Cardiovascular, diabetes, and cancer strips: New evidences from clinical cases in Nanchang, China

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Abstract

Since cardiovascular, diabetes, and cancer (CDC) strips were discovered, more and more evidences support this new concept. Here, we report that clinical features and shared major risk factors (SMRF) of the CDC strips as well as the distribution of hypertension, diabetes, and cancer in Nanchang, China. It aims to provide new and solid clinical evidences by cases randomly collected and carefully screened from 2012/2013 to 2017. Typical cases with the CDC strips were presented with unhealthy “environment-sleep-emotion-exercise-diet” intervention [E(e)SEEDi] related SMRF, the distribution of hypertension, diabetes, and cancer was approximately 2:1:4, and the distribution of various cancer cases was also presented. A graphical abstract showed the association of CDC strips with SMRF. In conclusion, there are indeed the CDC strips due to new and solid clinical evidences, and the CDC strips highly link to unhealthy E(e)SEEDi related SMRF.

Introduction

As we all know, major non-communicable diseases (mNCDs) which include cardiovascular diseases (CVD), diabetes, and cancer are going globally due to unhealthy lifestyles, obesity, and a rapidly aging. Cardiovascular, diabetes, and cancer (CDC) strips were discovered and the concept of CDC strips was proposed firstly in 2012. The related review article on evidences, mechanisms, and classifications of CDC strips was published in 2014[1]. Thus, it’s easy to understand the concept of CDC strips, which means that when an individual suffers from CVD or diabetes or cancer, then he or she suffers from cancer or diabetes or CVD. Currently, the development of CDC strips is mainly due to unhealthy lifestyle related shared major risk factors.

CVD, diabetes and cancer are now called the “new three mountains” that endanger human health, affect economic and social development[2], and result in high deaths as well as cost huge medical resources. When these diseases develop into the CDC strips, it can be said to “add insult to injury” for individual health. Thus, earlier and more effective prevention and halting the development of CDC strips have an important clinical significance. Since hypertension is the most common at department of cardiovascular medicine and easy to diagnose, moreover, hypertension is also an important risk factor of atherosclerosis and other CVDs, we use it as a representative of CVD in this study.

Here, we reported three typical cases with the CDC strips, clinical features and shared major risk factors of CDC strips as well as the distribution of hypertension, diabetes, and cancer at our hospital. It aims to provide new and solid clinical evidences for CDC strips we discovered.

Results

Clinical features of three typical cases of CDC strips

Here is a brief introduction on clinical features of three typical cases with CDC strips with E(e)SEED-based tables (Table 1. Case 1, Case 2, and Case 3).

The distribution of hypertension, diabetes and cancer patients

From 2012/2013 to 2017, the distribution of hypertension, type 2 diabetes (T2D) and cancer patients at our hospital and the distribution of all kinds of cancer patients were as follows (Table 2, Table 3).

According to data in two tables (Table 2 and Table 3), it's easy to find that the incidence of hypertension (513 cases), T2D (250 cases) and cancer (943 cases) patients in our hospital was approximately 2:1:4. Among these patients with cancer, cases with lung cancer are the most due to unhealthy lifestyle associated with E(e)SEED intervention [E(e)SEEDi] (e.g., air pollution, and the daily inhalation of lampblack and cigarettes). In fact, many of 943 cancer patients co-existed with various CVD (including hypertension, coronary heart disease, arrhythmia, etc.) and T2D, which developed the typical CDC strips (main and branch strips). Obviously, hypertension, T2D, and various tumors as well as the CDC strips will greatly affect Chinese residents' health status and cost a lot of medical resources. When compared to a single disease (CVD, diabetes, and cancer), the expected costs of CDC strips will definitely be more ($P < 0.001$).

The relationship between shared major risk factors and CDC strips

The following graphical abstract (Fig. 1) showed the association of CDC strips with shared major risk factors due to unhealthy E(e)SEED intervention [E(e)SEEDi]. Although the relationship between CVD and diabetes is well-established, we think that it is only a part or a branch of CDC strips. Moreover, we think that not only the relationship between CVD and diabetes, but also the relationship among CVD, diabetes, and cancer is due to unhealthy lifestyle related shared major risk factors, such as air pollution, stay up later, physical inactivity or obesity, and others.

