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Original Article

Relevant Risk Factor and Follow-Up of Lung Nodules in Physical Examination with Low-Dose CT Screening

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Abstract

Background: We aimed to explore the risk factors of lung nodules and lung cancer in physical examination population with low-dose multi-slice spiral CT (LDCT) screening, to provide basis for lung cancer screening and follow-up management after CT examination.

Methods: The general data, serum tumor markers and CT images of 2,274 patients underwent LDCT in the Physical Examination Center of the Fourth Hospital of Hebei Medical University, China in 2019 were retrospectively analyzed and followed up for three years.

Results: The detection rate of lung nodules was 48.42%. The detection rate of lung nodules was higher in females, those over 70, those with history of smoking, passive smoking, drinking, precious history of lung diseases and family history of malignant tumors, with statistically significant differences ($P<0.05$). The abnormal rate of serum tumor markers (CA199, CA125 female and CYFRA211) were higher than that in the non-nodule group, with statistically significant differences ($P<0.05$). Multivariate logistic regression analysis showed that gender, age, history of smoking, passive smoking, family history of malignant tumors and serum tumor markers (CYFRA211 and CA199) were independent risk factors for the occurrence of lung nodules.

Conclusion: Gender female, age>35, history of smoking, passive smoking, history of drinking, history of past lung disease, family history of malignant tumors, abnormal CYFRA211 tumor markers were detected and low dose multi-slice spiral CT image showed ground-glass nodules are risk factors for lung nodules and lung cancer, which should be paid close attention to during physical examination and follow-up.

Keywords: Lung nodules; Lung cancer; Risk factors; Follow-up

Introduction

According to the statistics in 2018, the number of new patients and deaths of lung cancer in China reached 774,000 and 691,000, respectively (1), and the incidence and mortality of lung cancer among urban residents in Shijiazhuang were 46.26 out of 100,000 people and 36.98 out of 100,000 people, respectively, both of the data rank the first place (2).

Early diagnosis and intervention are the key to improving survival and reduce mortality in lung cancer. Many international and domestic organizations have recommended low-dose multi-slice

spiral CT (LDCT) in lung cancer screening of high-risk population, but different authorities have different definitions on high-risk population (3, 4). The referred risk factors vary in different regions and different populations, which are difficult to define and quantify. With the popularity of LDCT in physical examination, the detection of lung nodules in different populations also triggered us to think about the relevant risk factors for lung nodules in this region and the follow-up management of patients with lung nodules receiving physical examination.

To this end, we reviewed the data of population receiving physical examination in 2019, followed up them for three years, analyzed the relevant risk factors for lung nodules and the detection rate of malignant nodules, and summarized the imaging characteristics of malignant nodules, so as to provide a theoretical basis for optimizing the screening program of lung cancer after physical examination and the follow-up management of population with lung nodules after physical examination.

Methods

A retrospective analysis was conducted on the data of population receiving physical examination screened by LDCT in the Physical Examination Center of the Fourth Hospital of Hebei Medical University, China in 2019. A total of 2,274 patients were excluded with original lung cancer and those who did not fill in the questionnaire, including 1,047 males and 1,227 females, aged 40-89 years old, with the median age of 53 years old.

General data collection

General data (name, gender, age), BMI, history of smoking, passive smoking, drinking, taking exercise, drinking tea, lung diseases and genetic tumors were collected with the Questionnaire on Risk Factors of Lung Cancer designed by the Cancer Institute approved by the Medical Ethics Committee of our hospital. All the patients had informed consent (Fig. 1).

