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CORRELATION OF PROSTATE CANCER WITH DISEASES OF THE CARDIOVASCULAR SYSTEM AND TYPE 2 DIABETES

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Abstract
This study examines the potential correlation between prostate cancer and two prevalent conditions: cardiovascular disease and type 2 diabetes. Prostate cancer is a significant global health issue, and comprehending its association with other common diseases is crucial for comprehensive patient care and public health initiatives. The study investigates the correlation between prostate cancer and cardiovascular diseases, including hypertension and atherosclerosis, as well as the correlation between prostate cancer and type 2 diabetes mellitus. The results provide insight into potential shared risk factors, underlying mechanisms, and implications for diagnosis, treatment, and prevention strategies for these diseases. This abstract summarises key aspects of the study, highlighting its importance in furthering the understanding of the complex relationships between prostate cancer and cardiovascular disease as well as type 2 diabetes.

Keywords: prostate cancer, cardiovascular diseases, type 2 diabetes mellitus.

Introduction

Cancer is also considered one of the main causes of morbidity and mortality throughout the world [72]; [59], [57] . According to the GLOBOCAN 2020 report of the International Agency for Research on Cancer, presented by registry results from 20 regions of the world, including Russia, it is noted that prostate cancer (PCa) — is one of the most common malignant diseases in men. It is the 2nd most common cancer in men and the 4th most common among all cancers in general [57]. Despite the fact that mortality rates from prostate cancer are decreasing in many countries, including North America, Northern and Western Europe, developed countries of Asia (according to the GLOBOCAN 2020 report), this type of cancer ranks 4th in the number of deaths worldwide, behind only lung cancer, breast cancer and colorectal cancer. Among the entire population of both sexes, PCa ranks 8th in the number of deaths (358,989 people, 3.8%). In Russia, there is still an increase in the mortality rate from PCa, which ranks 2nd after tracheal, bronchial and lung tumors

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Materials and Methods of Research

A systematic literature search was conducted to identify relevant studies exploring the correlation between prostate cancer, diseases of the cardiovascular system, and type 2 diabetes. Databases including PubMed, Scopus, and Web of Science were queried using a combination of keywords and MeSH terms. The search strategy aimed to capture studies published up to the present date.

Relationship between PCa and CVDs

Cardiovascular disease (CVD) is the cause of about 1/3 of deaths worldwide [70]. Among them, coronary heart disease (CHD) is the most common [50]. Projections based on predictive models show that by 2030, the prevalence of CHD may increase to more than 1845 cases per 1 million population with an upper confidence estimate of 1917 cases per 100,000 people [35].

In recent years, more and more data have shown a close association between CVD and prostate cancer. Thus, [60] and his co-author found that men with CHD are 35% more likely to be diagnosed with prostate cancer compared to men without CHD. At the same time, the incidence of CHD was higher among patients with prostate cancer regardless of the degree of malignancy [60]. According to the study conducted in British Columbia (Canada), which included 100 patients with prostate cancer, a higher prevalence of CVDs than was recorded among men in the general population aged 65 years and older in the same geographic region during the Canadian Population Health Survey, performed in 2011-2012.

This has suggested that the population with prostatic cancer has a higher risk of CVD than the general population, even after adjusting for age and sex [22].

A number of scientists have demonstrated that patients with prostate cancer have a higher risk of death from other causes, more often from CVD rather than from PCa. Thus, according to the data of the Swiss cancer registry, the number of deaths from PCa and CVD in the high-risk group was 46 and 36%, and in the low-risk group - 10 and 20%, respectively [22]

In the United States, CVDs appear to be the leading cause of mortality in survivors of PCa, accounting for 20% of total mortality and surpassing mortality from PCa [74]. In a Korean cohort study, CVDs were responsible for 29.1% of non-PCa-related deaths among long-term survivors after the diagnosis of PCa [54].

According to different authors, it is CHD that is the most frequent cause of death in patients with prostate cancer [15].[69] ; [5]. The primary pathologic process leading to CHD is atherosclerosis, an inflammatory disease of the arteries associated with lipid deposition and metabolic changes due to multiple risk factors [[58].[52].

