Impact of Common Medications on Serum Total Prostate-specific Antigen Levels and Risk Group Assignment in Patients with Prostate Cancer

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Abstract. *A recent study in men without prostate cancer suggested that extended use of common medications (nonsteroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics and statins) may lower serum total prostate-specific antigen (PSA) levels by clinically relevant amounts. The present study evaluated the impact of these drugs in patients with clinically localized prostate cancer. A retrospective analysis of 177 patients was performed. The multivariate regression analyses were adjusted for age, prostate volume, Gleason score, T stage, diagnostic setting (clinical symptoms versus elevated PSA only) and presence of diabetes mellitus. Drug use increased with age, e.g. to 50% in patients ≥70 years. The most commonly used drugs were statins (32% of all patients, including those who used drug combinations), followed by NSAIDs (21%) and thiazide diuretics (13%). Drug use was associated with a statistically significant PSA reduction (12%, when comparing 104 non-users to 73 users of any of the three drug types; adjusted analysis, p=0.01). Compared to the U.S.A. National Comprehensive Cancer Network risk group assignment based on measured PSA level, reassignment after correcting for medication use resulted in 8 changes among 57 patients with low or intermediate risk (14%). No such changes can be expected in patients belonging to the high-risk group. These results support the concerns expressed previously, given that risk group assignment, which may be inaccurate in patients using concomitant medications, eventually guides choice of treatment.*

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Chang *et al*. recently published a large cross-sectional study on the impact of nonsteroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics, statins and seven other commonly prescribed medication classes on serum total prostate-specific antigen (PSA) levels (1). The study included men older than 40 years of age (median age 53 years, median PSA 0.8 ng/ml) without prostate cancer from the 2003-2004 and 2005-2006 cycles of the U.S.A. National Health and Nutrition Examination Survey (n=1,864). Five-years use of NSAIDs, statin and thiazide diuretic was associated with PSA levels lowered by 6, 13 and 26%, respectively. PSA is one of the crucial baseline parameters, together with Gleason score and clinical T stage, that form the basis of the U.S.A. National Comprehensive Cancer Network (NCCN) prostate cancer risk group classification (2). For example, a patient with a PSA value of 9.1 ng/ml, Gleason score of 3+3, and T1c cancer would be classified as being at low risk and treated accordingly. If the same patient had hypertension and had been treated with thiazide diuretics, his true PSA value would have been >10 ng/ml, provided the hypothesis of 26% lower PSA level among thiazide diuretics users is true in prostate cancer patients. With a PSA level >10 ng/ml, the patient would belong to the intermediate-risk group and management according to low risk category guidelines may then result in under treatment. Based on these considerations, there is an urgent need to extend the study by Chang *et al*. (1) to men with histologically confirmed prostate cancer diagnosis. This study examined a cohort of men with clinically localised prostate cancer, diagnosed and treated in a well-defined geographical region of Norway to estimate the impact of use of NSAIDs, statins and thiazide diuretics on NCCN risk group classification.

Patients and Methods

Adhering to the design of the study by Chang *et al*. (1), patients treated with 5-alpha reductase inhibitors were ineligible for this study. All other men who presented to the Department of Oncology

and Palliative Medicine, Nordland Hospital (Bodo, Norway) with newly diagnosed, clinically localized prostate cancer for consultation on treatment options and/or active treatment during the period from the beginning of June 2007 until the end of September 2010 were included in the study. The starting date was chosen as the prospective registration of all prostate cancer patients in the host institute started on that date. Nordland Hospital is the exclusive oncology care provider for the county of Nordland, Norway. As previously described, this fact and the structure of the Norwegian health care system allows for evaluation of unselected patient groups almost comparable to population-based registries albeit with limited size (3). The patient cohort did not include patients with testosterone replacement or medical castration prior to cancer diagnosis. It was divided into two subgroups, one comprised patients who used at least one of the examined medications (NSAIDs, statins or thiazide diuretics) and the other comprised of patients who used none of these drugs. None of the patients participated in a formal prostate cancer screening program. All patients were Caucasians, born in Norway and covered by the national public insurance system.

Serum total PSA level was measured with a Siemens ADVIA Centaur immunoassay system (Siemens Healthcare, Erlangen, Germany). In patients with more than one value measured prior to biopsy (10 cores), the one triggering biopsy was used. In patients diagnosed incidentally after transurethral resection, the PSA level prior to resection was used. PSA levels were not controlled for obesity, as no consistent information on body mass index (BMI) was available. The clinical T stage (AJCC 2003) was determined by digital rectal examination and transrectal ultrasound performed by the referring urologist. Prostate volume was also measured by transrectal ultrasound. All patients with PSA >20 ng/ml, Gleason score >7 or T3/T4 tumours underwent isotope bone scans. When indicated, additional computed tomography or magnetic resonance imaging was performed. No evidence of metastatic disease was found in any of the patients. All medical records and information on concomitant medication were available in the hospital's electronic patient record (EPR) system. The system also contained patient self-reported medication lists, which are routinely collected during hospital admission. As several NSAIDs are available over the counter, self-reported information is important in order to gather full information regarding all examined medications (NSAIDs, thiazide diuretic or statins). For men using an examined medication when diagnosed with prostate cancer, the duration of use was set as being equal to the number of years since initiating therapy. To begin with, only patients with at least five years of drug use were selected but, as their number was too low, all patients with at least one year of drug use were included and compared to a combined group of patients who either never used any of the examined drugs or used any of the examined drugs for less than one year; this combined group was termed as the group of non-users. As discussed by Chang *et al*. (1), PSA-lowering effects after less than five years of drug use can be expected, although longer consumption accentuated the relative difference in PSA. Data on specific dosage or subtype of drug within a given class, *e.g*. NSAIDs, were not considered. Regarding statin users, those with concomitant calcium channel blocker medication were not eligible for further analysis, as Chang *et al*. suggested that these drugs negate the influence of statins on PSA value (1).