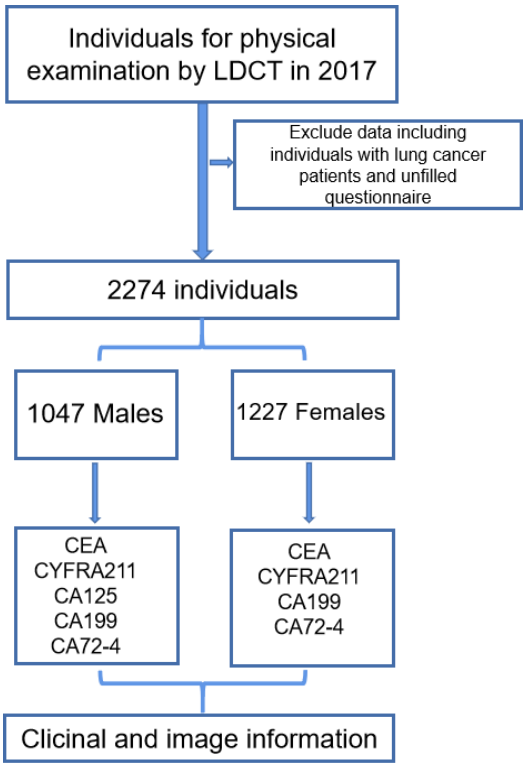

Fig. 1: The flow chart of the study

Definition standards for risk factor indexes

BMI: 18.5-23.9 kg/m^2 was normal, <18.5 kg/m^2 or > 23.9 kg/m^2 was abnormal; History of smoking: Smoking at least 1 a day, for 1 year or more, had smoked or had quit smoking; History of passive smoking: Daily exposure to other smokers for more than 15 minutes; History of taking exercise: Taking exercise at least 30 minutes once, for at least 3 times a week; History of drinking or drinking tea: Drinking at least once a week for more than half a year; History of lung diseases: The patient has suffered from chronic bronchitis, asthma, emphysema, tuberculosis, bronchiectasis and other diseases; Family history of malignant tumors: The patients had relatives related by blood have suffered from malignant tumors.

Determination of serum tumor markers and normal diagnostic standards

Three ml fasting venous blood was collected from the patients in the morning, and centrifuged at 3000 r/min for 10 min, to take the upper serum. According to the previous researches (5-11,

the levels of specimen carcinoembryonic antigen (CEA), cytokeratin (CYFRA211), carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199) and CA72-4 detected by automatic electrochemiluminescence immunoassay were reareded as the common detection methods. The detector and reagents were produced by Roche. The normal range of each index was CEA<5 ng/ml; CA125: 0-35 u/ml; CA199: 0-29 u/ml; CYFRA211: 0-3.3 ng/ml; CA72-4: 0-6.9 u/ml(5-11).

Low-dose multi-slice spiral CT scanning and image evaluation

The instrument for screening was the second-generation SOMATOM Definition Flash CT scanner produced by Siemens. The patients took the supine position, with both hands up, and was scanned with single breath hold continuous spiral scan at the end of inhalation from the entrance of thorax to the horizontal position of the tip of costophrenic angle, with the tube voltage of 120 kV and the reference value of 50mAs, by using the automatic tube current modulation method and the algebraic reconstruction technique. The gantry rotation speed was 0.5 s/r, the scanning matrix was set to 512*512, the layer thickness was 5.0mm, and the reconstruction layer thickness was 1.0 mm. Lung algorithm and standard algorithms were reconstructed simultaneously. Imaging data were transmitted to the picture archiving and communication systems (PACS), which were then reviewed by the image workstation to analyze small nodules. The diagnostic standards were subject to the reports issued by the CT imaging physician. Patients with at least one detected nodule with the diameter ≥4mm were included into the nodule group, those with no nodule detected were included into the non-nodule group, and those with nodules diagnosed as malignant by follow-up were included into the lung cancer group.

Statistical analysis

All the data were recorded in Excel by researchers according to the questionnaires and the results of the patients receiving physical examination, and the database was finally established. Statistical analysis of data was performed with SPSS 13.0 software (Chicago, IL, USA). Categorical variables were presented as numbers and percentages. The comparison was conducted with $\chi 2$ test, and then, the relationship of variables with detection rates were quantified by a multivariable logistics regression model with odds ratios (ORs) and their 95% confidence intervals (CIs). Multivariate analysis with $P<0.05$ regarded as statistically significant.

