

# Is there an association between coronary atherosclerosis and carcinoma of the prostate in men aged 50 years and older? An autopsy and coroner based post-mortem study

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## Abstract

**Background:** Atherosclerotic disease is the most common cause of death in the United States and prostate cancer has the highest incidence among males in the United States. Reports have indicated that atherosclerosis and cancers may share common pathoetiologic and pathogenetic cascades. If atherosclerosis and cancers have common pathoetiologic and pathogenetic cascades, both diseases will co-occur and patients may represent a potential target group for cancer screening interventions.

**Materials and Methods:** Prostates and coronary vessels were examined from 37 deceased men, aged 50 years and older, who died unexpectedly and suddenly from traumatic causes. Tissue sections of the entire prostate were examined for benign and malignant lesions. Analysis of Variance was used to compare mean coronary artery atherosclerosis scores among groups of men with diagnosis of adenocarcinoma, intraepithelial neoplasm, benign hyperplasia and normal prostate glands.

**Results:** Twelve prostates (32.5%) showed adenocarcinoma of the prostate, four with Gleason score 7 and eight with Gleason score 6. After adjustment for age and race, there remained no statistical difference between prostate pathology groups and atherosclerosis score ( $F = 0.72$ ;  $P = 0.55$ ).

**Conclusions:** To our knowledge, ours is the first study to use direct pathological examination of tissues for definitive identification of atherosclerosis and prostate cancer. In our case series, the occurrence and progression of coronary atherosclerotic disease and cancer of the prostate were not associated.

**Key words:** Atherosclerotic cardiovascular disease, pathology, prostate cancer

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## Introduction

Heart disease and malignant neoplasms are the two leading causes of death in the United States, accounting for approximately 50% (1.21 million) of all deaths in 2004.<sup>[1]</sup> Coronary Atherosclerotic Disease [CAD] is the

most common cause of death in the United States.<sup>[1]</sup> The cancer with the highest incidence in United States men is prostate cancer, representing approximately 33% of new cancer cases in men in 2006.<sup>[2]</sup>

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It has been reported that atherosclerosis and cancers may share common patho-etiological and pathogenetic cascades.<sup>[3-6]</sup> Given this possible commonality of disease causation and progression, atherosclerosis and cancer prevention and treatment may benefit from similar strategies. Moreover, patients with atherosclerotic cardiovascular disease may represent a potential target group for cancer screening interventions.<sup>[5,6]</sup>

We hypothesize that if atherosclerosis and cancers have common patho-etiological and pathogenetic cascades, both diseases will co-occur in the same individuals.

## Materials and Methods

Over a period of one year, we selected 37 deceased men, aged 50 years and older, who died unexpectedly and suddenly from traumatic causes, and whose deaths were investigated by the Allegheny County Medical Examiner's Office, Pittsburgh, Pennsylvania, with full autopsies performed to determine the causes and manners of these deaths. We excluded cases of traumatic deaths in men, aged 50 years and older, with external examination only or partial autopsies.

Following removal of the heart during the autopsy, the anatomic distribution of the coronary artery system was examined by direct visual inspection to identify the Right Coronary Artery (RCA) and ostium, the Left Coronary Artery Mainstem (LCA) and ostium, the Left Anterior Descending Coronary Artery (LAD), the Left Circumflex Coronary Artery (LCX) as well as the left obtuse marginal artery and diagonal artery branches.<sup>[7]</sup> Multiple, serial, transverse, through and through, cut sections, at 0.5 to 1.0 cm intervals were made along the entire length of each coronary artery. These sections were visually inspected and the presence of focal, multifocal or segmental, eccentric and/or concentric atherosclerosis was determined.

The focus of greatest luminal occlusion of each coronary artery was excised, fixed in formalin for at least two days, processed and stained by standard Hematoxylin and Eosin (H and E) tissue staining protocol.<sup>[8]</sup> Histologic sections were examined by two forensic pathologists and a senior pathology resident (BIO, AMK, JLL). The degree of atherosclerosis within each artery was categorized histologically according to the classification of the Council of Atherosclerosis of the American Heart Association, which stipulates sequential, stochastic histologic grades of I, II, III, IV, V, VI, VII and VIII.<sup>[9-17]</sup> Grades I – III and Grades IV – V are grouped as initial and intermediate atherosclerotic lesions respectively, while grades VI – VIII are grouped as advanced atherosclerotic lesions.

