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Characteristics of abnormal subjects in screening of tumor markers among middle-aged and elderly people in Weihai area

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Abstract. – OBJECTIVE: Based on the Huimin policy of Weihai Social Security Bureau, this project aims to investigate feasibility of screening through screening of serum tumor markers (TM) in the middle-aged and elderly population in Weihai area. According to the joint mode of examination institution and clinical department (oncology), we provide dynamic follow-up for subjects for early intervention of abnormal tumor screening and high-risk population, through which we can cut off pathogenic pathway of cancer and improve early diagnosis of cancer and enhance the cure rate.

PATIENTS AND METHODS: We continued to track subjects whose TM was not reduced to normal until it was normal or diagnosed, collecting the blood samples of eligible patients that we removed high-risk factors from the subjects so that TM could be lowered to normal.

RESULTS: A total of 83,049 blood samples were detected in our hospital, and 89 patients were diagnosed with newly diagnosed tumor. The positive expression rate of CEA in lung cancer patients was 91.4%.

CONCLUSIONS: The diagnosis of tumor relies not only on TM, but also on observation of clinical symptoms, continuous observation of TM dynamic changes and individualized comprehensive analysis. The main purpose of this policy is not only to find patients with "early tumor", but also to cut off the pathogenic pathway of cancer, achieve purpose of tertiary prevention and significantly save medical costs. The examination mechanism and the clinical-related departments are connected, and the pattern of screening, tracking and analysis of abnormal results in large samples is in line with the present situation of China and is worthy of clinical promotion.

Key Words:
Huimin policy, Screening for tumor markers, Risk factors, Dynamic tracking, Tertiary prevention.

Introduction

According to the 2020 global cancer incidence and mortality estimates compiled by the International Agency for Research on Cancer (IARC) to provide an update on the global cancer burden, the global cancer burden is expected to reach 28.4 million cases in 2040, with an annual growth of 47% compared to 2020[1]. Early detection of tumors is one key approach to improve patient survival. Through early treatment including surgical resection of local solid tumors, it may take years for many tumors to develop from initial lesions to metastases, which provides an opportunity for early detection of tumors[2]. The theme of World Cancer Day in 2015 pointed out the goals to be achieved by 2025: the universal promotion of cancer screening and early diagnosis programs and their integration into the residents' health system; the investment of technical strength in the field of early screening, etc. Weihai Social Security Bureau is one of the earliest institutions to incorporate cancer screening into the residents' health system. In September 2014, in order to further meet the needs of insured personnel and reduce medical insurance expenses, Weihai Social Security Center launched a fixed settlement project for the joint detection of multiple tumor markers. The Oncology Department of our hospital undertook the subject consultation and TM result analysis and diagnosis, dynamically tracked the trend of abnormal subjects' indexes, and reduced the TM to normal by removing the high-risk factors of the subjects. For subjects whose TM did not reduce to normal, further tracking is provided until normal result or diagnosis is achieved.

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Patients and Methods

Case Collection

According to the social benefiting policy of Weihai Social Security Service Center, for all eligible retirees participating in the basic medical insurance for employees and residents over 60 years old (inclusive) participating in urban and rural cooperative medical insurance, from September 30, 2014 to December 31, 2017, fasting blood samples from 83,049 people who underwent TM screening in our hospital were collected. The test contents mainly include: CA242, CYFRA21-1, NSE, AFP, CEA, CA125, CA153, free-β-HCG. In addition, male underwent additional t-PSA, f-PSA.

Methods

a) 2 ml fasting blood was drawn from the subjects, and TM was detected by flow fluorescence luminescence method. b) For the subjects whose TM was higher than the normal value, according to the multiple above the normal value, combining our hospital's low-dose lung CT, MRI, B-ultrasound, etc., conduct re-examination, follow-up, inductive analysis, and then perform further diagnosis or exclusion. c) Observe the distribution of benign and malignant diseases in which TM was highly expressed; calculate the positive rate of TM expression in diagnosed tumor patients.