Results

Detection rate of lung nodules in low-dose multi-slice spiral CT screening

A total of 2,274 patients were screened with LDCT, of which 1,101 were screened as lung nodules, with a detection rate of 48.4%, including 474 males and 627 females, and the other 1,173 as no lung nodules, including 573 males and 600 females.

Analysis of risk factors in general data of lung nodule population

Univariate analysis showed that the detection rates of lung nodules were different in females, at different ages, those with history of smoking, passive smoking, drinking, previous history of lung diseases and family history of malignant tumors, with statistical significance ($P<0.01$), while the detection rates of lung nodules in patients with different BMI, history of lampblack pollution, taking exercise and drinking tea were not statistically significant (Table 1).

Table 1: Analysis of risk factors in general data of lung nodule population

Factor	*Total number of patients*	*Number of patients with lung nodules*	*Detection ratio (%)*	*χ2*	*P*
Gender					
Male	1047	474	*45.27*		
Female	1227	627	*51.10*	7.683	0.006
Age					
35-50	892	371	*41.59*		
51-60	687	350	*50.95*		
61-70	438	220	*50.23*		
> 70	257	160	*62.26*	2324.651	< 0.001
BMI					
Normal	1014	499	*49.21*		
Abnormal	1260	602	*47.78*	0.462	0.497
History of smoking					
Yes	464	299	*64.44*		
No	1810	802	*44.31*	59.924	< 0.001
History of passive smoking					
Yes	778	413	*53.08*		
No	1496	688	*45.99*	10.318	0.001
History of lampblack pollution					
Little	210	91	*43.33*		
More	2064	1010	*48.93*	0.858	0.354
History of taking exercise					
Yes	1240	595	*47.98*		
No	1034	506	*48.94*	0.205	0.651
History of drinking					
Yes	812	363	*44.70*		
No	1462	938	*50.48*	6.97	0.008
History of drinking tea					
Yes	1418	674	*47.53*		
No	856	427	*49.88*	1.182	0.277
Previous history of lung diseases					
Yes	462	358	*77.49*		
No	1812	743	*41.00*	196.213	< 0.001
Family history of malignant tumors					
Yes	564	358	*63.48*		
No	1710	743	*43.45*	68.096	< 0.001

Analysis on risk factors for abnormal detection of tumor markers in lung nodules

Because CA125 was only for females, the total number of patients detected was 1,260, including

640 with lung nodules and 620 without lung nodules. The number of patients detected for other indexes was 2,274 for each, including 1,101 with lung nodules and 1,173 without lung nodules. As shown in Table 2, the abnormal rates of indexes, CA199, CA125 female and CYFRA211, in those with lung nodules were higher than those in patients without lung nodules, with statistically significant, $P<0.05$.

Table 2: Analysis on risk factors for abnormal detection of tumor markers in lung nodules [n (%)]

Tumor markers	*Number of patients without lung nodule (%)*	*Number of patients with lung nodule (%)*	*χ2*	*P*
CA199				
Normal	1101 (93.86)	995 (90.37)		
Abnormal	72 (6.13)	106 (9.63)	9.585	0.002
CA125 (female)				
Normal	604 (97.42)	609 (95.16)		
Abnormal	16 (2.58)	31 (4.84)	4.491	0.034
CYFRA211				
Normal	999 (85.17)	880 (79.92)		
Abnormal	174 (14.83)	221 (20.07)	10.573	0.001
CEA				
Normal	1109(94.54)	1035(94.00)		
Abnormal	64(5.45)	66 (5.99)	1.805	0.179
CA72-4				
Normal	1011 (86.18)	953 (86.56)		
Abnormal	162 (13.81)	148 (13.44)	0.042	0.838

Multivariate logistic regression analysis

The risk factors with statistical significance in univariate analysis were analyzed by the multivariate logistic regression analysis (Table 3). Gender, age, history of smoking, passive smoking, drinking, family history of malignant tumors, serum tumor markers, CYFRA211 and CA199, were screened as independent risk factors for lung nodules.

