



# Restoring the Metabolic Syndrome-Cancer Hypothesis; Implications for Cancer Research and Treatment

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## Abstract

The metabolic-cancer hypothesis was formulated in the 1990s and states that metabolic syndrome and its components are linked to cancer at all sites; however, the hypothesis collapsed in 2000s. A series of reports showed an inverse link between metabolic syndrome and its components and incident prostate cancer. Our research group recently showed that the inverse link between metabolic syndrome and its components and incident prostate cancer in the 2000s could be linked to bias mechanisms rather than prostate cancer biology. The findings restore the metabolic syndrome-cancer hypothesis and increase the interest in controlling lifestyle factors such as overconsumption of carbohydrates, chronic stress, smoking, vitamin D deficiency, and low physical activity as risk factors for cancer disorders. The data seem to suggest that by treating metabolic syndrome and its components, the risk of any cancer will decrease. The most robust data for achieving this goal come from reports of carbohydrate restriction.

## Introduction

In science, reports showing data deviating from what is expected are called anomalous observations. In the 1990s, metabolic syndrome was found to be a promoter of cancer in almost all organs [1,2] including prostate cancer [3-5]. This circumstance generated the metabolic-cancer hypothesis. However, in the 2000s, a series of reports were published showing an inverse relationship between metabolic syndrome and its components and the incidence of prostate cancer [6-13]. Thus, the metabolic syndrome-cancer hypothesis has been questioned. This lack of coherence in cancer research seriously hampers efforts to fight cancer disorders. It is therefore crucial to explain this incoherence. Our research group decided to challenge these anomalous observations.

## Metabolic Syndrome

The metabolic syndrome was previously called the Disease of the Western Civilization because it was more prevalent in countries with a Western lifestyle such as Western Europe, North America, and Australia. Nowadays, metabolic syndrome is prevalent in China, the Arabic states, Mexico, and other countries, and is a global epidemic. Metabolic syndrome is a leading cause of death. In Sweden, 80% of the annual death rate in 2016 could be ascribed to metabolic syndrome and its components [14]. The cause of metabolic syndrome is insulin resistance, which is most commonly caused by an overconsumption of carbohydrates and has been linked to cancer at most sites [15].

However, other lifestyle factors can also cause insulin resistance such as chronic stress [16], which has been linked to increased incidences of colorectal, lung, breast, and prostate cancer [16,17]. Smoking can also cause insulin resistance [18,19], and it has been linked to lung, oral cavity, pharyngeal, esophageal, laryngeal, liver, stomach, pancreatic, renal, and bladder cancers [20]. Vitamin D deficiency is another lifestyle factor characterized by insulin resistance [21] and, in several reports; it has been inversely linked to cancer mortality and colorectal cancer [22,23]. Still another lifestyle factor characterized by insulin resistance is low physical activity [24], which is associated with ten types of cancers including colorectal cancer, endometrial cancer, and breast cancer [25].

It is well established that a hormone is inversely linked to its receptor density and insulin is no exception [26]. If the insulin concentration increases, the insulin receptor density will decrease as demonstrated in patients with insulinoma. Overconsumption of sugar and carbohydrates are probably the most important lifestyle factors that contribute to insulin resistance and an increased insulin level.

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| Hormone      | Women | Men |
|--------------|-------|-----|
| Insulin      | ↑     | ↑   |
| IGF-1        | ↑     | ↑   |
| Testosterone | ↑     | ↓   |
| Oestrogen    | ↑     | ↑   |
| SHBG         | ↓     | ↓   |
| Adiponectin  | ↓     | ↓   |

**Table 1:** Endocrine aberrations seen in metabolic syndrome besides insulin that are associated with metabolic syndrome. Notably, men with metabolic syndrome and its components have lower testosterone levels than men without these disorders.

Table 1 shows other hormones besides insulin that are associated with metabolic syndrome. Of note, men with metabolic syndrome and its components have lower testosterone levels than men without these disorders [27,28].

