Postprint of a Prospective Cohort Study on the Association Between Chronic Disease Risk Score and Cancer Incidence Risk

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Abstract

Background Tumors, like other chronic diseases, exhibit a multidimensional state, and multiple chronic diseases share common risk factors with tumors. Objective To investigate the association between comprehensive chronic disease risk score and tumor incidence risk. Methods The study subjects were 18,009 examinees from the "Tianjin Chronic Disease Risk and Health Management Cohort" who received health examinations from January 2015 to December 2019. Using categorical variables of chronic disease-related indicators (including BMI, waist circumference, blood pressure, blood glucose, total cholesterol, triglycerides, uric acid, total bilirubin, heart rate, and estimated glomerular filtration rate) as independent variables, and tumor onset as the dependent variable, a multivariate-adjusted Cox proportional hazards regression model was used to evaluate the association between each chronic disease indicator and tumor incidence risk, and to calculate a comprehensive chronic disease risk score. Based on tertiles of the chronic disease risk score, participants were divided into a low-risk group (<6 points), a medium-risk group (6-9 points), and a high-risk group ($ 9 points). Cox proportional hazards regression models were used to calculate hazard ratios (HR) for tumor incide years (median follow-up 4.00 years), with 91 confirmed tumor cases diagnosed. Compared with the low chronic dis points) showed increased tumor incidence risk, with an HR (95% CI) value of 3.00 (1.32-6.82, P=0.009). Conclusion Higher chronic disease risk scores are associated with higher tumor incidence risk.

Full Text

Preamble

Association between Chronic Disease Risk Score and Cancer Risk: A Prospective Cohort Study

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Abstract

Background: Cancer and chronic diseases share a multidimensional nature and multiple common risk factors. **Objective:** To investigate the association between a comprehensive chronic disease risk score and cancer incidence. **Methods:** A total of 18,009 individuals who received physical examinations between January 2015 and December 2019 in the Tianjin Chronic Disease Risk and Health Management Cohort were enrolled. Using categorical variables of chronic disease-related indicators (including BMI, waist circumference, blood pressure, blood glucose, total cholesterol, triglycerides, uric acid, total bilirubin, heart rate, and estimated glomerular filtration rate) as independent variables and cancer incidence as the dependent variable, multivariate-adjusted Cox proportional hazards regression models were used to evaluate the association between each chronic disease indicator and cancer risk, and a comprehensive chronic disease risk score was calculated. Based on tertiles of the chronic disease risk score, participants were divided into low-risk (<6 points), medium-risk (6-9 points), and high-risk ($ 9 $points)groups.Coxproportionalhazardsregressionmodelswereusedtocalculatehazardratios(HR)forcance
*Results : * * Thestudyfollowed71,835person − years(medianfollow − up4.00years)andidentified91incidentcancercases.Comparedwiththelow − riskgroup,themedium − andhigh − riskgroupsshowedHRs(95 $9 points) showed increased cancer risk with an HR (95% CI) of 3.00 (1.32-6.82, P=0.009). **Conclusion:** Higher chronic disease risk scores are associated with increased cancer risk.

Key Words: Chronic disease; Risk score; Risk factor; Cancer risk; Cohort study

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Introduction

Chronic non-communicable diseases, including cancer, cardiovascular disease, chronic respiratory disease, diabetes, and chronic kidney disease, account for 71% of global mortality, with cancer being the leading cause of death. Global cancer burden estimates for 2020 included 19.3 million new cases, 10 million deaths, and 50.6 million 5-year prevalent cases, with projections indicating 28.4 million new cases by 2040—a 47% increase from 2020.

According to the Global Burden of Disease Study, the top six risk factors contributing to disability-adjusted life years (DALYs) in high and middle sociodemographic index countries include tobacco use, high systolic blood pressure, high body mass index (BMI), high fasting plasma glucose, high low-density lipoprotein cholesterol, and kidney dysfunction. Cancer shares a multidimensional state with other chronic diseases, and multiple chronic conditions have common risk factors with cancer, particularly metabolic abnormalities that can directly or indirectly promote tumorigenesis and progression. Studies have shown that type 2 diabetes or hyperglycemia increases cancer risk, while other research has linked cancer risk to cardiovascular indicators including blood pressure, heart rate, blood lipids, chronic kidney disease, and uric acid.