Table 3: Multivariate logistic regression analysis

Item	*β*	*SE*	*Wald*	*Exp(B)*	*95%CI*	*P*
Gender	.730	.122	36.014	2.076	1.635 ~ 2.635	.000
Age	.622	.122	25.857	1.863	1.466 ~ 2.368	.000
History of smoking	1.453	.137	112.274	4.276	3.268 ~ 5.595	.000
History of passive smoking	.268	.0.95	8.037	1.307	1.086 ~ 1.574	.005
History of drinking	-.270	.117	5.303	.764	.6.07 ~ .961	.021
Previous history of lung diseases	.168	.148	1.279	1.183	.884 ~ 1.582	.258
Family history of malignant tumors	.842	.105	63.946	2.322	1.889 ~ 2.854	.000
CA199	.381	.169	5.063	1.464	1.050 ~ 2.039	.024
CYFRA211	.471	.119	15.598	1.601	1.268 ~ 2.022	.000

Analysis on detection rate for lung cancer

In the lung nodule group followed up for three years, there were 30 patients underwent final surgical treatment, including 10 for baseline screening and 20 for enlarged or new nodules during follow-up. There were 29 patients with pathological diagnosis, 2 patients with atypical hyperplasia, and 27 patients with adenocarcinoma in situ and microinvasive adenocarcinoma, with the detection rate of lung cancer of 1.19%.

Analysis on risk factors for general conditions in lung cancer

The analysis on risk factors for general conditions showed that the detection rates of lung cancer in males, those at the age > 70, those with history of smoking, passive smoking and family history of malignant tumors were high, showing statistical significance after comparison, $P<0.05$ (Table 4).

Table 4: Analysis on risk factors for general conditions in lung cancer

Factor	*Number of patients receiving screening*	*Number of patients with lung cancer*	*Detection rate of lung cancer (%)*	*χ2*	*P*
Gender					
Male	1047	13	1.24		
Female	1227	14	1.14	7.683	0.006
Age					
35-50	892	7	0.78		
51-60	687	7	1.02		
61-70	438	7	1.60		
> 70	257	6	2.37	12.80	0.004
History of smoking					
Yes	464	10	2.16		
No	1810	3	0.17	22.335	0.000
History of passive smoking					
Yes	778	9	1.16		
No	1496	5	0.33	4.396	0.036
Family history of the malignant tumors					
Yes	564	17	3.01		
No	1710	10	0.58	21.335	0.000

Note: The results of smoking and passive smoking were correction chi square, and the result of age was Fisher exact probability method.

Follow-up analysis on abnormal rate of tumor markers in lung cancer

Table 5 shows that the abnormal rates of CA125 female and CYFRA211 in patients with lung cancer were higher than those without lung nodules, with statistical significance, $P<0.05$.

Imaging analysis on lung cancer

CT imaging of 27 patients with lung cancer showed site of nodules: 11 with nodules in the left lung, for 40.74%, 16 with nodules in the right lung, for 59.26%; Density of nodules: 16 with ground-glass nodules, for 59.26%, 3 with subsolid nodules, for 11.11%, 8 with solid nodules, for 29.63%; Size of nodules: 8 with 5-9mm nodules, for 29.63%, 19 with nodules > 9mm, for 70.37%; Shape of nodules: 9 with nodules in quasi-circular shape, for 33.33%, 8 with nodules in irregular shape, for 29.63%, 5 with nodules in circular shape, for 18.52%, 4 with nodules in oval shape,

for 14.81%, 1 with nodules in triangle shape, for 3.70%; Margin of nodules: lobed in 7 cases (25.93%), burr in 6 cases (22.22%), smooth in 8 cases (29.63%) and fuzzy in 6 cases (22.22%); Tumor-lung interface: clear in 18 cases (66.67%) and blurred in 9 cases (33.33%); Intrtuberous bronchial or vacuolar signs: existent in 8 cases (29.63%) and nonexistent in 19 cases (70.37%); Angiographic signs: existent in 9 cases (33.33%) and nonexistent in 18 cases (66.67%).

