy.[14]

TUMOR MARKERS IN COLORECTAL CANCER

Colorectal cancers (CRCs) accounted for approximately 10% of all cancer-related deaths in 2018.[15] Despite the improvement in cancer screening methods, 20% of patients are diagnosed at the metastatic stage (Stage 4). Forty percent of early-stage patients experience recurrence after surgery.[15]

Tumor markers are of great importance in the early diagnosis of CRCs, in evaluating the prognosis and the response to treatment during the follow-up, and even in their effect on the life span of the patient. Carcinoembryonic antigen (CEA), cancer antigen 15-3 (CA 15-3), cancer antigen 19-9 (CA 19-9), cancer antigen 72-4 (CA 72-4), and cancer antigen 50 (CA 50) have been used frequently in CRCs.[16]

Currently, the glycoprotein CEA is the most widely used blood-based CRC molecular marker, proven to be a valuable tool for patient monitoring. It seems reasonable to examine preoperative CEA expression, especially in patients with metastases.[17,18]

Today, developments in targeted therapies and genetic biomarkers have led to changes in the treatment of CRCs as in other types of cancer. Biomarkers/molecular tests have been developed in metastatic CRCs with the contribution of targeted therapies. Molecular biomarkers and their use in CRCs are as follows: KRAS determines the benefit of NRAS mutation anti-EGFR treatment; targeted therapies with the BRAF V600 mutation; HER2 amplification; significant survival advantages have been provided with drugs developed against NTRK1-3 mutation.[19]

TUMOR MARKERS IN BREAST CANCER

Commonly used tumor markers associated with breast cancer are CEA and CA 15-3. In recent years, oncogenes HER2 and tumor suppressor genes BRCA 1 and BRCA 2 have been added to these markers.[20] The sensitivity and specificity of the tumor markers CEA and CA15-3 are not very high in serum since these markers are not tissue-specific and may increase in benign conditions. With the help of ultrasonography and tumor markers, abnormalities detected during screening with mammography can be distinguished as benign or malignant.[21]

According to a meta-analysis conducted in 2018 with 12,993 breast cancer patients, CA15-3 and CEA have significant predictive values in primary and secondary cancer and in different thresholds. In addition, high CA15-3 was associated with advanced histological grade and younger age, while high CEA was associated with triple-positive tumors and advanced age. These two elevated signs were all associated with a higher tumor burden.[22] Another study yielded promising results with targeted agents such as poly (ADP-ribose) polymerase (PARP) inhibitors and DNA repair agents in BRCA-related breast tumors.[23] Furthermore, HER2 status is also very important in breast cancer. It is an overexpressed proto-oncogene in 15 to 30% of invasive breast cancers. It is useful in determining the prognosis and predicting the response to treatment.[24] Levels of this substance are determined in the tissue. However, the extracellular domain (ECD) can be mixed into the blood from cells spilled from the tumor tissue, and the blood level of HER2 ECD may be high in some patients with metastatic breast cancer.[25] Patients with high blood levels of HER2 ECD have a more severe clinical manifestation and less response to treatment, and this finding may be useful in detecting disease recurrence in the preclinical period.[25,26]

As a result, drugs targeting HER2 have become indispensable for their use in combination with chemotherapy, as they significantly increase the life span of patients with stage 4 HER2-positive breast cancer.[27]

TUMOR MARKERS IN PROSTATE CANCER

Prostate-specific antigen (PSA) is the most commonly used marker in the diagnosis of prostate cancer. Determining the total level of PSA, a protein that can pass into the bloodstream of the person to a certain extent after being secreted from the prostate, is important in the diagnosis of malignant disease of the prostate, but it should be kept in mind that it may increase in the case of benign growth or inflammation of the prostate.[28,29]

According to a study, mutations in the gene called Anoctamin 7 (ANO7) can be an effective biomarker that will provide early diagnosis of aggressive prostate cancer.[30] In the study, DNA samples taken from 1,769 prostate cancer patients and 1,711 healthy individuals were analyzed to find disease-related mutations. It was found that changes in the ANO7 gene determine the aggressiveness of prostate cancer in patients and that the mutation (mutation name: rs77559646) detected in the ANO7 gene increases the risk of aggressive prostate cancer and causes poor prognosis. Anoctamin 7 is a gene active in prostate epithelial cells. It enables the production of proteins that take part in the cell membrane. This protein has high activity in prostate cancer cells. With this study an important biomarker in detecting aggressive prostate cancer was discovered, and genetic tests developed to detect ANO7 gene mutations can contribute to personalized oncology in prostate cancer.[30-32]