Discussion

According to the new standard 130/80 mmHg in the revised guidelines for hypertension in the United States in 2017[3], the number of patients with hypertension will rise sharply[4]. The incidence of T2D is also on the rise in China due to unhealthy lifestyles, such as the increase of obesity and physical inactivity. In particular, the incidence of cancer patients in China in the recent decade showed a "blowout" trend. Of course, cases with lung cancer are the most, and consistent with the annual report of cancer statistics in China in 2015[5].

Novel and solid evidences from basic and clinical science

The compelling basic researches on molecular levels are emerging as powerful new evidences of CDC strips. There is a regulatory pathway that links glucose and AMP-activated kinase (AMPK) to TET2 and 5-hydroxymethylcytosine (5hmC), which connects diabetes to cancer[6]. Antidiabetic agent Metformin was associated with a significant decrease in cancer incidence since it can activate AMPK, lowers blood glucose levels and stimulates cancer-suppressing gene LKB1 which links to T2D due to changing AMPK activity. Diabetes is an important risk factor for cancer for both women and men[7], and women suffering from diabetes have higher risk of cancer than men. Individuals with T2D have higher risks of cancers. Thus, women with T2D should be individualized screened for breast, cervical, and colorectal cancer. However, current screening rates remain below the recommended levels.

Some indicators or biomarkers are found in not only CVD but also diabetes, and even cancers, such as body mass index, resting heart rate, D-dimer, vitamin D, CA 125, CA 19-9[8], fasting proneurotensin[9]. As important biomarkers of CVD, diabetes, and cancer, circulating microRNAs can also be potential biomarkers of CDC strips. There are also shared genetic variants from genome-wide association studies which are important risk factors for common brain disorders included intracerebral hemorrhage, ischemic stroke, and early onset stroke[10]. Genetic variants associated with T2D and coronary heart disease are also therapeutic targets[11]. Therefore, some genetic loci or signal pathways probably link to potential molecular mechanisms of CDC strips. Of course, more and further studies need to finish in the future.

Evidences from extensive clinical studies are also interesting and convincing. Patients with hypertension combined either diabetes or pre-diabetes are more likely to suffer from coronary heart disease and have also a higher proportion of chronic heart failure[12]. There is a deadly association between diabetes and ischaemic stroke[13], and there are also multiple recurrent ischaemic strokes in patient with cancer. Gestational diabetes was positively associated with CVD later in life due to subsequent weight gain and lack of healthy lifestyle[14], but continuing physical activity may be sufficient to reduce all-cause, CVD, and cancer mortality risks[15].

An online survey "*Taking Diabetes to Heart*" developed by the International Diabetes Federation (IDF) found that 2 in 3 of T2D had CVD risk factors (such as high blood pressure, uncontrolled blood glucose levels and high cholesterol) and/or had experienced CVD events (such as angina, heart attack, stroke or heart failure). The survey also showed that those with T2D underestimated their CVD risk, despite a high incidence of CVD events.

In fact, younger individuals with T2D have higher mortality and cardiovascular risks for stroke, myocardial infarction, atrial fibrillation, and heart failure[16]. However, lower levels for glycohemoglobin, systolic blood pressure, and low-density lipoprotein cholesterol are associated with significantly lower risk for

cardiovascular outcomes in type 1 diabetes (T1D) [17]. In contrast, there is an increased risk of not only CVD and cancer, but also mortality among individuals with liver diseases and T2D[18]. Thus, specific interventions to screen, prevent, and treat T2D or T1D will help improve outcomes.

Patients with breast cancer are more likely to die from CVD. Cardiovascular toxic effects of targeted cancer therapies are often found in patients with blood tumors. Among patients receiving a heart, lung, kidney, or liver transplant, the risk of skin cancer remains much higher than in the general population. There are now new solid evidences on the CDC strips since among patients with CVD, diabetes, and cancer, there are shared risk factors related to unhealthy lifestyles, such as obesity, physical inactivity, chronic inflammation or other chronic diseases[19,20]. Specifically speaking, chronic heart failure shares with cancer several most common causes or similar risk factors[21]. Hence, it's worth paying more attention to the CDC strips due to these emerging basic and clinical evidences.

Possible mechanisms and therapeutic strategies

Possible molecular mechanisms on the CDC strips may involve chronic inflammation and ageing because it's highly linked to CVD, T2D, and cancer[22]. Since healthy lifestyle, nut, coffee, some chemical agents (e.g., statins)[23-25] can lower the risk of mNCDs including CVD, T2D, and cancer, thus, these measures may also lower the risk of CDC strips. Individual recommendation on alcohol consumption should be made due to its risks and benefits[26].