Following the en-bloc removal of the pelvic organs, the prostate gland was dissected off the bladder neck and

the urethra was transversely excised at this level. The entire prostate gland was fixed in formalin for two weeks before multiple, serial, through and through, transverse sections of the gland were made at 0.5 cm intervals from the apex to the base. The sections were bisected into the right and left sides and the prostate was submitted completely for histologic tissue analysis and standard Hematoxylin and Eosin histochemical staining protocol.<sup>[18]</sup> The tissue sections of the entire prostate were examined by two genitourinary pathologists (AVP, JB) for histologic diagnosis. We classified diseases of the prostate into ten histologic diagnoses,<sup>[18]</sup> which are shown in Table 1. Each histologic diagnosis is represented by the numbers 1 to 10 as shown in Table 1. The most advanced histologic diagnosis present was used to categorize the prostate pathology for each case. Histologic grading of prostatic carcinoma was performed with the Gleason Grading System.<sup>[19-21]</sup>

Analysis of Variance [ANOVA] was the primary statistical method used to compare mean coronary artery atherosclerosis scores among groups of men with diagnoses of adenocarcinoma, intraepithelial neoplasm, benign hyperplasia, and normal prostate glands. In analyses of covariance, we adjusted for age and race while making these comparisons. The main dependent variable in all models was the worst atherosclerosis score in a given individual. We also re-ran models separately for each reader to ensure robustness of results.

## Results

We examined the coronary arteries and prostates of 37 autopsy cases, composed of 32 white and 5 black men. Cases ranged in age from 50 to 86 years with a mean age of 65.8 years. Table 2 shows the causes and manners of death including 24 accidental and 13 suicidal deaths.

Histologic sections of the right coronary artery, the left coronary artery-mainstem, the left anterior descending coronary artery and the left circumflex coronary artery were not taken at autopsy in two, five, four and three cases respectively. Thus, associations were based on 35 cases.

**Table 1: Histologic diagnosis of the prostate gland used for our study**

No significant pathologic changes
Benign Prostatic Hyperplasia
Prostatic Intraepithelial Neoplasm
Adenocarcinoma of the Prostate
Transitional Cell Carcinoma of the Prostate
Benign Mesenchymal Tumors of the Prostate
Malignant Mesenchymal Tumors of the Prostate
Basal Cell Hyperplasia
Basal Cell Carcinoma
Other

**Table 2: Underlying causes of death, contributory factors to death and manners of death of our 37 cases**

Case number	Underlying cause of death/ contributory factor to death	Manner of death
1	Drug toxicity	Accident
2	Hanging	Suicide
3	Gunshot wound	Suicide
4	Hanging	Suicide
5	Fire/Carbon monoxide intoxication	Accident
6	Hypertensive cardiovascular Disease/Blunt force trauma	Accident
7	Coronary atherosclerotic disease/ Blunt force trauma	Accident
8	Blunt force trauma	Accident
9	Blunt force trauma	Accident
10	Gunshot wound	Suicide
11	Pneumonia/Blunt force trauma	Accident
12	Gunshot wound	Suicide
13	Mechanical asphyxiation	Accident
14	Drug toxicity	Accident
15	Drug toxicity	Accident
16	Gunshot wound	Suicide
17	Blunt force trauma	Accident
18	Coronary atherosclerotic disease/ Blunt force trauma	Accident
19	Fire/Carbon monoxide intoxication	Suicide
20	Thermal burns/Blunt force trauma	Accident
21	Gunshot wound	Suicide
22	Gunshot wound	Suicide
23	Blunt force trauma	Accident
24	Gunshot wound	Suicide
25	Blunt force trauma	Accident
26	Drowning	Accident
27	Coronary atherosclerotic disease/ Blunt force trauma	Accident
28	Chronic obstructive pulmonary Disease/Blunt force trauma	Accident
29	Coronary atherosclerotic disease/ Blunt force trauma	Accident
30	Coronary atherosclerotic disease/ Blunt force trauma	Accident
31	Blunt force trauma	Accident
32	Gunshot wound	Suicide
33	Fire/Carbon monoxide intoxication	Accident
34	Gunshot wound	Suicide
35	Gunshot wound	Suicide
36	Blunt force trauma	Accident
37	Blunt force trauma	Accident

The mean atherosclerosis grade for the left coronary -mainstem, left anterior descending, and right coronary arteries were 4.8, 4.6, and 4.4 respectively on a scale of 1-8. Only one (2.7%) of the 37 prostate glands showed no pathologic changes. Seven (18.9%) of the prostate glands

showed benign prostatic hyperplasia. Seventeen (46.0%) cases showed benign intraepithelial neoplasm, and twelve (32.4%) prostates showed adenocarcinoma of the prostate. Four of the adenocarcinoma cases revealed a Gleason Score of 7 and eight of these cases revealed a Gleason Score of 6 with a mean Gleason Score of 6.33.