Table 5: Analysis of the abnormal rate of tumor markers in lung cancer

Index	*Abnormal rate in patients without lung nodules (%)*	*Abnormal rate in patients with lung nodules (%)*	*χ2*	*P*
CA199	72/1173 (6.13)	2/27 (7.40)	0.000	1.00
CA125 (Female)	16/620 (2.58)	2/14 (14.29)	6.773	0.009
CYFRA211	171/1173 (14.58)	10/27 (37.03)	6.650	0.010
CEA	55/1173 (4.69)	3/27 (11.11)	0.827	0.363
CA72-4	162/1173 (13.81)	3/27 (11.11)	0.109	0.741

Note: The result of CA125 were Fisher exact probability method, and the rest results were corrected chi square

Discussion

LDCT had an important role in improving the detection rate of lung nodules, early lung cancer and reducing the mortality of lung cancer (12). At present, all the people receiving physical examination older than 35 in the provincial examination package of provincial medical insurance are subjected to low-dose multi-slice spiral CT for chest screening. The detection rate of lung nodules in this study was 48.42%, exceeding 11.67% in another study, which might be relevant to different times and selected objects (13). According to the univariate analysis of lung nodules, the detection rates of lung nodules in those with different gender, age, history of smoking, passive smoking, drinking, precious history of lung diseases, family history of malignant tumors, CA125 female, CYFRA21-1 and CA199 were higher than those without lung nodules were. Multivariate regression showed that gender, age, history of smoking, passive smoking, drinking, family history of malignant tumors, CYFRA211 and CA199 were independent risk factors for lung nodules in people receiving physical examination.

Lung nodule is the early manifestation of lung cancer, and about 5% of lung nodules may eventually evolve into lung cancer, and monitoring and follow-up of patients with lung nodules is as important as early detection (14). In this study, patients with lung nodules were monitored and followed up for three years, and 30 patients were surgically treated. The pathological results were invasive adenocarcinoma and adenocarcinoma in situ, with the detection rate of lung cancer of 1.19%, lower than 1.3% in another study, which might be relevant to the duration of follow-up and the number of people screened (15). According to the analysis on general conditions of patients with lung cancer, the detection rates of risk factors including male, age > 70, history of smoking, passive smoking and family history of malignant cancer were higher, and the abnormal rates of CA125 female and CYFRA211 in tumor markers were high, with statistical significant. The analysis on imaging characteristics showed that those with nodules in right lung had a higher proportion than those with nodules in left lung, so were those with ground-glass nodule density, nodules > 9 mm, clear-tumor lung interface, and those who had no bronchial signs, vacuoles and no angiographic signs in nodules also had a higher proportion.

In this study, age was correlated with the occurrence of lung nodules and lung cancer. Multivariate analysis on lung nodules showed OR=1.863, 95%CI (1.466-2.368), $P<0.001$, which was consistent with another study (16), with the ratio to age-related risk of lung nodules of 1.132, 95%CI

(1.045-1.218). With the increase of age, the detection rate of lung nodules and lung cancer showed an increasing trend, and the detection rate of those at the age > 70 was the highest, in line with the trend of incidence and mortality of patients with lung cancer at different ages and genders in Hebei Province (17). Although the detection rate of lung nodules was not high in people under 40, two patients with lung cancer of them were still detected by follow-up, both of which were female non-smokers, and cannot be ignored.

This study showed that the detection rates of lung nodules and lung cancer in patients with history of smoking and passive smoking were higher than non-smokers. Smoking could induce the production of lung nodules by affecting transcriptional and translation processes (18), or by directly damaging DNA. The incidence of lung nodules in smokers was higher than that in non-smokers, history of smoking was an independent risk factor for lung cancer (OR=7.9, 95%CI: 2.6~23.6) (19). 68.04% of male patients with lung cancer was attributable to smoking, and 26.51% of non-smokers was attributable to passive smoking (20). In this study, of 14 female patients with lung cancer, 9 patients had a history of passive smoking.

This study showed that the detection rate of lung nodules and lung cancer was higher in patients with a family history of malignant tumors, which confirmed that the family history of malignant tumors is an independent risk factor for lung cancer and lung nodules. A study identified family history of malignant tumors as a risk factor for lung cancer, with OR=6.6.06, 95%CI: 3.439-12.689 (21). Family history of lung cancer or other cancers increased the risk for lung cancer, and family history of cancers is a strong predictor of lung cancer for females (22).