### The metabolic syndrome–cancer hypothesis was formulated in the 1990s

The general idea was that metabolic syndrome and its components promote cancer by creating a microenvironment favorable for cancer growth. Some authors stated that metabolic syndrome and the associated increased insulin level act as fertilizers for cancer. This metabolic-cancer hypothesis was supported by numerous epidemiological reports showing a positive link between metabolic syndrome and its components and practically all cancer manifestations in the 1990s [1,2]. Metabolic syndrome and its aspects were also linked to prostate cancer during this period of time. Our research group published three reports concerning prostate cancer with clinical materials mainly collected in the 1990s; two longitudinal studies and one cross-sectional study supporting the metabolic syndrome-cancer hypothesis [29,4,30].

In one longitudinal study, we very thoroughly examined 389 men for the exclusion of prostate cancer. Then, we followed these men for about ten years. At the follow-up, 44 of these men had a prostate cancer diagnosis. Seven different aspects of metabolic syndrome were risk factors (higher systolic and diastolic blood pressure, higher Body Mass Index (BMI), waist and hip measurements, higher uric acid level, and fasting insulin level) for having an incident prostate cancer diagnosis [29].

In the second longitudinal study, we included 320 men with incident prostate cancer. We followed these men for about 10 years. At follow-up, 54 of the men had died due to prostate cancer. Six different aspects of metabolic syndrome (larger prostate gland volume, faster growth of benign prostatic hyperplasia, higher prevalence of type 2 diabetes mellitus, higher prevalence of treated hypertension, lower high-density lipoprotein cholesterol level, and higher fasting plasma insulin level) were risk factors for lethal prostate cancer. In both prospective studies, fasting plasma insulin level was the strongest risk factor, showing an independent link between fasting plasma insulin levels and incident and lethal prostate cancer, respectively [29,4].

In one cross-sectional study, we compared the metabolic profile of 68 men with localized prostate cancer (T2) with the metabolic profile of 231 men with non-localized prostate cancer (T3). Five different aspects of metabolic syndrome (larger prostate gland volume, faster growth of benign prostatic hyperplasia, increased body weight, increased BMI, and increased prevalence of treated hypertension)

were risk factors for non-localized prostate cancer, linking metabolic aspects to high-stage prostate cancer [30].

### The downfall of metabolic syndrome-cancer hypothesis in the 2000s

In the 2000s, reports began to appear showing a negative link between metabolic syndrome and its aspects and incident prostate cancer [6-13]. Now, more than twenty reports have been published showing a negative link between metabolic syndrome and its components and incident prostate cancer. In these reports, metabolic syndrome and its components appear to protect against incident prostate cancer. Of course, the metabolic syndrome–cancer hypothesis collapsed.

### Challenging the anomalous observation

Our research group decided to challenge the anomalous observation showing that metabolic syndrome and its components protect against incident prostate cancer. We asked ourselves why men with metabolic syndrome and its components in the 1990s had an increased risk of incident prostate cancer and a reduced risk of having incident prostate cancer in the 2000s [31].

### Formulation of a hypothesis

We formulated the following hypotheses. In the 1990s, the diagnostic procedures were symptom-driven and larger incident prostate cancers were identified. Men referred in the 1990s were more often referred due to a lump in the prostate gland, lower urinary tract symptoms, haematuria, or even evidence of metastases. Thus, men with metabolic syndrome and its components and incident prostate cancer had larger tumors in the 1990s. In the 2000s, the diagnostic procedure was PSA-driven and more men with smaller prostate cancers were identified.