Inclusion Criteria

Subjects with initial cancer confirmed by TM and medical examination.

Exclusion Criteria

Subjects with a history of tumor or recurrence and metastasis were excluded from the scope of this analysis.

Re-Examination and Tracking Criteria

According to the different multiples of TM screening results above the critical value, different intervention measures were taken. All patients with confirmed tumors received a cytological or pathological diagnosis.

TM is normal or slightly abnormally elevated (suspicious positive): inquire about the medical history for any abnormal symptoms. If the TM results are normal but with clinically suspicious symptoms, or the results are abnormal but ≤1.5 times of the normal value, it is recommended to perform relevant examinations or continuously perform 3 months of follow-up review, and if the index still rises, continue to follow up; if the increase is unobvious, review it in 3-6 months; if the result falls to normal, review it in the second year.

Moderately abnormal elevation of TM (dynamic observation): 1.5 times the normal value < TM result of the subject < 2.5 times the normal value: closely follow-up based on clinical symptoms for 3 months, if the result is significantly elevated, systemic or key site examination should be performed immediately. Otherwise, it will be treated as mild elevation.

TM height abnormality (exhaustive examination, close attention): the subject's TM result is ≤2.5 times of the normal value. Combining clinical symptoms, carefully inquire about the medical history and perform physical examination and decide whether to conduct exhaustive physical examination and pay close attention. Otherwise, continuously follow-up until the TM decreases significantly, and then treat it as mild or moderate. If the index is still high after intervention, continue to follow-up until it is normal or diagnosed.

Results

Screening, Tracking and Intervention Results

From September 30, 2014 to December 31, 2017, a total of 83,049 people in our hospital participated in TM screening (Table I), among whom, 4,900 were suspected positive, 2,940 were dynamically observed, 357 had precancerous lesions, and 89 had new diagnosed tumor. For those with abnormally elevated TM index, 156 cases had TM decreased to normal through various interventions such as smoking cessation, alcohol cessation, and truncation of HBV DNA replication. Among the 89 cases of confirmed tumors, gastrointestinal tumors (42 cases of stomach, intestine, liver, bile duct and pancreas) accounted for 47.2%; lung cancer (35 cases) accounted for 39.3%; ovary (5 cases), prostate (5 cases) accounted for 5.6%. There were 1 case of lymphoma and 1 case of unexplained tumor (tumor cells were found in ascites). Early and mid-term diagnosis rate (with opportunity for surgery) from September 2014 to December 2016 was 47.0% (early + middle/total 31/66), compared with 78.3% (18/23) in 2017. Most abnormal subjects require a dynamic follow-up of 2-7 months, and one case has a follow-up time of nearly 2 years.

The Positive Rate of Each TM Index in 89 Tumor Patients

In TM, no related tumor was detected by free-β-HCG; NSE is more sensitive, which may cause

Table I. 2014.9-2017.11 staging of patients participating in TM screening and diagnosed with tumor.

Time	Number of participants	Early stage	Middle stage	Late stage	Diagnosed patients
2014.9-2014.12	9,444	2	1	5	8
2015.1-2015.12	14,581	8	8	12	28
2016.1-2016.12	26,824	6	6	18	30
2017.1-2017.11	32,200	8	10	5	23
Total	83,049	24	25	40	89

hemolysis due to the long-term specimen placement, vascular factors of the subjects, and differences in sample collection techniques, etc. The results are susceptible to the outside world. Based on the long-term comparative observation by the receiving physician, it is not used as the basis for disease diagnosis. As can be seen from Table II, the positive rate of CEA for tumor diagnosis can reach 57.3%, indicating that CEA has a broad spectrum; both liver cancer and prostate cancer are accurately diagnosed by AFP and PSA; the positive rate of CA125 in ovarian cancer is 100%; CA199 is expressed in nearly 90% pancreatic tumors, indicating the relative specificity of TM. In this data, lung cancer ranks first, followed by gastrointestinal tumors, and liver cancer ranks third.