Tumor markers used in clinical for lung cancer screening include CEA, CYFRA211, SCC and NSE. CYFRA211 is mainly expressed in squamous cancer cells, but it is also seen in adenocarcinoma and small cell carcinoma (23). This study showed that the positive detection rate of CYFRA211 was higher in those with lung nodules and lung cancer than that in those without nodules, and its sensitivity was higher than other indexes. A study pointed out that CYFRA211 level in the serum was significantly higher in males with lung cancer than that in females with lung cancer, and the combined detection of CEA, CA125 and CYFRA211 is more conducive to the early detection of lung cancer (24). Abnormal alteration of a certain tumor marker in histological cells often suggests the potential for developing a certain disease in a patient. Therefore, patients with lung nodules combined with positive CYFRA211 should be followed up regularly.

Ground-glass nodules refer to the limited thin density enhancement shadow with clear or unclear boundaries on CT, which are divided into mixed and simple ground-glass nodules according to the solid components of nodules. In this study, the highest proportion of pure ground-glass nodules was 59.26%, much higher than that of solid nodules, which was consistent with the conclusion of a previous study (25). The judgment of CT signs such as nodule diameter, shape, margin, lobulation, burr sign, vacuole sign, bronchial inflation sign, vascular cluster sign, pleural depression sign and density is helpful for the differentiation and diagnosis of benign and malignant nodules (26). In this study, the proportion of nodule analysis of CT signs was not prominent, which may be relevant to the small number of patients with lung cancer. According to the Fleishner guidelines, solitary ground-glass nodules with a diameter > 5 mm, solitary partial solid ground-glass nodules and multiple ground-glass nodules should be followed up for whether the nodules were stable (27). Of the 27 patients with lung cancer in review, 17 were operated on due to increased nodules and density during follow-up, and one was treated for new-onset nodules.

Conclusion

In general, the independent risk factors included age above 35 years old, females, history of active and/or passive smoking, history of drinking, previous history of lung disease and family history of malignancy for the health examination popula-

tion. The population who with these characteristics above should select LDCT as the screening method, which was benefited to early detection for pulmonary nodule and lung cancer. During the post-examination follow-up, we should pay more attention to the patients who had both positive CYFRA211 and pulmonary ground glass nodules, which was more significant for early diagnosis of lung cancer.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