Novel strategies, for example, SEEDi[1.0-3.0] technologies, which had been developed successfully, can help to halt the CDC strips[2]. Since weight gain during adulthood was associated with significantly increased risk of mNCDs[27], A magic "polypill" [28], that is, E(e)SEEDi, is a powerful tool to prevent and control those major and higher risk factors that contribute to the CDC strips. We had already setup standardized comprehensive programs for mNCDs, such as hypertension[29], acute myocardial infarction[30], chronic heart failure[31], arrhythmogenic right ventricular cardiomyopathy[32], T2D and cancer[33], but these programs still need to conduct for clinical application in countries worldwide.

In addition, targeted critical cells[34], focal adhesion kinase[35], key signal transduction pathways (such as G protein-coupled receptors) and mitochondria based therapeutic strategies, will also help to treat and prevent CVD, diabetes, and cancers. In fact, to control obesity or BMI is an important strategy for prevention of CDC strips since an open-label, cluster-randomized trial showed that only intensive weight management within routine primary care would achieve remission of T2D to a non-diabetic state and off antidiabetic drugs[36].

Whether there is the observed beneficial effect of antidiabetic agent metformin on cancer risk or not, it needs further studies, but the discoveries on the CDC strips and related new evidences will definitely affect and change patients' and clinicians' care for more benefits. Since gut microbiota Akkermansia muciniphila is a possible therapeutic options to target obesity associated mNCDs[37], it may also help to control and prevent CVD, diabetes, cancer and the related CDC strips.

Especially, during the COVID-19 pandemic[38-40], we need to protect vascular endothelial functions[41] for better prevention of CDC strips, and CVD and its complications in China[42], since microvascular endothelial dysfunction can predict CVD, diabetes, and solid-tumor cancer[43]. It may be a new useful marker to predict the future risk of CDC strips. However, whether this viral infection links highly to CDC strips or not, it's indeed a novel project. In addition, during cancer treatment and follow-up[44], there are significant prevalence and incidence of CV risk factors. Thus, long-term follow-up is needed to observe the outcome and prognosis. According to global cancer statistics 2020, female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer[45], but the latter remained the leading cause of cancer death[46]. Moreover, cancer has become a major life-threatening disease in China[47]. Hence, effective prevention of shared major risk factors as well as health care is critical for control of CDC strips.

There are several limitations of this study. First, this study is just a preliminary report on clinical evidences of CDC strips, and there are not enough data due to the small samples and lack of research funding for further studies on the pathogenesis and key genes of CDC strips. Second, long-term follow-up is indeed needed to observe further the clinical outcomes of these cases, especially during the COVID-19 pandemic[48-50] and in the era of the post-COVID-19. In addition, medical cost on the patients of CDC strips also needs to further study. Studies in the future should also disclose further its molecular mechanisms and vital genes, and develop new strategies for prevention and treatment of CDC strips.

In conclusion, there are indeed the CDC strips due to solid clinical evidences. The CDC strips highly link to unhealthy E(e)SEEDi related shared major risk factors. Moreover, this discovery helps us to modify current unhealthy lifestyle and early control shared major risk factors so as to halt the development of CDC strips. Exception for the magic "polypill" and our comprehensive iRT-ABCDEF program, it's believed that new biomedical technologies and novel molecular tools will help to develop novel strategies for control and prevention of CDC strips. After it is more sufficiently approval internationally, the concept of CDC strips we established should be helpful to a paradigm shift of mNCDs management.

Methods

Data Collection

Patients with CVD, diabetes, and cancer, as well coexisting these diseases, were randomly collected at departments of outpatients and inpatients from 2012/2013 to 2017. As a retrospective survey of a previously collected database, we stated here that all patients in this study were screened by careful clinical consultation about five core elements [unhealthy E(e)SEEDi], and all these patients met the diagnostic criteria of CVD, diabetes, and cancer. The incidence and risk factors were analyzed and evaluated from these patients with coexisting CVD and diabetes, diabetes and cancer, cancer and CVD, and classified as a main strip or a branch of CDC strips.

Clinical investigations

Patients were examined by physical examination and biochemical examination (including routine blood and urine, liver and kidney function, fasting blood glucose, blood lipid, blood viscosity, uric acid, myocardial enzymes, troponin I, oral administrative glucose tolerance test or postprandial 2-hour blood sugar), hepatitis virus examination, four items of tumors, carbohydrate antigen, prostatic antigen and other related auxiliary examinations (including chest X-ray, routine electrocardiogram, exercise test and 24-hour ambulatory electrocardiogram, ambulatory blood pressure monitoring, color Doppler ultrasound, computer tomography (CT) or magnetic resonance imaging (MRI), coronary angiography, mammography, etc). Relevant data were retained for analysis.