The unadjusted mean atherosclerosis score for each prostate pathology category was as follows: Normal prostate 6.0; benign hyperplasia 6.3; intraepithelial neoplasm 5.1; adenocarcinoma 5.3. Between group differences were not statistically significant ( $F = 0.84; P = 0.48$ ). After adjustment for age and race, there remained no statistical difference between prostate pathology groups and atherosclerosis score ( $F = 0.72; P = 0.55$ ). The association was similarly null when analyzing data from each of the separate readers.

### Discussion

In our case series, the occurrence and progression of coronary atherosclerotic disease and cancer of the prostate were not associated. Ross J *et al.*,<sup>[4]</sup> in their comprehensive review of the molecular pathways of atherosclerosis and cancers, have identified possible common molecular pathways of disease pathogenesis and disease progression for atherosclerosis and cancers including cell adhesion molecules, beta-catenin and tumor growth factor, beta growth factor pathways etc. If atherosclerotic cardiovascular disease and cancers are truly two manifesting variants of a common disease pathway, patients who present with clinical manifestations of atherosclerotic cardiovascular disease would be expected to exhibit an increased prevalence of cancers and vice versa.

Several studies have found no association between atherosclerotic disease and cancers especially prostate cancer.<sup>[5,6,22,23]</sup> To investigate whether there was an association between atherosclerosis and cancer, Dreyer L and Olsen JH<sup>[5]</sup> evaluated the cancer pattern of patients with atherosclerosis of the aorta and of peripheral and cerebral vessels in 69,485 patients with atherosclerosis who were identified through the Danish National Registry of Patients between 1977 and 1989. The incidence of cancer in this group was calculated by linkage to the Danish Cancer Registry for the period 1977 to 1993. No consistent excesses over the expected figures were seen for cancer at any site unrelated to tobacco smoking in either the total cohort or in subgroups. They found no association at the individual level between atherosclerosis and colorectal cancers or hormone-related cancers, except for a decreased standardized incidence ratio of 0.7 [95% confidence interval, 0.5 - 0.9] for endometrial cancer. Their study did not support the view that patients with atherosclerotic disease represent a high risk group for prostate cancer and potential future targets for prostate cancer screening interventions.

In contrast, several other studies may have found an

association between atherosclerotic disease and prostate cancer.<sup>[24-26]</sup> To investigate whether there was an association between cancers of the breast, prostate and colon, Neugut AI *et al.*<sup>[26]</sup> conducted a hospital-based case-control study based on 252 breast cancer cases, 256 colorectal cancer cases, 319 prostate cancer cases; 322 benign surgical controls and 189 benign prostatic hypertrophy controls, all of whom underwent biopsy or surgery between January 1984 and December 1992. Using unconditional logistic regression with adjustment for appropriate confounders, they found no association between a history of coronary atherosclerotic disease and breast or colorectal cancer but an elevated risk was found for prostate cancer [odds ratio, 2.00; 95% confidence interval, 1.18-3.39].

These previous studies have been limited by possible biases related to their reliance on medical records and patient interview questionnaires. A cancer may be present in a patient with atherosclerotic cardiovascular disease but may not be identified by patient reports, patient interviews and medical records. Cancers or atherosclerosis may be present in an individual in a pre-clinical stage, which may not be clinically manifest and cannot be detected by studies based on medical record reviews and patient interviews. A large subset of patients with coronary atherosclerotic disease may be absent from the analysis set as they have died from this disease.

To our knowledge, ours is the first study to use direct pathological examination of tissues for the definitive identification of atherosclerosis and prostate cancer. Direct pathologic examination of disease, in cases those who have died from acute trauma identifies both clinical and sub-clinical disease. Moreover, it is the gold standard for disease diagnosis.

In conclusion, our study shows that among men aged 50 and older, who died from trauma, direct examination of the prostate gland and coronary arteries at autopsy, revealed no association between degree of coronary atherosclerotic disease and cancer of the prostate. This may suggest that atherosclerosis and cancers do not have common pathoetiologic and pathogenetic cascades.

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