The Distribution of Benign and Malignant Diseases with High Expression of Tumor Markers in Middle-Aged and Elderly People in Weihai Area

In clinical work, many patients cannot find the cause of high TM. Through inquiry into medical history or relevant laboratory tests, similar patients are summarized and it is found that the distribution of benign and malignant disease in these subjects with high TM is as follows (Table III).

Discussion

China is one of the countries with the fastest growing aging population in the world. By the end of 2020, China's population aged ≥ 60 is 260 million. It is expected that the proportion of the population aged ≥ 60 will exceed 30% in 2035. The accelerated aging of the population will keep China's cancer burden on an upward trend[3]. According to the data provided by the American Cancer Center, the incidence of cancer decreased by an average of 0.6% per year in 2012-2016[4]. Several tools are currently used for cancer screening, such as serum tumor marker testing for routine physical examination, low-dose chest CT for lung cancer, mammography for breast cancer, Pap smear test for cervical cancer and fecal occult blood test for colorectal cancer, etc. Serum protein tumor markers such as CEA, AFP, CA-125, CA-199, PSA, etc., have been used to assist the diagnosis and treatment of various tumors for decades[2]. In Asia, these tumor markers are routinely used as part of the physical examination of tens of millions of people every year, and have been successfully used for early detection of tumors[5]. By using this method in the health examination of middle-aged and elderly people, it is possible to screen out high-risk groups, cut off the path of tumor incidence as soon as possible, and achieve the purpose of early detection,

Table II. The ratio of positive cases (%) of each TM index in 89 tumor patients.

Cancer	Number of cases	Number of positive cases (%)					
		CEA	CA199	CYFRA21-1	CA125	AFP	PSA
Lung cancer	35	32 (91.4)	4 (11.4)	6 (17.1)	3 (8.6)	0	0
Gastrointestinal cancer	20	13 (65.0)	6 (30.0)	1 (5.0)	0	0	0
Pancreatic cancer	9	2 (22.2)	8 (88.9)	0	0	0	0
Liver cancer	13	0	0	0	0	13 (100)	0
Prostate Cancer	5	0	0	0	0	0	5 (100)
Ovarian cancer	5	2 (40.0)	2 (40.0)	0	5 (100)	0	0
Other	2	2 (100)	0	0	0	0	0
Total	89	51 (57.3)	20 (22.5)	7 (7.9)	8 (9.0)	13 (14.6)	5 (5.6)

Table III. The distribution of benign and malignant diseases with high expression of tumor markers in middle-aged and elderly people in Weihai area.

Cause	CA242	CEA	AFP	CA125	PSA
Malignant Lesions	Cholangiocarcinoma Pancreatic cancer Ovarian cancer Stomach cancer Liver cancer	Lung cancer Gastrointestinal cancer Pancreatic cancer Bile duct cancer Ovarian cancer	Liver cancer stomach cancer	Liver cancer stomach cancer	Prostate cancer
Benign Lesions	Cholecystitis Pancreatitis Adenomyosis of the gallbladder Gastrointestinal inflammation Gastrointestinal polyps Interstitial pneumonia Pulmonary fibrosis	Smoking Drinking Gastrointestinal polyps Gastrointestinal inflammation Upper respiratory tract infection pneumonia Pulmonary congestion Connective tissue disease Heart failure Various inflammations	Hepatitis B and C virus Replication liver cirrhosis Alcoholism	Adenomyosis Dysmenorrhea Pneumonia Pulmonary fibrosis	Prostatitis benign Prostatic hyperplasia Prostatic hyperplasia

early diagnosis and early treatment. The following three aspects are discussed in the next:

a) The significance of continuous detection and dynamic tracking after the launch of medical insurance policy activities in Weihai, the Oncology Department of our hospital set up an expert group to be responsible for the tracking and screening of abnormal TM results. We went deep into community streets and villages to conduct health education on early cancer screening, thus raising public awareness of cancer. From Table I, it can be seen that the number of people participating in TM screening has increased year by year, and the subjects have changed from passive detection recipients to active participants now, indicating that people have stronger and stronger awareness of health care. With the continuous detection and dynamic tracking of high-risk population with abnormally elevated TM, the diagnosis rate of patients in the early and mid-term was significantly higher in 2017 than in 2014-2016, and the operation rate of the former was 31.3 percentage points higher compared to the latter (78.3% and 47.0%). Most of the tumor patients diagnosed by dynamic tracking are early operable patients. In the process of dynamic tracking, if the corresponding examination cannot be carried out at the appropriate time, it is very likely that the tumor is too small to be diagnosed, or the examination is too late to stop tumor metastasis. Pancreatic cancer is a group of extremely malignant tumors with insidious onset, difficult early-stage diagnosis, rapid progress, short survival time and the worst prognosis. Early detection is the most important potential factor in improving the prognosis of pancreatic cancer patients. One of the most effective strategies for early detection of tumors is screening of the general population[6]. Johannes et al[7] assessed CA19-9 levels in blinded serum from 175 subjects collected 5 years before pancreatic cancer diagnosis and 875 matched controls for the prostate, lung, colorectal and ovarian (PLCO) cancer screening test. It was found that in the PLCO cohort, CA19-9 levels increased exponentially from 2 years before diagnosis, and all cases achieved 60% sensitivity and 99% specificity for CA19-9 within 0-6 months before diagnosis. In cases diagnosed with early disease, CA19-9 has a sensitivity of 50% and a specificity of 99%. Comparability was found (sensitivity 64%, specificity 99%) in differentiating newly diagnosed cases of resectable pancreatic cancer from healthy controls. Among the 9 patients with pancreatic cancer diagnosed in our hospital in Table I, the CA199 index of 5 patients was continuously tracked month by month for 3-7 months, and the terminal diagnosis was pancreatic cancer. The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) was conducted by Menon et al[8]. To determine whether population screening can reduce deaths from ovarian cancer. The results showed that screening did not significantly reduce ovarian and fallopian tube cancer mortality. The European Randomized Prostate Cancer Screening Study[9] showed that prostate-spe-

cific antigen screening can reduce prostate cancer (PC) mortality by 20%. In addition, screening has been shown to reduce the risk of advanced prostate cancer. Only 4 of the 89 tumor patients had related symptoms after careful inquiry into medical history, and 95.5% of the patients had no clinical symptoms. All patients were diagnosed by high follow-up tracking criteria for TM.

b) Early detection, early diagnosis, and early treatment are the keys to cancer cure. On February 9, 2022, the team of Professor Chen Wanqing from the National Cancer Center and Cancer Hospital of the Chinese Academy of Medical Sciences compared the cancer profiles, trends and determinants in China and the United States in 2022. The findings show that lung cancer is expected to be the most common cancer in China and also the leading cause of cancer death in both China and the United States[3]. Early tumor screening is critical for reducing colorectal cancer (CRC)-related mortality[10]. Screening for prostate cancer using the prostate-specific antigen (PSA) test can lead to problems of underdiagnosis and overdiagnosis. However, the combination of magnetic resonance imaging (MRI) or transrectal ultrasonography may overcome these limitations and ultimately confirm or exclude the disease by biopsy[11]. In this data, the tumor incidence rate in our statistics is 107.17/100,000, but it is limited to the incidence of middle-aged and elderly people in Weihai area, and the sample size needs to be expanded. Among 35 patients with lung cancer, the positive expression rate of CEA was as high as 91.4%, of which 5 cases of lung cancer were micro adenocarcinomas, which were radically treated by minimally invasive surgery through thoracoscopy. The positive expression rate of CEA in gastrointestinal tumors was 65%, of which 3 cases of gastric cancer were carcinoma *in situ* and was radically cured by gastroscopic submucosal dissection. Among the 2 patients with normal TM, 1 had a history of chronic atrophic gastritis, and the epigastric discomfort did not ease for nearly 1 month. The other case had occasional intestinal symptoms such as abdominal distension, abdominal pain and tenesmus, etc., which was finally diagnosed as early gastric and colon cancer by gastrointestinal endoscope after the doctor's careful inquiry of medical history. For the 2 patients with prostate cancer diagnosed in 2017, the tPSA was 13.5-33.4 ng/ml, and no abnormality was found in digital rectal examination, prostate B-ultrasound and MRI. The diagnosis was made by 8-needle or 12-needle puncture under B ultrasound guidance, all were early-stage patients. These early-stage patients can be cured only after minimally invasive surgery or radical surgical resection.