References

1. Wang N, Liu S, Yang L, et al (2019). Interpretation of the 2018 Global Cancer Statistical Report. *Electronic Journal of Comprehensive Cancer Therapy,* 5(1): 87-97.
2. Dong H, Gao C, Ma X (2017). Analysis of the incidence and mortality of malignant tumors in Shijiazhuang City, Hebei Province in 2013. *China Oncology,* 26(06): 430-433.
3. Wood DE, Kazerooni E, Baum SL, Dransfield MT, et al (2015). Lung cancer screening, version 1.2015: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw,* 13(1):23-34.
4. Wang L, Hong Q (2019). Interpretation of Chinese expert consensus on diagnosis and treatment of pulmonary nodules (2018 edition). *Chinese Journal of Practical Internal Medicine,* 39(5):440-442.
5. Wang HP, Wu HY, Wang Y, Wang L (2017). Combined detection of tumor markers and serum inflammatory factors in the diagnosis and treatment of gynecologic oncology. *J Biol Regul Homeost Agents,* 31(3):691-5.
6. Zhang C, Zheng W, Lv Y, Shan L, et al (2020). Postoperative carcinoembryonic antigen (CEA) levels predict outcomes after resection of colorectal cancer in patients with normal preoperative CEA levels. *Transl Cancer Res,* 9(1):111-8.
7. Sasamoto N, Babic A, Rosner BA, et al (2019). Development and validation of circulating CA125 prediction models in postmenopausal women. *J Ovarian Res,* 12(1):116.
8. Guo B, Lian W, Liu S, Cao Y, Liu J (2019). Comparison of diagnostic values between CA125 combined with CA199 and ultrasound combined with CT in ovarian cancer. *Oncol Lett,* 17(6):5523-8.
9. Xu C, Liu J, Xing L, Liu S (2010). [Clinical significance of serum cytokeratin 19 fragment in the prediction of chemotherapy efficacy and prognosis in patients with advanced non-small cell lung cancer]. *Zhongguo Fei Ai Za Zhi,* 13(10):954-61.
10. Zhao B, Zhang M, Liang Y, Yang Z (2019). An abnormal elevation of serum CA72-4 rather than other tumor markers can be caused by use of colchicine. *Int J Biol Markers,* 34(3):318-21.
11. Liu P, Zhu Y, Liu L (2015). Elevated serum CA72-4 levels predict poor prognosis in pancreatic adenocarcinoma after intensity-modulated radiation therapy. *Oncotarget,* 6(11):9592-9.
12. Becker N, Motsch E, Trotter A, et al (2020). Lung cancer mortality reduction by LDCT screening-Results from the randomized German LUSI trial. *Int J Cancer,* 146(6):1503-1513.
13. Wang J, Liang D, Jin J, et al (2020). Screening of lung cancer and pulmonary nodules with positive low-dose spiral CT in physical examination in Hebei Province. *Chinese Public Health,* 36(1):20-24.
14. Carlos RC, Sicks JD, Chiles C, et al (2019). Lung Cancer Screening in the National Cancer Institute Community Oncology Research Program: Availability and Service Organization. *J*

Am Coll Radiol, 16(4 Pt A):427-434.
15. Heuvelmans MA, Groen HJ, Oudkerk M (2017). Early lung cancer detection by low-dose CT screening: therapeutic implications. *Expert Rev Respir Med,* 11(2):89-100.
16. Chen NA, Ma J (2014). A multivariate risk factors analysis study comtributing to so Iitary Pulmonary nodules. *Chin J Clinicians,* 8(14):2602-2607.
17. Shi J, Liang D, Li D, et al (2018). Analysis of the incidence and mortality of malignant tumors in Hebei Province in 2014. *Oncology,* 38(4):329-338.
18. Wang S, Tu J, Chen W (2019). Development and Validation of a Prediction Pneumothorax Model in CT-Guided Transthoracic Needle Biopsy for Solitary Pulmonary Nodule. *Biomed Res Int,* 2019:7857310.
19. Gould NS, Min E, Huang J, et al (2015). Glutathione Depletion Accelerates Cigarette Smoke-Induced Inflammation and Airspace Enlargement. *Toxicol Sci,* 147(2):466-474.
20. Kurahashi N, Inoue M, Liu Y, et al (2008). Passive smoking and lung cancer in Japanese non-smoking women: a prospective study. *Int J Cancer,* 122(3):653-657.
21. Pallis AG, Syrigos KN (2013). Lung cancer in never smokers: disease characteristics and risk factors. *Crit Rev Oncol Hematol,* 88(3):494-503.
22. Lin H, Huang YS, Yan HH, et al (2015). A family history of cancer and lung cancer risk in never-smoking: a clinic based case control study. *Lung Cancer,* 89(2):94-98.
23. Huang WY, Kemp TJ, Pfeiffer RM, et al (2017). Impact of freeze-thaw cycles on circulating inflammation marker measurements. *Cytokine,* 95:113-117.
24. Grunnet M, Sorensen JB (2012). Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. *Lung Cancer,* 76(2):138-143.
25. Liu B (2019). Diagnosis and Treatment of Pulmonary Ground-glass Nodules. *Zhongguo Fei Ai Za Zhi,* 22(7):449-456.
26. Li Q, Fan L, Cao ET, Li QC, Gu YF, Liu SY (2017). Quantitative CT analysis of pulmonary pure ground-glass nodule predicts histological invasiveness. *Eur J Radiol,* 89:67-71.
27. Naidich DP, Bankier AA, MacMahon H, et al (2013). Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. *Radiology,* 266(1):304-317.