Informed consent

Data collection was followed by a study protocol that was approved by the local ethics committee. It was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000, and all enrolled patients gave written informed consent. No potential sources of bias.

Statistical analysis

The results of original records were used. Data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS version 17.0, SPSS Inc., Chicago, IL, USA) with t-test for comparisons between two groups. A P-value of <0.05 was considered statistically significant.

Declarations

Ethics statement

This work was approved by Human Research Ethics Committee of the Nanchang University, Hospital of Nanchang University, Jiangxi Academy of Medical Science (approval 20120312).

Role of the funding source

No funding for this study was received. All authors had full access to all study data, and the corresponding author had final responsibility for the decision to submit for publication.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The data that support the findings of this study are not publicly available but are available upon reasonable request from the corresponding author.

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Contributions

C.H. designed the study, collected and analyzed all data, performed statistical analyses, wrote original draft and revised the final manuscript, and contributed to writing-review & editing; G.H., H.H., L.Z., L.L., W.X. and Y.Z. contributed to interpretation of data and data evaluation; Q.W. contributed to supervision, interpretation of data and data evaluation, writing-review & editing. All authors discussed the results, critically reviewed the paper, and approved the manuscript for submission.

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Ethics declarations

Competing interests

The authors declare no competing interests.

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Tables

Table 1. Clinical Characteristics of Typical Cases with CDC strips.

Items	Case 1. Hypertension-T2D-Cervical cancer and lung cancer	Case 2. Hypertension-T2D- Right lung adenocarcinoma	Case 3. Hypertension/hyperuricemia-T2D-Central lung cancer (Right)/ Mediastinal secondary malignancy with atelectasis
General information	Female, 58yrs, married, a retired worker	Male, 67yrs, married, a masons	Female, 85yrs, married, a retired civil servants
Chief complaint	Cough and fever for 20 days	Adenocarcinoma of the right lung for less 2 years, radiotherapy with γ radiation for over one year, voice hoarse for five months	Cough, bloody sputum with chest tightness for over one month
Past history	Hypertension for over 20 years, T2D for over 10 years, laparoscopic surgery for uterine accessory abscess, cervical cancer (moderately differentiated squamous cell carcinoma) surgery in 2014, and with 4 courses of chemotherapy and 1 course of radiotherapy.	Hypertension over 30 years, T2D over 20 years, right cryptorchidism and right testicular excision	Hypertension over 20 years, T2D 5-6 years
Family history	No family history of tumour	No family history of tumour	No family history of tumor, no cardiovascular abnormalities, children all smoke, the eldest son 1-2 packs a day for 40 years
Environment	Living in a city	Rural life	Living in a city
Sleep	Good	OSA (+++)	OSA (+++)
Emotion	Good	Good	Depression and poor mood
Exercise	Often physical activity	Physical farm work and a masons	Physical inactivity
Diet	No history of smoking or drinking	Smoking, 20-40 cigarettes/day with over 40 years, drinking, half to a pound a day with over 30 years	20 years ago smoking (20 cigarettes /day for 40 years), no drinking
Blood pressure	150/80 mmHg (Right), 145/80 mmHg (Left)	170/98 mmHg (Right), 176/100 mmHg (Left)	150/90 mmHg (Right),140-150/90 mmHg (Left)
BMI	55 Kg/1.56	75 Kg/1.70 M^2	60 Kg/1.65 M^2

	M^2		
Others	In December, 2016, the malignant tumor of the left lung was treated with radiotherapy with γ radiation and followed up by telephone after the operation, and so far so good.	Right mediastinal secondary malignant tumor with atelectasis, died one month after surgery (June 2017)	In August 2017, the right lung malignant tumor was treated with radiotherapy with γ radiation and followed up by telephone after the operation. Current, there are dyspnea and pulmonary fibrosis and the targeted chemotherapy drugs have been discontinued. Blood pressure and blood sugar are normal. Antihypertensive and hypoglycemic drugs have been discontinued. Other conditions are good.

Table 2.

The distribution of hypertension, diabetes and cancer patients from 2013 to 2017.