c) According to the distribution of TM-positive malignant tumors, carry out targeted health education. In 2022, the number of newly diagnosed cancers in China will be twice that of the United States, and the number of cancer deaths will be five times that of the United States. China and the United States are expected to have 4.82 million and 2.37 million new cancer diagnoses and 3.21 million and 640,000 cancer deaths in 2022, respectively. The top five cancer diagnoses in China are: lung cancer, colorectal cancer, gastric cancer, liver cancer, and breast cancer[3]. It can be seen from Table III that the benign and malignant diseases pointed to the main highly expressed tumor markers can provide a reliable basis for the rapid diagnosis of abnormal populations in Weihai area, so that we can provide targeted health education for the prevention of tumor occurrence, and warn high-risk groups. In this data, the incidence of lung cancer ranks first (39.3%). The National Cancer Statistics Agency of Korea[12] conducted a statistical analysis of cancer incidence data from the National Cancer Database in 1999-2018. It was found that the most common cancer site was the lung, followed by the thyroid, colon and rectum, breast and stomach. In annual updates on cancer rates and trends in the United States provided by the American Cancer Society, Centers for Disease Control and Prevention, etc[6]. Study on data of newly diagnosed cancers found that the incidence of cancer decreased by an average of 0.6% per year in 2012-2016, but trends varied depending on gender, race/ethnicity, and cancer type. Many tumors can be effectively prevented or treated if detected early[13].

Conclusions

The diagnosis of tumors cannot rely on TM alone. Real results can only be obtained after combining clinical symptoms, continuous observation of the dynamic TM changes, "individualized" comprehensive analysis, and excluding interfering factors. Therefore, it is best to have an oncologist with clinical experience to intervene. The model is worthy of clinical promotion, and can be included in routine physical examination items for large-area and multi-age early tumor screening. Second, tumor screening is not only to find "early tumor" patients, but more importantly, to cut off the tumor development pathway, identify high-risk groups through risk assessment, and then conduct further targeted

examinations and diagnoses, so as to effectively eliminate tumors in the initial stage, thus achieving the purpose of prevention and cure, while greatly saving medical costs. It is believed that after years of continuous testing and follow-up of high-risk groups, the risk can be minimized as soon as possible. In the future, early operable patients will have greater proportion than the middle and late stage population. This is also the original intention behind Weihai Medical Insurance Bureau's implementation of this social benefiting policy. However, in the process of differential diagnosis of TM, over-examination and overtreatment should be avoided. Although prostate-specific antigen (PSA) is widely used in specific scenarios, its role in screening for prostate cancer in asymptomatic men remains controversial. As a screening method for prostate cancer, PSA has limited specificity and is prone to overdiagnosis and therefore overtreatment[14]. In addition, there are also some "dumb" tumors, in which, tumor has metastasized, but the tumor markers are normal. It is advisable for the subject to receive systemic examination on a regular basis to avoid missed diagnosis.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Chunbo Wang and Huiguang Gao drafted manuscript. Kexia Bi and Xiaoling Liang analyzed and interpreted data. Xiaodan Tang and Leilei Du acquied the data. All authors read and approved the final version of the manuscript.

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Ethics Approval

The research contents and process of the project were reviewed by the 970 Hospital of the PLA JLSF. The research work was approved in accordance with the international and national ethical requirements on biomedical research.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

Informed Consent

Informed consent was obtained from all the individual participants included in the study.

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