TUMOR MARKERS IN PANCREATIC CANCER

Pancreatic cancer is one of the most fatal, aggressive, malignant cancers, which is more common in males and occurs more frequently in older ages (40-85 years). Today, there are opinions in favor of the fact that pancreatic cancer begins with a genetic predisposition (stem cell disorders).[33-35] The presence of certain types of colon polyps, cancer in the family, or an individual's history and the existence of BRCA1, BRCA2, KRAS mutations increase the likelihood of pancreatic cancer.[36] In the diagnosis of pancreatic cancer, tumor markers such as CEA, CA 19-9, CA 72-4, CA 50, cancer antigen 242, and alpha-fetoprotein (AFP) are used. The increase of these markers in conditions such as pancreatitis and cirrhosis limits their use for cancer detection.[36,37] Cancer antigen 19-9 is the only biomarker approved by the United States Food and Drug Administration (FDA) for monitoring response to treatment in pancreatic cancer.[38] In addition, the high genetic mutation rates associated with pancreatic carcinoma have also led to the investigation of cell-free DNA and tumor cells in systemic circulation as a screening or test. In another study, they found that despite high rates of KRAS mutations in pancreatic tumor tissue, circulating tumor cells or cell-free DNA concentrations did not have the sensitivity or specificity required to be used as screening tests.[39] As the discovery of biomarkers for the diagnosis of pancreatic adenocarcinoma continues, a recent review concluded that the lack of validated and specific biomarkers for this disease is a significant challenge.[40]

TUMOR MARKERS IN LUNG CANCER

Lung cancer is the leading cause of cancer-related death worldwide. According to the global cancer statistics 2018, the number of new lung cancer cases occurring in a year was 2.09 million, while the number of deaths due to this cancer was 1.79 million.[15]

Carcinoembryonic antigen, squamous cell carcinoma antigen (SCCA), neuron-specific enolase (NSE), cytokeratin 19 fragment (CYFRA 21-1), and pro-gastrin-releasing peptide (pro-GRP) can be used as tumor markers for lung cancer.[41] Carcinoembryonic antigen is sensitive for adenocarcinoma; SCCA and CYFRA 21-1 are sensitive for squamous cell carcinoma; NSE and proGRP are sensitive for small cell carcinoma.[42,43] A tumor marker is generally used as a marker to monitor the clinical course. However, since these markers are also elevated in other diseases, their clinical utility is minimal.

The role of genomic changes in lung cancer, called the effect of inheritance and gene mutations, is known.[44] Today, the genomic changes associated with lung cancer are EGFR, KRAS, MET, LKB1, BRAF, PIK3CA, ALK, RET, and ROS1. Mutations detected in these genes in lung cancer also affect drug selection. This demonstrates how important biomarkers are for treatment selection.[45-47]

TUMOR MARKERS IN OVARIAN CANCER

Early diagnosis of ovarian cancer is very important as in all other cancers. For early diagnosis, it is recommended that women do not delay their annual routine gynecological checkups. A palpable mass detected during gynecology examination or masses seen in ovaries during ultrasound gives the chance to intervene early in cancer. In the advanced stages of ovarian cysts and masses with tumor characteristics, tumor markers are examined in the blood. Cancer antigen 125 (CA 125) is increased in some types of ovarian tumors.[48] Cancer antigen 125 is a protein found on the surface of many ovarian cancer cells. It can be high in the blood of females with ovarian cancer.[49] However, the increased level of CA125 and other tumor markers does not always indicate that the mass is cancer, nor does a fall in tumor markers rule out cancer. Apart from tumor markers, Doppler ultrasonography can also help in the differentiation of benign and malignant tumors by showing blood flow changes. All these methods are auxiliary methods. None of them are sufficient to make a definitive diagnosis.[50]

About half of patients with advanced serous ovarian cancer, the most common ovarian cancer, lack homologous recombination (HR) repair due to a germline (hereditary) or somatic (non-hereditery) mutation, and these individuals are known to benefit from PARP inhibitors.[51] It has been determined that the BRCA gene plays a critical role in the development of ovarian/fallopian tube cancers.[52] About 10 to 15% of females with ovarian cancer have the germline BRCA mutation, while about 7% harbor somatic BRCA gene mutations. Apart from this mutation, patients carry a few other mutations unrelated to BRCA. Patients with BRCA1/2 mutation show different clinical characteristics in ovarian cancer. Consequently, their response to treatment also varies.[52] The BRCA gene is involved in DNA repair by HR. Therefore, mutations in BRCA genes cause HR deficiency. In patients with advanced ovarian cancer, HR deficiency and other hereditary cancer genes should be tested in addition to the BRCA1/2 test. As a result, PARP inhibitors are now a standard of treatment for advanced ovarian cancer. Those with BRCA mutations benefit more from these drugs. BRCA mutations should be considered in every ovarian cancer patient, which will be revealed when looking at the groundbreaking success of these PARP inhibitors approved by the FDA in the last five years. Treatment of those who have this gene mutation should be done this way.[53] This once again demonstrates the importance of genomic biomarkers.

