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Use of aspirin, but not other non-steroidal anti-inflammatory drugs is associated with decreased prostate cancer risk at the population level

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Abstract The cyclooxygenase 2 (COX-2) enzyme overexpression in prostate cancer has led to the hypothesis that COX-2 inhibition may reduce prostate cancer growth. Some previous studies have linked the usage of COX-2 inhibiting non-steroidal anti-inflammatory drugs (NSAIDs) with a decreased prostate cancer risk. We estimated the association between cumulative COX-2 inhibition by NSAID usage and prostate cancer risk at population level.

All new prostate cancer cases in Finland during 1995–2002 and matched controls (24,657 case–control pairs) were identified from national registries. Detailed information on medication purchases was obtained from a national prescription database. A total cumulative COX-2 inhibition value was calculated based on total cumulative mg amount of each NSAID drug and the drug-specific COX-1/COX-2 inhibition ratio. Prostate cancer risk was analysed with propensity score-matched conditional logistic regression model.

In total, 53.8% of the cases and 46.5% of the controls had any prescription-use of NSAIDs, while 8.1% and 7.9%, respectively, had used aspirin. Compared to the non-users, any NSAID use was associated with an elevated overall prostate cancer risk (46.4% versus 53.6%, respectively; odds ratio [OR] 1.3, 95% confidence interval [CI] 1.3, 1.4) and risk of advanced cancer (11.8% versus 14.1%; OR 1.6, 95% CI 1.5, 1.8). The risk remained elevated despite the amount of cumulative COX-2 inhibition. In a separate analysis, the risk increase was similar for each NSAID with the exception of aspirin, which was associated with a decreased overall prostate cancer risk (OR 0.90, 95% CI 0.84, 0.96) in a dose-dependent fashion.

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NSAID use is associated with an increased prostate cancer risk at the population level regardless of the COX-2 inhibition. This may be explained by systematic differences between prescription NSAID users and non-users. In contrast, aspirin use is associated with a decreased overall prostate cancer risk. Further studies on aspirin and prostate cancer will be needed.

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1. Introduction

Despite being a common malignancy,[1,2] the aetiology of prostate cancer remains unclear. Age, race and familial predisposition are known risk factors.[3,4] Chronic inflammation also influences prostate carcinogenesis.[5] Cyclooxygenase 2 (COX-2) is an inducible enzyme that facilitates inflammation by catalysing prostaglandin production.[6] COX-2 is overexpressed in prostate carcinoma[7] and could play a role in cancer cell growth.[8] High COX-2 expression in tumour cells has been associated with poorer prognosis.[9]

Thus it has been suggested that non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit the COX pathway, could reduce prostate cancer risk. NSAIDs have been linked with decreased risks of many cancer types.[10–13] In a recent study, COX-2-selective drug celecoxib decreased the growth of prostate tumours by inducing mitotic failure and increasing apoptosis.[14] However, the association with prostate cancer risk remains controversial. In a recent meta-analysis, the epidemiologic evidence for a protective effect of aspirin and other NSAID use against prostate cancer was suggestive, but not conclusive.[15]

In the current study, we evaluated the overall and advanced prostate cancer risk among users of NSAIDs and acetaminophen. We quantified COX-2 inhibition by NSAID usage and estimated prostate cancer risk stratified by cumulative COX-2 inhibition in a large population-based case–control setting.

2. Materials and methods

2.1. Study design

All newly diagnosed prostate cancer cases in Finland during 1995–2002, totalling 25,029 men were identified from the Finnish Cancer Registry, a population-based nationwide register that covers more than 99% of all cancer patients in Finland.[16] The information includes primary site of cancer, histology, date and method of diagnosis, but does not cover information on differentiation or serum prostate-specific antigen (PSA) values.

Of the cases, 99.3% were histologically confirmed. Information on stage was available for 55% of the cases ($n = 13{,}616$). Of these, 73% ($n = 9879$) were localised, while 27% ($n = 3737$) were advanced (presence of extracapsular extension, involvement of regional lymph nodes or metastasis). The median age was 68 and 69 years for cases with or without information on stage, respectively. In a small number of cases the diagnosis was based solely on clinical (0.4%), radiologic (0.3%), or specific laboratory (0.02%) findings. We excluded 66 duplicate cases and 185 cases (0.7%) with an unknown method of diagnosis.

The Population Register Center of Finland selected male controls that were individually matched to cases by age (±1 year) and residential area at the time of the corresponding case's prostate cancer diagnosis using incidence density sampling; a total of 963 controls were diagnosed with prostate cancer later during the study period and appeared twice, first as a control and later as a case in another case–control pair. Matched controls could not be found from the same municipality for 121 cases in the oldest age group, thus were excluded from the study. A total of 24,657 case–control pairs were included.

Information on reimbursed physician-prescribed medication purchases during 1995–2002 was obtained from the comprehensive nationwide prescription database of the Social Insurance Institution (SII) of Finland. The SII is a governmental agency financed through tax revenues,[17] providing reimbursements for the cost of medicines prescribed by a physician with the exception of hospital inpatients. The reimbursement is available to all Finnish residents, for each purchase of a SII approved reimbursable drug and covers 50–100% of the costs depending on the severity of the disease.

All reimbursements are recorded in the prescription database along with the amount, dose and date for each purchase. Most prescription drugs in clinical use in Finland are reimbursable, thus recorded by the database. This includes all NSAIDs, although some of them are also available prescription-free. The database does not cover prescription-free purchases.

The ethics committee of the Pirkanmaa health care district, Finland approved of the study protocol.

2.2. Statistical analysis

All medical reimbursements between 1st of January 1995 and the month of diagnosis were included in the analyses, regardless of the length of usage. To ensure identical exposure time between cases and controls the medication use was followed for each case–control pair until the diagnosis date of the case, which also served as

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