The association between individual chronic disease indicators and cancer risk is relatively weak, yet chronic diseases often cluster with multiple abnormal indicators. Therefore, this study constructed a comprehensive chronic disease risk score using multiple chronic disease indicators and examined its association with cancer incidence after long-term follow-up.

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1. Methods

1.1 Study Design and Population

This prospective cohort study utilized the Tianjin Chronic Disease Risk and Health Management Cohort, which routinely collects de-identified health examination data from individuals receiving annual or biennial comprehensive physical examinations at the Health Management Center of Tianjin Medical University General Hospital. Most participants were employees from local enterprises and institutions undergoing group examinations, with some self-paying individuals.

Inclusion criteria: (1) Age >18 years; (2) No cancer diagnosis at baseline; (3) Complete baseline data for all chronic disease indicators. **Exclusion criteria:** (1) Only one health examination during the study period; (2) Cancer diagnosis within one year of follow-up; (3) Cancer recurrence or metastasis. The study endpoint was incident primary cancer. Follow-up ended at the date of cancer diagnosis or cohort follow-up completion (December 31, 2019), whichever occurred first. A total of 114 cancer cases were identified during follow-up, with 23 cases diagnosed within one year excluded, resulting in a final sample

of 18,009 participants. The study was approved by the Ethics Committee of Tianjin Medical University General Hospital (Approval No.: IRB2021-WZ-095), and all participants provided informed consent.

1.2 Data Collection

Questionnaire Survey: All participants completed a pre-examination health risk assessment questionnaire collecting demographic information (age, sex, marital status, education level, income), lifestyle factors (smoking, alcohol consumption, physical activity), medical history, and diseases diagnosed in the past year.

Physical Examination: Conducted by trained professionals, including height, weight, waist circumference, blood pressure measurement, and electrocardiography. Height and weight were measured using an Inbody stadiometer (Inbody Co. Ltd, Korea) with participants wearing light clothing without shoes, and BMI was calculated. Waist circumference was measured twice consecutively using a non-elastic tape and averaged. After 5 minutes of seated rest, systolic and diastolic blood pressure were measured twice in the left arm using a TM-2655P automatic sphygmomanometer and averaged. Heart rate was measured using a 12-lead electrocardiogram automatic analysis system (MAC800).

Laboratory Testing: All participants provided fasting venous blood samples for measurement of fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), serum uric acid (SUA), total bilirubin (TBil), and serum creatinine (Sr). All samples were sent to the laboratory within 1 hour of collection for analysis using a Hitachi 7170 automatic biochemical analyzer (Japan). Estimated glomerular filtration rate (eGFR) was calculated using the modified MDRD formula: eGFR $= 186\times(\mathrm{Sr})^{-1}.^{154}\times(\mathrm{Age})^{-0}.^{203}\$\times\$0.742$ (for females). Variable classifications and assignments are shown in .

1.3 Calculation of Chronic Disease Risk Score

We used the disease risk scoring method reported by Sullivan et al. to calculate the comprehensive chronic disease risk score. The steps were: (1) Using categorical variables of chronic disease-related indicators as independent variables and cancer incidence as the dependent variable, multivariate-adjusted Cox proportional hazards regression models (adjusting for age [continuous], sex, smoking status, alcohol consumption, and all chronic disease indicators) were used to evaluate the association between each chronic disease indicator and cancer risk; (2) Risk values for each category or level of chronic disease indicators were calculated by dividing their regression coefficients by a constant representing one point in the final risk scoring system. In Framingham Study scoring systems, calculating this constant based on age has demonstrated importance. Therefore, our constant was derived from the regression coefficient for age (continuous variable) in the Cox model (0.0402) multiplied by median follow-up time (4.0 years), yielding 0.1608; (3) Risk values were rounded to the nearest integer; (4) Individual risk values for each chronic disease indicator were summed to calculate

the comprehensive chronic disease risk score, as shown in .

1.4 Chronic Disease Risk Score Grouping

Based on the calculated comprehensive chronic disease risk score, participants were divided into three groups according to tertiles: low-risk (<6 points), medium-risk (6-9 points), and high-risk ($ $9 points).

1.5 Cancer Ascertainment

Participants completed a pre-examination health risk assessment questionnaire reporting diseases diagnosed in the past year. If participants reported any cancer diagnosis during follow-up, they were required to provide pathological reports and informed consent.