No.	Hospitalized diseases	Cases (n=)
1	Hypertension	513
2	Type 2 diabetes	250
3	All kinds of tumor (lung cancer, brain malignancy, pituitary tumor, meningioma, liver cancer, etc.)	943

Table 3.

The distribution of all kinds of cancer patients hospitalized from 2013 to 2017.

No.	Types of tumor	Cases (totally, n=943)
1	Lung cancer	240
2	Brain malignancy	173
3	Pituitary adenoma	138
4	Meningioma	110
5	Liver cancer	87
6	Trigeminal neuroma	34
7	Acoustic neuroma	33
8	Pancreatic cancer	30
9	Retroperitoneal malignancy	20
10	Esophageal cancer	8
11	Bone malignancy	6
12	Cervical malignancy	6
13	Pelvic malignancy	5
14	The pineal gland tumor	5
15	Nasopharyngeal carcinoma	4
16	Thymic carcinoma	3
17	Sternal malignancy	3
18	Malignant tumor of thoracic vertebra	3
19	Lumbar malignancy	3
20	Other	32

Notes: Most of cancer cases received precise positioning radiotherapy with γ radiation.

Figures

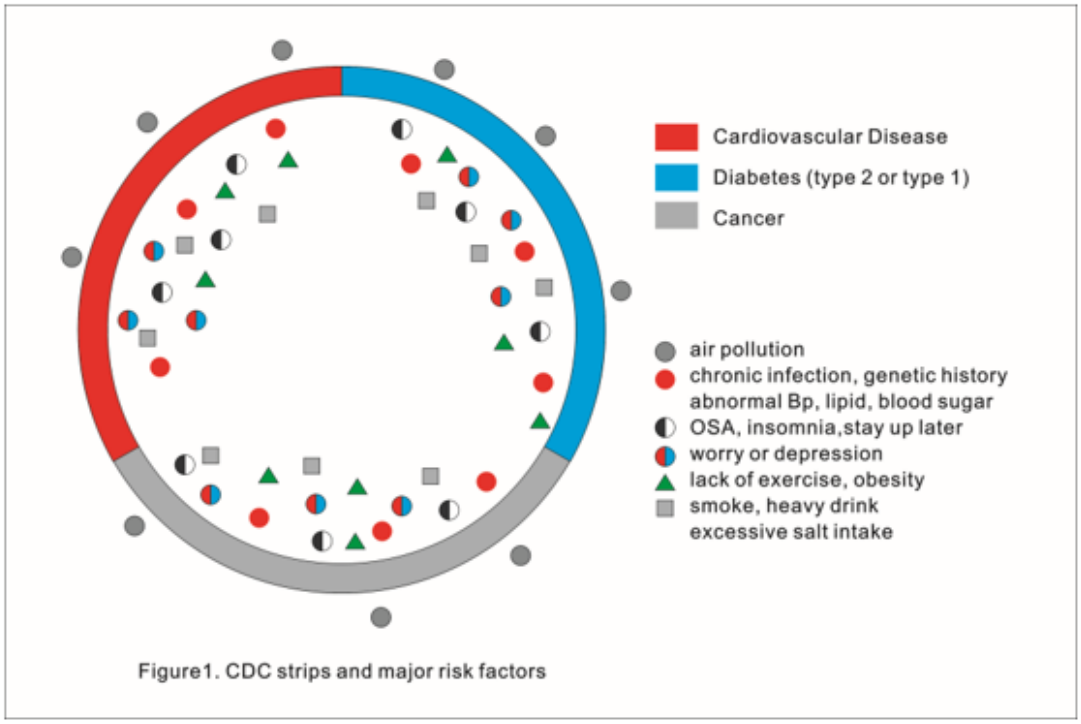

Figure 1

The relationship between common major risk factors and the CDC strips. Since cardiovascular disease and diabetes, diabetes and cancer, cancer and cardiovascular disease link each other, respectively, a lot of previous and current evidences show that there are cardiovascular, diabetes, and cancer (CDC) strips. Five core elements of human health include “environment (external and internal)-sleep- emotion-exercise-diet” [E(e)SEED]. The associated shared major risk factors can induce cardiovascular disease, diabetes, and cancer as well as the CDC strips. As a magic “polypill”, E(e)SEED intervention [E(e)SEEDi], that is, SEEDi1.5, can help to prevent and control the development of the CDC strips. Obviously, it’s easy to develop unhealthy E(e)SEEDi-associated risk factors score for prediction and prevention of the CDC strips.