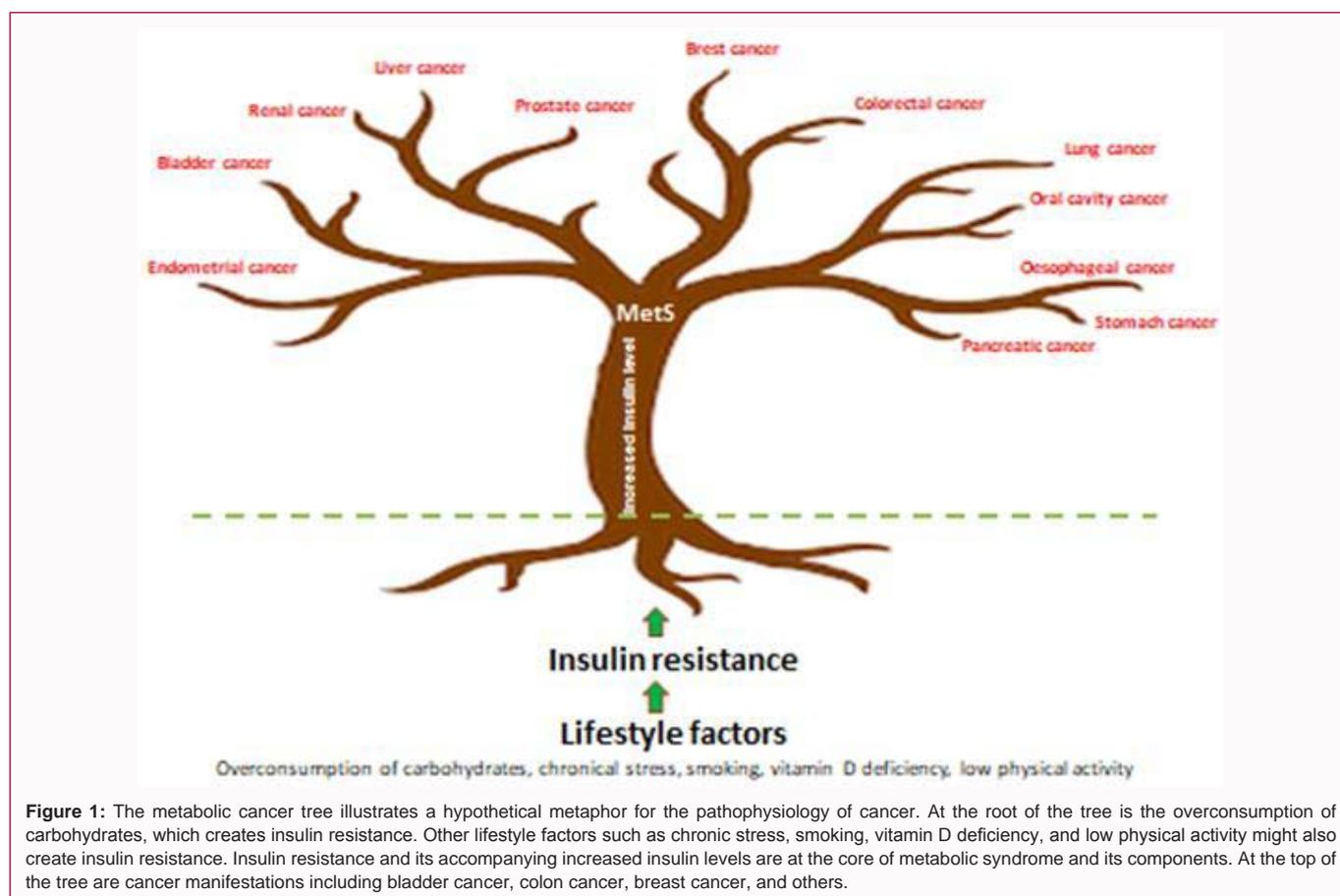
### Test of the hypothesis

We tested the hypothesis by analyzing 42 data sets investigating the association between metabolic syndrome and its components and prostate cancer published between 2000 and 2016. All studies used the TNM classification and had accurate stage characteristics and definitions of metabolic syndrome and its components. The links between metabolic syndrome and its components and low-stage incident PC were compared with the same links between metabolic syndrome and its components and high-stage incident PC [31].

## Results

Reports considered to represent low-stage incident prostate cancer populations, including a high proportion of men with T1c and T1-T2 incident prostate cancer, showed no association or a negative association between components of metabolic syndrome and incident prostate cancer. These low-stage incident prostate cancer reports are characteristic for reports generated from PSA-driven diagnostic procedures. This pattern was seen in all reports in which the percentage of T1c prostate cancer was >26% (mean 39%) and in all reports in which the percentage of T1-T2 incident prostate cancer was >48% (mean 73%). In total, 14 components of metabolic syndrome were negatively associated with low-stage incident prostate cancer in 18 reports.