1.6 Statistical Analysis

Data processing and statistical analysis were performed using Stata 13.0. Age, which was not normally distributed, was expressed as median (P25, P75) and compared between sexes using Mann-Whitney U test. Smoking status, alcohol consumption, and all chronic disease indicator variables were expressed as frequencies and percentages, with between-sex differences compared using ^{2} tests. Cox proportional hazards regression models were used to calculate the association between chronic disease risk score (both categorical and continuous) and cancer incidence, expressed as HRs with 95% confidence intervals (CI), with proportional hazards assumption testing. Trend tests were evaluated using median scores in each chronic disease risk score group. P<0.05 was considered statistically significant.

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2. Results

At follow-up completion, the median follow-up duration was 4.0 years (range: 3.02-5.05 years), totaling 71,835 person-years, with 91 incident cancer cases identified (33 men, 58 women; ^{2}=6.81, P=0.009). Cancer types included thyroid cancer (38 cases, 41.8%), breast cancer (17 cases, 18.7%), lung cancer (9 cases, 9.9%), colorectal cancer (5 cases, 5.5%), renal cancer (3 cases, 3.3%), prostate cancer (3 cases, 3.3%), gynecological tumors (5 cases, 5.5%), liver cancer (2 cases, 2.2%), gastric cancer (2 cases, 2.2%), and other types (7 cases, 7.7%). The mean age at cancer diagnosis was 50.3 $\pm$ 13.4 years, with an average time from baseline to diagnosis of 2.35 $\pm$ 0.91 years.

2.1 Baseline Characteristics

The 18,009 participants had a median baseline age of 38.5 years (range: 18.4-89.1), including 8,987 men (49.9%, age range 18.4-89.1 years) and 9,022 women

(50.1%, age range 19.4-88.3 years). Men were older and had higher rates of current smoking and alcohol consumption, as well as higher proportions in categories of BMI $ 24.0kg/m^{2}, $elevated waist circumference$, $pre hypertension and hypertension$, $elevated blood$ as shown in .

2.2 Association Between Chronic Disease Indicators and Cancer Risk

Multivariate-adjusted Cox regression analysis revealed a U-shaped relationship between SUA level and cancer risk. Compared with SUA levels of 302-368 mol/L, HRs (95% CI) for cancer risk were 2.46 (1.19-5.07, P=0.014), 1.98 (1.01-3.88, P=0.045), and 1.34 (0.64-2.79, P=0.433) for SUA levels <247 mol/L, 247-302 mol/L, and $ $368 mol/L, respectively. No other chronic disease indicators showed statistically significant associations with cancer risk, as presented in .

2.3 Association Between Chronic Disease Risk Score and Cancer Risk

Compared with the low-risk group (<6 points), the medium-risk (6-9 points) and high-risk ($ $9 points$) $groups showed HRs$ ($95^{\{2\}} = 1.98, P = 0.371$). $Each one-point increase in chronic disease risk score was asso$ $0.31, P = 0.579$). $Among women, the high-risk group$ ($9 points$) $showed increased cancer risk with an HR$ (95^{2}$ P=0.538), as shown in .

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3. Discussion

Our findings demonstrate that a higher comprehensive chronic disease risk score, calculated from 10 indicators including BMI, waist circumference, blood pressure, glucose, total cholesterol, triglycerides, uric acid, total bilirubin, heart rate, and eGFR, is associated with increased cancer risk after a median follow-up of 4.0 years, showing a dose-response relationship.

These results align with previous studies reporting associations between combined metabolic indicators and cancer risk. Tu et al. calculated a chronic disease risk score using blood pressure, total cholesterol, glucose, uric acid, heart rate, urine protein, and eGFR in a Taiwanese health examination cohort, finding that the highest risk group had 2.21 times the cancer risk of the lowest group (95% CI: 1.77-2.75) after a mean follow-up of 8.7 years, similar to our findings. Stocks et al. used BMI, blood pressure, glucose, total cholesterol, and triglycerides to calculate a metabolic risk score, demonstrating a linear positive association with cancer risk, where each one-standard-deviation increase in metabolic risk score was associated with 5% (95% CI: 3-8%) and 8% (95% CI: 5-11%) increased cancer risk in men and women, respectively. Our sex-stratified analysis showed that women in the high-risk group had 3.00 times (95% CI: 1.32-6.82) the cancer risk of the low-risk group, while no statistically significant increase was observed in men, possibly due to the predominance of female-related cancers (thyroid and breast cancer) in our cohort.

