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# Metformin Use and Prostate Cancer Risk

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**Abstract**

***Background:*** Metformin may decrease prostate cancer (PCa) risk by reducing hyperinsulinemia-associated carcinogenesis or through direct effects on cancer cells.
***Objective:*** To evaluate the association between metformin use and PCa diagnosis.
***Design, setting, and participants:*** We used the Danish Cancer Registry and the Aarhus University Prescription Database to conduct a nested case–control study among men residing in northern Denmark from 1989 to 2011. We identified 12 226 cases of PCa and used risk-set sampling to select 10 population controls per case ($n$ = 122 260) from among men alive on the index date and born in the same year. A sensitivity analysis was conducted using subjects who had prostate-specific antigen (PSA) testing prior to 1 yr before the index date.
***Intervention:*** Metformin exposure was assessed using prescriptions redeemed before the index date.
***Outcome measurements and statistical analysis:*** Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. The association between metformin use and PCa diagnosis was determined, controlling for diabetes severity and other potential confounders.
***Results and limitations:*** Metformin users were at decreased risk of PCa diagnosis compared with never-users (adjusted OR [aOR]: 0.84; 95% CI, 0.74–0.96). Diabetics on no medication (aOR: 0.98; 95% CI, 0.89–1.09) or on other oral hypoglycemics (aOR: 0.98; 95% CI, 0.86–1.10) did not have a reduced risk of PCa, while users of insulin did have a reduced risk (aOR: 0.77; 95% CI, 0.64–0.93). In the PSA-tested group, metformin use was associated with decreased risk of PCa compared with nonuse (aOR: 0.66; 95% CI, 0.51–0.86). Diabetics on no medication (aOR: 1.03; 95% CI, 0.86–1.24), diabetics on other oral hypoglycemics (aOR: 0.92; 95% CI, 0.70–1.20), and insulin users (aOR: 0.83; 95% CI, 0.56–1.24) did not have a statistically significant reduced risk of cancer.
***Conclusions:*** Metformin use was associated with decreased risk of PCa diagnosis, whereas diabetics using other oral hypoglycemics had no decreased risk.
***Patient summary:*** We studied the relationship between metformin (a diabetic medication) and prostate cancer in Denmark. We found that metformin reduced the risk of prostate cancer diagnosis, whereas other oral antidiabetic medications did not.


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## 1. Introduction

Prostate cancer (PCa) is the second leading cause of cancer mortality in men and the most commonly diagnosed noncutaneous malignancy [1,2]. Because of the high incidence, substantial personal distress [3–5], and societal costs [6] associated with the diagnosis and treatment of PCa, prevention would have a powerful impact.

Hyperinsulinemia, associated with type 2 diabetes, may play a role in carcinogenesis and be negatively associated with cancer prognosis [7,8]. Increased levels of insulin in obese men may lead to worse PCa prognosis [7,9,10]. This theory is supported by laboratory evidence showing that hyperinsulinemia upregulates insulin receptors in PCa cells and increases tumor growth [11]. However, diabetes has also been associated with decreased diagnosis of PCa, potentially mediated by lower levels of testosterone in these patients [12,13].

Metformin, a biguanide, is the most widely prescribed antidiabetic drug in the world because of its clinical effectiveness and tolerability [14]. Its primary mechanism is to activate 5′ AMP-activated protein kinase in the liver, inhibit gluconeogenesis, and reduce circulating insulin levels [15]. Metformin may reduce insulin-stimulated cancer growth [16] through this mechanism, in addition to possessing other antineoplastic properties such as reduction of the c-Myc oncogene [17]. However, no randomized trial has evaluated the effect of metformin on PCa risk, while observational studies have yielded conflicting results [18–24].

We performed a large population-based study of metformin use and PCa. We hypothesized that metformin use would be associated with decreased risk of PCa diagnosis.