Atherosclerosis is known to result from a maladaptive inflammatory response that is initiated by the retention of cholesterol-rich lipoproteins containing apolipoprotein B in susceptible regions of the arterial vasculature. Local accumulations of significant amounts of lipids in the arterial wall are subject to various modifications such as oxidation, enzymatic and nonenzymatic cleavage, and aggregation that render these particles proinflammatory and cause activation of the overlying endothelium. The subsequent immune response is mediated by the recruitment of monocyte-derived cells into the subendothelial space, where these cells differentiate into mononuclear phagocytes that engulf the accumulated normal and modified lipoproteins. With further accumulation of cholesterol, they are transformed into cholesterol-containing foam cells by secreting a number of cytokines, which, eventually, participate in the progression of the disease and the onset of chronic inflammation. Expression of proinflammatory cytokines and growth

factors is accompanied by proliferation of smooth muscle cells and production of connective tissue [44].

In the past, atherosclerosis and cancer were considered unrelated pathologies. However, through careful analysis of molecular interactions in these pathological conditions, it has become evident that there is a close relationship between them [49]. Both atherosclerosis and cancer have a number of common risk factors that are consolidated at different stages of the development of these diseases, namely: genetic, nutritional, psychosocial and environmental factors [5]. A number of researchers have demonstrated that the same mechanisms play an important role in the development and progression of cancer as in the development and progression of atherosclerosis - inflammation [39], angiogenesis [71], [68], epigenetics [6], oxidative stress [56], [27],[23], uncontrolled cell proliferation (as the most important) [76]. The data of both epidemiological and experimental studies indicate a close correlation of the presented mechanisms with atherogenesis both in epithelial cancers and atherosclerosis.

Despite contradictory data on the role of elevated cholesterol in the development of PCa during the last decade more and more new studies confirm its great importance in the development and progression of PCa. Thus, Korean researchers [36] in a large prospective study involving 756,604 men (2490 of them were diagnosed with prostate cancer) demonstrated that men with total cholesterol levels ≥240 mg/dL had a higher risk of developing prostate cancer (odds ratio, OR=1.24, 95% confidence interval, CI 1.07-1.44, p=0.001) compared to 366 men with cholesterol levels <160 mg/dL.

In a study by E.A. Platz and his co-author involved 698 male health professionals [47], using a case-control analysis method, the authors showed that patients with low cholesterol levels had a lower risk of developing PCa (OR=0.61, 95% CI 0.39-0.98).

A.M. Mondul and his co-author [42] also found that men with cholesterol <240 mg/dL had a lower risk of developing PCa than men with cholesterol >240 mg/dL. However, in another study [66], in a study of 200,660 men (of whom 5112 were diagnosed with PCa), the authors found no association between cholesterol concentration and PCa. However, in a later analysis, the same authors [66] concluded that only after 3 years of follow-up, high-density lipoprotein (HDL) levels began to correlate negatively with the risk of developing PCa (OR=0.79, 95% CI 0.68-0.92, p=0.003). It was also observed that an increase in the ratio of total cholesterol to HDL >5.45 was associated with an increased risk of developing PCa (OR=1.26, 95% CI 1.07-1.49, p=0.005) in contrast to patients who had a ratio of <3.44. In addition, a low-density lipoprotein (LDL) to HDL ratio >3.70 was also associated with an increased risk of developing PCa compared to a ratio <2.11 (OR=1.21, 95% CI 1.03-1.41, p=0.026).

In the work of W.R. Farwell and co-auth. [29] also demonstrated the relationship between the level of total cholesterol and the risk of developing prostate cancer. The researchers noted that in patients with a level of total cholesterol >237 mg / dl RPH occurred 45% more often compared with patients with total cholesterol <176 mg / dl (OR = 1.45, 95% CI 1.07-1.97). K. Shafique and his co author [53] found that of 650 men who developed PCa, higher cholesterol levels (235.9-258.7 mg/dL) were positively associated with the incidence of high-risk PCa (Gleason score ≥8) compared to patients with cholesterol levels <195.3 mg/dL. G.D. Batty and his co-author [14] report more cancer deaths in the group with high cholesterol concentration.