TUMOR MARKERS IN TESTICULAR CANCER

Testicular cancer is the most common solid tumor among males 15 to 34 years of age.[54] Some blood tests play an active role in the diagnosis of testicular tumors. Many testicular cancers secrete high amounts of AFP and human chorionic gonadotropin (hCG).[55] If these proteins are found in the blood, it may indicate the presence of a testicular tumor. The tumor can also increase the level of the enzyme lactate dehydrogenase (LDH). However, LDH may increase for reasons other than cancer.[56]

Nonseminomatous tumors, a type of testicular cancer, increase the levels of AFP and hCG. Therefore, any increase in AFP means that the tumor has nonseminomatous components (Tumors may coexist in seminomatous and nonseminomatous areas).[56] Thus, the histological type of the tumor can be predicted by looking at whether AFP and hCG are elevated. Stage and prognosis can be determined, as they increase in proportion to tumor volume. It is also useful in the follow-up of tumor destruction during treatment due to its short half-life. The increase in tumor markers in follow-up shows relapse much earlier than screening methods. In addition, they are easy to measure, safe, fast, and inexpensive.

In a recent study, the data of 10,310 British and Swedish patients with testicular cancer were

analyzed. It was found that 49% of all factors that increase the probability of getting testicular cancer are hereditary. Therefore, males with a family history of testicular cancer have a higher risk for testicular cancer.[57]

In conclusion, tumor markers developed by a personal approach in oncology as a result of systematic and critical evaluation of the scientific literature are a clinical guide. The use of the tumor marker alone is not sufficient since the case should be considered in all aspects (for example, diagnosis and treatment). Various publications shed light on how to use different tumor markers developed for this purpose. The primary purpose of these guides should be to disseminate their use and provide clear and appropriate information on how to use them. Particularly the results on the genetic-based markers developed in recent years indicate that they are sufficient, and studies in this area should be widespread.