Reports considered representing high-stage incident prostate cancer populations, which are characteristic of patient groups generated by symptom-driven diagnostic procedures, showed either no relationship or a positive correlation between metabolic syndromes



and its components and incident prostate cancer. Five reports with a high percentage of T2-T4 cancers ( $\geq 59\%$ ) and four reports with a high percentage of T3-T4 cancers ( $>61\%$ ) showed either no relationship or a positive relationship between metabolic syndrome and its components and incident prostate cancer. In total, metabolic syndrome and 16 of its components showed no association or a positive association with incident prostate cancer. The finding of a positive link between metabolic syndrome and its components and high-stage incident prostate cancer is in keeping with reports involving non-localized and lethal prostate cancer. A positive link between 16 components of metabolic syndrome and high-stage prostate cancer, a positive link between metabolic syndrome itself and 10 of its components and non-localized prostate cancer, and a positive link between 14 components of metabolic syndrome and lethal prostate cancer were found.

### Bias Mechanism

Our findings support the hypothesis that the inverse link between metabolic syndrome and its components and low-stage incident prostate cancer in the 2000s is related to a bias mechanism rather than to prostate cancer biology. Men with metabolic syndrome and its components have lower testosterone levels than men without these conditions [27,28] (Table 1). The testosterone level controls Prostate-Specific Antigen (PSA) production and metabolic syndrome has a lowering effect on serum PSA [32,33]. Thus, men with metabolic syndrome and its components have lower PSA levels than men without these disorders. Consequently, fewer men with metabolic syndrome and its components than men without these conditions have a prostate cancer diagnosis, as more men will end up under the

PSA cut off level (PSA  $>3.0 \mu\text{g/l}$ ) for prostate biopsy. By contrast, in high stage, non-localized and lethal prostate cancer a reduced androgen level has no influence on the prostate cancer diagnosis because of the high PSA levels of these cancer manifestations. A minor reduction of the PSA level has no relevance for the prostate cancer diagnosis at these high PSA levels. The findings suggest that the negative link between metabolic syndrome and its components and incident prostate cancer in low-stage prostate cancer is related to a bias mechanism rather than related to prostate cancer biology. Thus, the falsification of the metabolic syndrome–cancer hypothesis suggested by reports published during the 2000s could be rejected. The findings suggest a restoration of the metabolic syndrome-cancer hypothesis.

### Discussion

The most important implication of the present review article for cancer research is that prostate cancer shares the same pathophysiology as other cancer manifestations, but this circumstance has been masked in recent years by a bias mechanism in reports based on PSA-driven diagnostics. This finding that the negative link between metabolic syndrome and its components and low-stage prostate cancer is related to a bias mechanism seems to restore the metabolic syndrome-cancer hypothesis. Furthermore, it was concluded that our findings that metabolic syndrome and its components are positively related to high-stage, non-localized and lethal prostate cancer, indicated that prostate cancer could be considered a new component of metabolic syndrome. Another conclusion was that men with higher-stage, non-localized, and lethal prostate cancer were metabolically sicker than men with lower-stage, localized, and non-lethal prostate cancer.

Still another conclusion is that our data indicate that the presence of metabolic syndrome and its components at diagnosis should alert the clinician that the patient might be at risk of developing advanced prostate cancer since prospective studies show that non-localized and lethal prostate cancer is positively linked to components of metabolic syndrome, despite the fact that the clinical material was dominated by low-stage, incident prostate cancer at baseline [31]. Another consequence in the clinical setting could be a reduction in overtreatment of prostate cancer detected by PSA screening because a low-risk group could be identified.

Our findings that the anomalous observations concerning prostate cancer could be ascribed to a bias mechanism rather than to prostate cancer biology will reopen the interest in the metabolic syndrome-cancer hypothesis. Our findings suggest a hypothetical metaphor referring to the pathophysiology of cancer disorders called the metabolic cancer tree (Figure 1).

At the root of this tree are lifestyle factors such as overconsumption of carbohydrates, chronic stress, smoking, D-vitamin deficiency, and low physical activity over a longer period of time that all also lead to insulin resistance. Insulin resistance and its accompanying increased insulin level are at the core of metabolic syndrome and its components. At the top of the tree there are a number of cancer manifestations including bladder cancer, colon cancer, breast cancer, and others [1,2]. Our findings seem to suggest that cancer at multiple sites shares the same pathophysiology. It is reasonable to conclude that the most prevalent lifestyle factor linked to metabolic syndrome and its components is overconsumption of sugar and other carbohydrates, although other lifestyle factors may play a role. All these lifestyle factors generate insulin resistance and an increased insulin level in accordance with our findings [4,29,30], which, in turn, might increase the risk of developing cancer and thereby contribute to the progression of these conditions.