Among the 10 chronic disease indicators, SUA had the largest weight in the risk score calculation, followed by triglycerides, total bilirubin, and heart rate, suggesting these indicators may be more strongly associated with cancer risk. Studies have found that elevated SUA levels increase cancer risk. SUA has been identified as a common factor linking four core components of metabolic syndrome: HOMA-IR measurement of insulin resistance, mean arterial pressure, triglyceride-to-HDL cholesterol ratio, and waist circumference. While SUA can act as a systemic antioxidant, its pro-inflammatory properties are hypothesized to play an important role in cancer pathogenesis. Alternatively, elevated SUA may serve as a surrogate marker for lifestyle changes that increase cancer risk. Two lifestyle-related risk factors—chronic inflammation and metabolic syndrome —play important roles in cancer development. Metabolic syndrome and cancer share common pathogenic mechanisms such as oxidative stress, chronic inflammation, and compensatory hyperinsulinemia resulting from insulin resistance. Obesity is a risk factor for numerous chronic diseases, particularly hypertension, dyslipidemia, metabolic syndrome, type 2 diabetes, cardiovascular disease, and cancer, and has been confirmed to increase risk for at least 13 cancer types. Serum xanthine oxidoreductase (XOR) levels are associated with obesity-related metabolic disorders. XOR contributes to metabolic syndrome and cancer pathogenesis through inflammatory responses and oxidative stress triggered by its active products. XOR-derived reactive oxygen and nitrogen species and SUA interact with hypertension, dyslipidemia, and insulin resistance, participating in cell transformation, proliferation, disease progression, and metastasis. Obesity, type 2 diabetes, insulin resistance, hypertension, metabolic syndrome, and gout constitute a syndrome cluster associated with hyperuricemia, chronic inflammation, and activated innate immunity, with their development potentially mediated by uric acid effects that increase cancer risk as demonstrated in large epidemiological analyses.

Few studies have reported on the relationship between serum bilirubin and cancer risk, with inconsistent results. Vitek et al. suggested that low serum bilirubin is associated with cancer incidence, while slightly elevated bilirubin reduces cancer risk. Song et al. found higher serum bilirubin levels in Chinese lung cancer patients compared to controls. These inconsistencies may reflect a non-linear dose-response relationship between serum bilirubin and cancer risk, which our results also suggest. While bilirubin is recognized as an effective antioxidant, whether its pathogenic mechanism involves pro-inflammatory properties like uric acid remains unreported.

Studies have found that resting heart rate >80 beats/min was associated with 1.66 times (95% CI: 1.23-2.26) the cancer mortality risk compared to <60 beats/min, though no studies have reported associations with cancer incidence. Elevated heart rate may indicate sympathetic activation leading to autonomic imbalance, which increases adrenergic activity, produces proliferation-stimulating neurotrophic factors, and affects inflammation, angiogenesis, tissue invasion, cellular immune response, and epithelial-mesenchymal transition, thereby increasing cancer risk. Xu et al. found a U-shaped rela-

tionship between eGFR and cancer risk, with increased risk at both eGFR $ 105mL/min/1.73m^{2}$ and eGFR <90 mL/min/1.73m^2 compared to 90-104 mL/min/1.73m^2. Kidney dysfunction leads to chronic inflammation and oxidative stress, while inflammatory microenvironments contribute to tumorigenesis. Both heart rate and eGFR are influenced by obesity and may act as risk factors mediating obesity-related effects on specific cancer types.

Our study's strengths include its prospective cohort design and large sample size. Limitations include: (1) Participants were from a single center with relatively better socioeconomic and educational status, potentially introducing selection bias; (2) The median follow-up of 4.0 years was relatively short; (3) Cancer ascertainment relied on self-reported diagnoses in the pre-examination questionnaire, which may underestimate cancer incidence. Future studies with longer follow-up are needed to confirm these findings.

In summary, cancer risk increases with higher comprehensive chronic disease risk scores. The substantial prevalence of risk factors such as obesity and metabolic abnormalities may continue to drive cancer incidence upward. Therefore, shifting the prevention of chronic disease risk factors upstream is crucial for comprehensive cancer prevention and control in China.

Author Contributions: GAO Ying conceptualized and designed the study and drafted the manuscript; JIN Yujing and WEI Wei processed the data; XU Xiaoqian conducted literature review; LI Shu and YANG Hongxi performed feasibility analysis and revised the manuscript; ZHANG Qing supervised quality control.

Conflict of Interest: The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.