It is assumed that there are several mechanisms of influence of elevated cholesterol levels on the development of PCa.

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It is known that cholesterol, a steroid lipid, makes up about 1/3 of the lipid content in the plasma membrane. It is an important membrane component of body cells, which affects the structure, functionality of the cell membrane [55], and also plays an important role in steroidogenesis. In addition, it is proved that cholesterol plays a key role in the development of metastatic tumor, acting as a mediator in cell proliferation, inflammation and steroidogenesis [67],[30]. Thus, a number of studies have reported that cholesterol content in tumor tissues is significantly higher than in normal tissues [62], [19]. Many mechanisms including regulated cholesterol uptake, synthesis, conversion to esters, bile acids and steroid hormones, and its excretion from the cell maintain the required concentration of intracellular cholesterol. Cellular cholesterol content is very tightly regulated, despite wide fluctuations in serum cholesterol levels. However, all cells are potentially susceptible to pathologic loss of homeostatic control over cholesterol metabolism. As a result, high cholesterol concentrations can cause cytotoxicity, largely due to the propensity of LDL cholesterol to oxidize.

Lipid peroxidation triggers the formation of reactive oxygen species, which can significantly alter the physical properties of cell membranes or transform into reactive compounds that cross-link DNA or proteins, producing additional toxic effects. All this changes the intensity and rate of apoptosis, sensitivity or resistance to external agents, and promotes the growth of tumor cells [45] [7].

In addition, epidemiologic and preclinical studies have shown that elevated serum cholesterol also contributes to the progression of PCa by increasing the production of highly active androgens by PCa cells and activating androgen receptors, since cholesterol is a precursor to androgens in their intratumoral biosynthesis. Elevated serum cholesterol also correlated with tumor volume, intratumoral testosterone levels, and the expression of key steroid genes, such as the cytochrome enzyme gene (CYP17A) [9].

According to some authors, atherosclerosis causes tissue ischemia, which leads to local hypoxia. A number of factors induced by hypoxia cause the appearance of reactive oxygen species, which, in turn, leads to oxidative DNA damage. At the same time, if oncogenes or tumor suppressor genes are subject to mutations, it can also provoke cancer initiation and/or its progression [31].

To study the prevalence and degree of local atherosclerosis in prostate cancer M. Hager and co-author [31] compared local atherosclerotic changes of arteries in cancer-affected prostate with those in non-tumor prostate specimens. Determination of the intima-media ratio of the arteries of the prostate capsular tissue was measured in 50 prostate cancer-positive and 29 prostate cancer-negative specimens.

The intima-media ratio of normal arteries can range from 0.1 to 1 mm. Prostate cancer-positive specimens were found to have an intima-media ratio >1 about twice as often as negative specimens.

X. Zhang and co-author [75] evaluated the prevalence of atherosclerosis in the lower vesicular arteries of the prostate capsule depending on the presence of prostate cancer using transrectal ultrasound.

The state of the prostate microcirculatory channel was assessed quantitatively by calculating the resistance index (RI), which is the most sensitive marker of atherosclerosis. A statistically significantly higher value of the IR of the capsular arteries of the prostate gland was found in patients with biopsy-proven prostate cancer compared to patients without cancer (0.78±0.08 vs 0.72±0.08, $p < 0.05$). In addition, the authors found that high-risk prostate capsular artery IR was significantly higher in high-risk prostate cancer patients and in patients with advanced stages of

disease than in low-risk patients and in patients with localized prostate cancer. The researchers also noted a direct correlation between Gleason score and prostatic capsular artery IR. In addition, according to a retrospective analysis of patients with prostate cancer between 2005 and 2009, it was noted that hypercholesterolemia was significantly associated with metastasized prostate cancer [24].

Diabetes mellitus and PCa

DM2 increases the risk of death in several solid malignancies, including colorectal cancer and breast cancer, but conflicting data exist in the case of prostate cancer. The impact of preexisting DM2 has also been studied in relation to the extent and stage of PCa in presentation with conflicting results. Moreover, there is emerging evidence that the presence of DM2 and other metabolic disorders (dyslipidemia, hypertension, obesity) are associated with more rapid progression of PCa. This relationship is further complicated by the fact that the standard treatment for advanced PCa, androgen deprivation therapy (ADT), leads to an increased incidence of DM2 [34], as well as the development of DM2 in individuals with pre-existing prediabetes.