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REFERENCES

1. Sturgeon C. Practice guidelines for tumor marker use in the clinic. Clin Chem 2002;48:1151-9.
2. Cooper DL. Tumor markers. In: Goldman L, Bennett JC, Cecil RL, editors. Cecil textbook of medicine. 21st ed. Philadelphia: WB Saunders Company; 2000. p 1099-103.
3. Henry NL, Hayes DF. Cancer biomarkers. Mol Oncol 2012;6:140-6.
4. Diamandis EP. Cancer biomarkers: Can we turn recent failures into success? J Natl Cancer Inst 2010;102:1462-7.
5. Lindblom A, Liljegren A. Regular review: Tumour markers in malignancies. BMJ 2000;320:424-7.
6. Sokoll LJ, Chan DW. Clinical chemistry: Tumor markers. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. In Abeloff: Clinical Oncology. 3rd ed. Pennsylvania: Elsevier Churchill Livingstone; 2004. p. 277-83.
7. Matsuoka T, Yashiro M. Biomarkers of gastric cancer: Current topics and future perspective. World J Gastroenterol 2018;24:2818-32.
8. Izuhara K, Yamaguchi Y, Ohta S, Nunomura S, Nanri Y, Azuma Y, et al. Squamous Cell Carcinoma Antigen 2 (SCCA2, SERPINB4): An emerging biomarker for skin inflammatory diseases. Int J Mol Sci 2018;19:1102.
9. Gao Y, Wang J, Zhou Y, Sheng S, Qian SY, Huo X. Evaluation of serum CEA, CA19-9, CA72-4, CA125 and Ferritin as diagnostic markers and factors of clinical parameters for colorectal cancer. Sci Rep 2018;8:2732.
10. Isgrò MA, Bottoni P, Scatena R. Neuron-specific enolase as a biomarker: Biochemical and clinical aspects. Adv Exp Med Biol 2015;867:125-43.
11. Yu SS, Cirillo N. The molecular markers of cancer stem cells in head and neck tumors. J Cell Physiol 2020;235:65-73.
12. Sharma S. Tumor markers in clinical practice: General principles and guidelines. Indian J Med Paediatr Oncol 2009;30:1-8.
13. Nebbioso A, Tambaro FP, Dell'Aversana C, Altucci L. Cancer epigenetics: Moving forward. PLoS Genet 2018;14:e1007362.
14. Zhang W, Mao JH, Zhu W, Jain AK, Liu K, Brown JB, et al. Centromere and kinetochore gene misexpression predicts cancer patient survival and response to radiotherapy and chemotherapy. Nat Commun 2016;7:12619.
15. Erratum: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2020;70:313.
16. Carpelan-Holmström M, Louhimo J, Stenman UH, Alfthan H, Järvinen H, Haglund C. CEA, CA 242, CA 19-9, CA 72-4 and hCGbeta in the diagnosis of recurrent colorectal cancer. Tumour Biol 2004;25:228-34.
17. Shah R, Jones E, Vidart V, Kuppen PJ, Conti JA, Francis NK. Biomarkers for early detection of colorectal cancer and polyps: Systematic review. Cancer Epidemiol Biomarkers Prev 2014;23:1712-28.
18. Zhong W, Yu Z, Zhan J, Yu T, Lin Y, Xia ZS, et al. Association of serum levels of CEA, CA199, CA125, CYFRA21-1 and CA72-4 and disease characteristics in colorectal cancer. Pathol Oncol Res 2015;21:83-95.
19. Afrăsânie VA, Marinca MV, Alexa-Stratulat T, Gafton B, Păduraru M, Adavidoaiei AM, et al. KRAS, NRAS, BRAF, HER2 and microsatellite instability in metastatic colorectal cancer - practical implications for the clinician. Radiol Oncol 2019;53:265-74.
20. Narod SA, Salmena L. BRCA1 and BRCA2 mutations and breast cancer. Discov Med 2011;12:445-53.
21. Fang C, Cao Y, Liu X, Zeng XT, Li Y. Serum CA125 is a predictive marker for breast cancer outcomes and correlates with molecular subtypes. Oncotarget 2017;8:63963-70.
22. Li X, Dai D, Chen B, Tang H, Xie X, Wei W. Clinicopathological and prognostic significance of cancer antigen 15-3 and carcinoembryonic antigen in breast cancer: A meta-analysis including 12,993 patients. Dis Markers 2018;2018:9863092.