An important implication for the treatment of cancer is that our findings seem to suggest that carbohydrate restriction could be a way to prevent and treat cancer. Inherent to this concept lays the possibility that treating one or several risk factors or disease states might reduce the risk of cancer disorders. The link between carbohydrate restriction and metabolic syndrome is the most studied link between one particular lifestyle factor and metabolic syndrome. It is well established that carbohydrate restriction can reduce the incidence of metabolic syndrome and metabolic disorders. The mechanism of action is increased insulin sensitivity, leading to a reduced insulin level. The most convincing evidence of the effect that carbohydrate restriction has on metabolic syndrome and its components comes from studies on Low Carbohydrate and High Fat Diets (LCHF), which includes a decreased consumption of carbohydrates and an increased consumption of unsaturated fats. Leading authorities in nutrition, endocrinology, metabolism, and internal medicine concluded that carbohydrate restriction is the single most effective intervention for reducing all features of metabolic syndrome and metabolic disorders [34]. In a recent open-label, non-randomized, controlled study by Hallberg et al., 262 adults with type 2 diabetes mellitus were subjected to carbohydrate restriction during one year. After one year, the following statistically significant average changes were revealed: fasting insulin (-43%), C-reactive peptide (-23%), HOMA-IR (-55%), fasting glucose (-22%), HbA1c (-17%), triglycerides (-24%), and HDL cholesterol (+18%). Body weight declined by  $13.8 \pm 0.71$  kg and blood pressure improved. The control

groups comprising 87 adults with recently diagnosed type 2 diabetes mellitus were subjected to usual care and had no significant changes in biomarkers after one year [35]. In conclusion, the evidence suggests that carbohydrate restriction is an efficient way to prevent and treat metabolic syndrome and its components.

The present report provides evidence for restoring the metabolic syndrome-cancer hypothesis. It seems reasonable to conclude that carbohydrate restriction could reduce the incidence of cancers. The data suggest that carbohydrate restriction could be one measure that could be used to curb the threatening global cancer epidemic.

## Concluding Remarks

This review article could be viewed as an answer to the call for pragmatism in cancer research as published in a recent editorial [36]. A critical question raised in that editorial was, "what is the most important aim of cancer research today?" Cancer is a complex disease with few entirely effective measures available that could be implemented to prevent all types of cancers at the population level. Most efforts are focused on showing that a specific cancer can be cured using ever more clever and costly approaches. In this respect, we are clearly going in the right direction. The past decade has seen numerous innovations in treatment that have dramatically improved survival outcomes in several forms of advanced-stage cancer including melanoma, small-cell lung cancer, and others. Additionally, the Nobel Prize Committee of 2018 awarded James P Allison and Tasuko Honjo, leading authorities in this field, the Nobel Prize in Physiology and Medicine. However these treatments come at a high cost; the annual cost for treating one single patient could surmount 300 000 US dollars.

On the other hand, if the most important aim of cancer research is an optimal level of improvement at the population level by utilizing life style changes to reduce both the incidence and progression of any cancer for most people at a minimum cost, then our data suggest that putting more effort into exploring the link between metabolic syndrome and cancer could be worthwhile. This review article is an effort to highlight possible improvements in cancer prevention and treatment by using low-hanging fruit to curb the metabolic and cancer epidemics. One obvious advantage for the community of using lifestyle changes is that this strategy could be used for both prevention and treatment and comes with practically no cost.

Finally, for the clinical setting, this review article underscores the possibility of telling patients that they can take some steps to reduce their cancer risk or cancer progression. Our patients should be informed about this new knowledge that carbohydrate restriction could possibly reduce the cancer incidence and progression. Carbohydrate restriction might be recommended even before its value in cancer prevention and treatment in interventional studies has been proven, because carbohydrate restriction has been proven to reduce the incidence of many metabolic disorders including diabetes mellitus, atherosclerosis, hypertension, obesity, and others [35,37]. This proposal is not a denunciation of the efforts made to cure a specific cancer, but emphasizes new understandings that are applicable at the population level. We need to convey this message to the community and to the medical profession for the purpose of curbing the growing global cancer epidemic.

## Authors Contribution

JH wrote the manuscript. J-E.D., M.A.H., D.M., and R.P. reviewed

and edited the article before submission.

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