Chronic hyperglycemia in DM2 is accompanied by damage, dysfunction and failure of various organs, especially eyes, kidneys, nerves, heart and blood vessels [1].

It is now well known that DM2 increases the risk of malignancies [63]. Some studies show that people with DM2 are twice as likely to die from cancer than people without it. However, there is an inverse negative correlation in PCa, and data have been published in several meta-analyses [64]. S. Bonovas and co-author published a meta-analysis studying DM2 and the risk of developing prostate cancer (2004). They included 14 studies and concluded that DM2 provides a statistically significant reduction in the relative risk (RR) of developing prostate cancer by 9% [16]. In 2006, the data of meta-analysis conducted by J.S. Kasper et al. were published, which included the results of 19 studies. The authors reported an inverse correlation of a similar value with OR 0.84 (95% CI 0.76-0.93) [33]. Thereafter, D. Bansal and co-auth. published an updated meta-analysis of 45 studies involving 8.1 million patients and including 132331 cases of PCa, which also reported an inverse association with an OR of 0.86 (95% CI 0.80-0.92) [13]. Recently, P. Gang with co-authors published an updated meta-analysis with a literature review up to and including April 2012. This meta-analysis contained 56 studies that reported backtesting, OR 0.88 (95% CI 0.82-0.93) [32].

Of the 8 studies cited (Table 1), five were cohort studies [20]; [63]; [37] [43], three were "case-control" studies [28]; [40]. [12]. Three studies were performed on patients from European populations, two from the USA, two from Israel and one from Australia.

The pooled studies include 2716302 observational cases. Six studies reported an inverse correlation between DM2 disease and risk of developing PCa [20] [63]; [37]; [38]; [28]; [12], 1 reported no association [40], and another 1 reported a positive association [43]. The 6 studies that reported an inverse association showed similar rates of association in terms of a 20% reduction in the risk of developing PCa in those with manifest DM2 compared with those without the disease. One article that did not report a statistically significant association was a case-control study in which DM2 cases were represented by patients enrolled in The Fremantle Diabetes Study (FDS) [40].

This is the smallest of the studies, with 1,289 follow-up cases and 5,156 control patients, which may explain the statistical insignificance of their results (OR 0.83, 95% CI: 0.60-1.14) - although the direction and magnitude of the association are consistent with other studies. The study that reported a positive association was a retrospective review of 3162 men who underwent prostate

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biopsy due to elevated prostate specific antigen (PSA) levels and/or an abnormal palpebral rectal examination (PRI) result [43]. This design differs from other studies described previously, which are based on a general, rather than a selected population, with prostate biopsy results. This heterogeneity in design may explain the presence of a 26% increased odds of a positive biopsy in patients with DM2 compared to patients without DM (OR 1.26; 95% CI: 1.01-1.55).

Hyperinsulinemia is associated with many cancers including prostate cancer. IR in peripheral tissue leads to hyperinsulinemia to maintain normal blood glucose levels [51]. However, insulin is also a potent growth factor and is associated with accelerated prostate tumor growth and greater disease spread [10]. It has been shown that high-risk prostate tumor is characterized by a large number of insulin receptors (IR) on its membrane, as well as increased expression of the IR-A isoform in both in vitro and in vivo models [46]. IR activation stimulates both the PI3K/Akt/mTOR pathway and the MAP/ERK kinase pathway, ultimately leading to cell proliferation and migration and inhibition of apoptosis [10]. Thus, elevated circulating blood insulin concentrations, such as those associated with IR, combined with an increased number of insulin receptors on aggressive prostate tumors support the hypothesis of the importance of insulin in prostate cancer development and growth.