23. Zimmer AS, Gillard M, Lipkowitz S, Lee JM. Update on PARP inhibitors in breast cancer. Curr Treat Options Oncol 2018;19:21.
24. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177-82.
25. Perrier A, Gligorov J, Lefèvre G, Boissan M. The extracellular domain of Her2 in serum as a biomarker of breast cancer. Lab Invest 2018;98:696-707.
26. Lam L, Czerniecki BJ, Fitzpatrick E, Xu S, Schuchter L, Xu X, et al. Interference-free HER2 ECD as a serum biomarker in breast cancer. J Mol Biomark Diagn 2014;4:151.
27. Tripathy D, Brufsky A, Cobleigh M, Jahanzeb M, Kaufman PA, Mason G, et al. De novo versus recurrent HER2-positive metastatic breast cancer: Patient characteristics, treatment, and survival from the SystHERs registry. Oncologist 2020;25:e214-e222.
28. Sadi MV. PSA screening for prostate cancer. Rev Assoc Med Bras (1992) 2017;63:722-5.
29. Uçer O, Yücetas U, Çelen I, Toktas G, Müezzinoglu T. Assessment of PSA-Age volume score in predicting positive prostate biopsy findings in Turkey. Int Braz J Urol 2015;41:864-8.
30. Kaikkonen E, Rantapero T, Zhang Q, Taimen P, Laitinen V, Kallajoki M, et al. ANO7 is associated with aggressive prostate cancer. Int J Cancer 2018;143:2479-87.
31. Atasoy Ö, Erbaş O. Up to date of prostate cancer. D J Med Sci 2020;6:92-102.
32. Ün M, Sel M. Urinary tumor markers for diagnosis of prostate cancer. D J Tx Sci 2019;4:67-72.
33. Gnoni A, Licchetta A, Scarpa A, Azzariti A, Brunetti AE, Simone G, et al. Carcinogenesis of pancreatic adenocarcinoma: Precursor lesions. Int J Mol Sci 2013;14:19731-62.
34. Fang Y, Yao Q, Chen Z, Xiang J, William FE, Gibbs RA, et al. Genetic and molecular alterations in pancreatic cancer: Implications for personalized medicine. Med Sci Monit 2013;19:916-26.
35. Wood LD. Pancreatic cancer genomes: Toward molecular subtyping and novel approaches to diagnosis and therapy. Mol Diagn Ther 2013;17:287-97.
36. Chen F, Roberts NJ, Klein AP. Inherited pancreatic cancer. Chin Clin Oncol 2017;6:58.
37. Del Chiaro M, Segersvärd R, Lohr M, Verbeke C. Early detection and prevention of pancreatic cancer: Is it really possible today? World J Gastroenterol 2014;20:12118-31.
38. Kim JE, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. J Gastroenterol Hepatol 2004;19:182-6.
39. Riva F, Dronov OI, Khomenko DI, Huguet F, Louvet C, Mariani P, et al. Clinical applications of circulating tumor DNA and circulating tumor cells in pancreatic cancer. Mol Oncol 2016;10:481-93.
40. Zhou B, Xu JW, Cheng YG, Gao JY, Hu SY, Wang L, et al. Early detection of pancreatic cancer: Where are we now and where are we going? Int J Cancer 2017;141:231-41.
41. Greenberg AK, Lee MS. Biomarkers for lung cancer: Clinical uses. Curr Opin Pulm Med 2007;13:249-55.
42. Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) Consortium for Early Detection of Lung Cancer, Guida F, Sun N, Bantis LE, Muller DC, Li P, et al. Assessment of lung cancer risk on the basis of a biomarker panel of circulating proteins. JAMA Oncol 2018;4:e182078.
43. Muley T, Rolny V, He Y, Wehnl B, Escherich A, Warth A, et al. The combination of the blood based tumor biomarkers cytokeratin 19 fragments (CYFRA 21-1) and carcinoembryonic antigen (CEA) as a potential predictor of benefit from adjuvant chemotherapy in early stage squamous cell carcinoma of the lung (SCC). Lung Cancer 2018;120:46-53.
44. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: Epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83:584-94.
45. Rios Velazquez E, Parmar C, Liu Y, Coroller TP, Cruz G, Stringfield O, et al. Somatic mutations drive distinct imaging phenotypes in lung cancer. Cancer Res 2017;77:3922-30.
46. Hirsch FR, Scagliotti GV, Mulshine JL, Kwon R, Curran WJ Jr, Wu YL, et al. Lung cancer: Current therapies and new targeted treatments. Lancet 2017;389:299-311.
47. Akbulut H, İncedayı S, Atasoy Ö. Non-small cell lung cancer and its treatment. D J Tx Sci 2019;4:23-40.
48. Chen X, Zhang J, Cheng W, Chang DY, Huang J, Wang X, et al. CA-125 level as a prognostic indicator in type I and type II epithelial ovarian cancer. Int J Gynecol Cancer 2013;23:815-22.
49. Henderson JT, Webber EM, Sawaya GF. Screening for ovarian cancer: Updated evidence report and systematic review for the US preventive services task force. JAMA 2018;319:595-606.
50. Kim B, Park Y, Kim B, Ahn HJ, Lee KA, Chung JE, et al. Diagnostic performance of CA 125, HE4, and risk of Ovarian Malignancy Algorithm for ovarian cancer. J Clin Lab Anal 2019;33:e22624.
51. Mittica G, Ghisoni E, Giannone G, Genta S, Aglietta M, Sapino A, et al. PARP inhibitors in ovarian cancer. Recent Pat Anticancer Drug Discov 2018;13:392-410.
52. Ding L, Kim HJ, Wang Q, Kearns M, Jiang T, Ohlson CE, et al. PARP inhibition elicits STING-dependent antitumor immunity in Brca1-deficient ovarian cancer. Cell Rep 2018;25:2972-2980.e5.
53. Zimmer AS, Gillard M, Lipkowitz S, Lee JM. Update on PARP inhibitors in breast cancer. Curr Treat Options Oncol 2018;19:21.
54. Baird DC, Meyers GJ, Hu JS. Testicular cancer: Diagnosis and treatment. Am Fam Physician 2018;97:261-8.

55. Hires M, Jane E, Mego M, Chovanec M, Kasak P, Tkac J. Glycan analysis as biomarkers for testicular cancer. Diagnostics (Basel) 2019;9:156.
56. Leão R, Ahmad AE, Hamilton RJ. Testicular cancer biomarkers: A role for precision medicine in testicular cancer. Clin Genitourin Cancer 2019;17:e176-e183.
57. Litchfield K, Thomsen H, Mitchell JS, Sundquist J, Houlston RS, Hemminki K, et al. Quantifying the heritability of testicular germ cell tumour using both population-based and genomic approaches. Sci Rep 2015;5:13889.