## 2. Material and methods

### 2.1. Source population and study design

We conducted a nested case–control study within a well-defined cohort of Danish males identified between January 1989 and December 2011. Individuals eligible for case and control sampling resided in the former counties of North Jutland (1989–2011), Aarhus (1996–2011), Ringkoebing (1998–2011), and Viborg (1998–2011). In 2007, the Danish regions replaced counties as the main administrative units. Because the four counties started contributing data to the Arhus University Prescription Database (AUPD) at different times, they differ with respect to the earliest availability of prescription data (the earliest being 1989) [25]. The Central and North Denmark Regions encompass the four former counties, and the periods of required residence correspond to the period of availability of data on prescription medication use. Together, the two regions represent approximately one-third of the Danish population (approximately 1.8 million inhabitants). Health-related services are recorded using the unique civil personal registration (CPR) number assigned to all Danish citizens since 1968 by the Danish Civil Registration System (CRS). The CPR number encodes gender and date of birth [26] and permits accurate individual-level linkage among all Danish registries.

The Danish National Health Service provides tax-supported universal health care to all residents of the country and refunds part of patients' expenditures for most physician-prescribed drugs, including drugs used to treat diabetes [25]. The Danish regions are served by pharmacies equipped with computerized accounting systems, through which data on prescriptions for refundable drugs are sent to the AUPD [25]. The database includes information on each patient's CPR number, the type of drug prescribed (coded according to the Anatomical Therapeutic Chemical classification system), the amount of drug dispensed, and the date of sale [25,27].

### 2.2. Cases

Cases were men with an incident diagnosis of PCa and no previous cancer diagnosis (except nonmelanoma skin cancer) who were identified using the Danish Cancer Registry (see Appendix A for International Classification of Diseases codes), which has recorded all incident cancers diagnosed in Denmark through December 31, 2011 [28]. To be included in the study, men had to be residents of the Central or North Danish Regions, with $\geq$2 yr of prescription history before their index date (date of PCa diagnosis).

### 2.3. Population controls

Controls were identified using the CRS [26,29]. For each man in the case series, 10 controls were randomly selected from among male residents of the two regions who had the same birth year, were alive, and were free of PCa diagnosis on the index date. Men who resided in the study area for $<$2 yr before the index date and men with a diagnosis of cancer (except nonmelanoma skin cancer) before the index date were excluded.

### 2.4. Exposure

We used the AUPD [25] to identify all prescriptions for antidiabetic medications before the index date, disregarding 365 d prior to that date. Diabetic treatment categories were defined as metformin use with no prior insulin prescription, metformin and insulin use, any metformin use, other oral antidiabetic medication use, and no medication. The primary analysis included only metformin users with no exposure to insulin. We identified hospital diagnoses of diabetes in the Danish National Registry of Patients (DNRP), which contains records on all nonpsychiatric hospital admissions since 1977 and records on outpatient and emergency department visits since 1995 [30].

### 2.5. Covariates

From the available sources, we obtained data on the use of selected medications (proton pump inhibitors [PPIs], statins, and 5$\alpha$-reductase inhibitors [5-ARIs]) from the AUPD and data on selected hospital diagnoses (diabetes complications and comorbidities) from the DNRP before the index date (see Appendix A). We assessed diabetic severity using the presence of diabetic complications and hemoglobin A1c (HbA1c) levels measured in the year prior to the index date. We disregarded prescriptions and diagnoses recorded within the year prior to the index date.

### 2.6. Statistical analysis

We tabulated distributions of the demographic variables and other covariates among cases and controls. We used conditional logistic regression analysis to compute crude ORs and adjusted ORs (aORs) and their associated 95% confidence intervals (CIs), with simultaneous adjustment for comorbidities (Charlson Comorbidity Index scores 0, 1–2, $\geq$3), diabetic complications, marital status (married, never married, divorced, or widowed), and ever use of PPIs, statins, and 5-ARIs.

An analysis was conducted stratified by localized and advanced-stage (regional or distant metastases) PCa. To assess potential confounding through prostate-specific antigen (PSA) testing, we repeated the analysis restricted to subjects who had PSA testing during the 5-yr period ending 1 yr prior to the index date. Laboratory data on PSA levels were recorded from 1997 on, covering all hospitals in the regions as of 2007 [31]. We also studied the association between metformin use and PCa restricted to diabetic men by rematching controls to cases among diabetic men with the

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