A wide range of studies have demonstrated a positive association between hyperinsulinemia, the risk of developing prostate cancer and its greater aggressiveness. Although not all studies support this relationship, fasting insulin concentrations close to the upper ranges of reference values have been positively associated with prostate cancer [8]. On the other hand, a negative association is usually observed with the risk of prostate cancer in patients with a long history of DM2 and decreased insulin concentrations due to β-cell death [21]. Metformin, commonly used to control blood glucose levels in patients with DM2 by decreasing hepatic glucose production and increasing the sensitivity of peripheral tissues to glucose uptake, is also associated with a reduced risk of prostate cancer [48]. Despite these data supporting the role of insulin in the development of prostate cancer, a meta-analysis found no significant associations between insulin treatment and prostate cancer risk [18].

Other factors involved in glucose metabolism have also been implicated in the development of PCa. IGF-I and IGF-II have been shown to increase the risk of PCa and act through the same signaling pathways as insulin. Although they can bind to IR, they have their own IGF-IR that can activate signaling cascades. IGF-I and IGF-II have been shown to be released from tumor cells and induce autocrine and paracrine function in addition to their endocrine function.

Insulin-like growth factor binding protein-3 (IGFBP-3) is a peptide involved in the regulation of cell growth. More than 95% of the IGF-1 available in serum is bound to carrier proteins, which are categorized into 6 classes. The most important of these is the IGFBP-3 carrier protein. This peptide has equal affinity for both IGF-1 and IGF-2. An increase in the amount of insulin-like protein-3 is inversely proportional to the risk of prostate cancer [17].

Elevated fasting C-peptide concentrations are associated with the risk of developing PCa and higher cancer rates [26]. Insulin secretion is judged by C-peptide content when insulin is separated from proinsulin in the beta cell. Since C-peptide and insulin are secreted in equimolar concentrations, the level of insulin secretion can be estimated from the level of C-peptide. Measurements of C-peptide can distinguish between increased insulin secretion or decreased clearance, revealing a potential mechanism of hyperinsulinemia.

P.F. Zamboni and co-auth. [73] demonstrated that fasting insulin concentrations and homeostatic model of assessment of IR (HOMA-IR) were higher in patients with PCa with varying degrees of

disease severity compared with non-oncologic control patients with similar body mass index (BMI), despite normal glucose concentrations after 2 hours in the oral glucose tolerance test (OGTT). Since insulin levels are important in aggressive growth of PCa, it is important here to determine whether insulin and C-peptide levels are elevated to manage glucose concentrations during the PGTT. K.M. Di Sebastiano and co-auth. [25] demonstrated that patients with RA at diagnosis had lower glucose concentrations after 2 hours of PHTT and had higher insulin and C-peptide levels compared to men of the same age and body weight without cancer. U.Y. Tekdoğan and co-auth. [60] found that IGF-1 and IGFBP-3 did not differ between patients with PCa and benign prostatic hyperplasia (BPH) during PGTT; however, insulin concentrations were significantly higher in the BPH group than in cancer patients [60]. These data suggest that insulin may promote prostate cell growth, but its role in the development of malignization is unclear.

Insulin deficiency and IR play a central role in the development of DM2. This review begins by discussing the impact of IR and existing DM2 on the incidence of PCa, confirming previously published results suggesting that DM2 may have a protective effect on the risk of PCa [3]. Several potential biological mechanisms and possible biases explaining this feedback are presented.

Conclusion

Our present data support the belief that a thorough assessment of cardiovascular risk factors, presence of concomitant cardiovascular diseases in patients with PCa in order to apply prevention and treatment of atherosclerosis-related diseases to reduce cardiovascular risk and decrease the progression of PCa is necessary.

The effect of existing DM2 on the type of tumorigenesis has been investigated. Some studies have suggested that the inverse association is only seen in low-risk cancers and that patients with DM2 actually have a higher risk of developing an PCa. However, this is inconsistent with existing meta-analysis, and no conclusion can be drawn at this time about the effect of DM2 on the risk of developing PCa in different grades and stages. Existing literature suggests that DM2 is consistently associated with an increased risk of all-cause mortality and of PCa. The relationship between DM2 and PCa is further complicated by the interaction between the two conditions and their treatment. The relationship between ADT and DM2 has been investigated and there is good concordance between all studies, with all showing an increased risk of DM2.

We suppose that it is necessary to continue research in this area.

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