Statistical analysis and ethics. Patients were selected from the hospital's EPR system and SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used for the database and statistical analysis. For comparison of dichotomous variables, the Chi-square and Fisher's exact tests, where applicable, were used, while for continuous variables, the Mann-Whitney *U*-test was used. Significance was set to 5%. All tests were carried out two-sided. The statistical power of the study was calculated based on the two-sided 5% alpha error level for comparison of the median PSA value in non-users *versus* users of statins only, NSAIDs only, thiazide diuretics only and the combination of statins and thiazide diuretics because Chang *et al*. reported intriguing results for these four comparisons (1). In sufficiently powered groups, multivariate linear regression analyses of log-transformed PSA data was performed, adjusted for imbalances in baseline parameters, as described by Chang *et al*. (1). The study was performed as a retrospective analysis of the possible impact of common drugs on PSA level. As a quality of care analysis, no approval from the Regional Committees for Medical and Health Research Ethics (REK) was necessary.

Results

The study population included 177 men with a median age of 70 years. Table I shows their clinical characteristics. The majority of patients had high-risk disease. As mentioned earlier, no formal screening is offered to the population of Nordland region, Norway. After consultation with both a urologist and a clinical oncologist, 7 patients (4%) chose active surveillance, 27 (15%) radical prostatectomy, 65 (37%) radiotherapy and 78 (44%) endocrine treatment, as an initial treatment approach. Table II shows the use of the examined medications (NSAIDs, statins or thiazide diurectics for at least one year, median duration 5.5 years) according to age group. Eighty-eight percent of patients younger than 60 years did not use any of these drugs. This figure declined to 50% among patients older than 70 years. The correlation between increased age and drug use was statistically significant (p=0.006). The most commonly used drugs were statins (32% of all patients, including those who used drug combinations), followed by NSAIDs (21%) and thiazide diuretics, with or without other drugs (13%). Drug users were not more likely to have PSA-detected cancer (27%) than non-users (37%).

After establishing the patient demographics, the next step was to use the patient figures displayed in Table II to calculate the statistical power of analyses, where the log-transformed PSA in non-users would be compared to that of drug users. It was found that the numbers of patients using statins only, NSAIDs only or thiazide diuretics only were too low to detect the expected differences in median PSA reported by Chang *et al*. (1); *i.e*., a reduction by 6% in those using NSAIDs. The statistical power of these comparisons was <80%. However, two comparisons with a power >80% were possible: (i) non-users (n=104) *versus* users of statins plus thiazide diuretics (irrespective of the additional use of any NSAIDs, n=16, expected PSA difference 36%) and (ii) non-users (n=104) *versus* users of any examined drug (n=73, powered to detect at least 10% difference in PSA).

Table I. *Patient baseline parameters. Drug users had statistically significantly higher median age (p=0.01) and lower rate of low-risk disease (p=0.048). Median PSA, prostate volume, Gleason score, T-stage, diagnostic setting and diabetes prevalence were not significantly different between drug users and non-users.*

Parameter (n=177)	All patients (n=177)	Non-drug users (n=104)	Drug users (n=73)
Age, years (median, range)	70, 48-83	67, 48-81	72, 59-83
Serum PSA, ng/ml (median, range)	15.5, 4.1-124	16.0, 4.2-124	15.0, 4.1-80
Prostate volume, cc (median, range)	30, 14-125	30, 14-125	30, 14-75
Diagnostic setting			
Symptoms	117 (66.1%)	64 (61.5%)	53 (72.6%)
No symptoms, elevated PSA only	60 (33.9%)	40 (38.5%)	20 (27.4%)
Biopsy Gleason score			
4-5	5 (2.8%)	2 (1.9%)	3 (4.1%)
6	29 (27.9%)	13 (17.8%)	42 (23.7%)
3+4	52 (29.4%)	27 (26.0%)	25 (34.2%)
4+3	24 (13.6%)	14 (13.5%)	10 (13.7%)
8	17 (16.3%)	11 (15.1%)	28 (15.8%)
9-10	26 (14.7%)	15 (14.4%)	11 (15.1%)
T stage			
T1a or b	10 (5.6%)	5 (4.8%)	5 (6.8%)
T1c	26 (14.7%)	19 (18.3%)	7 (9.6%)
T2a	28 (15.8%)	14 (13.5%)	14 (19.2%)
T2b	24 (13.6%)	12 (11.5%)	12 (16.4%)
T2c	14 (7.9%)	6 (5.8%)	8 (11.0%)
T3a	61 (34.5%)	37 (35.6%)	24 (32.9%)
T3b	7 (4.0%)	6 (5.8%)	1 (1.4%)
T4	7 (4.0%)	5 (4.8%)	2 (2.7%)
NCCN			
Low risk#	10 (5.6%)	9 (8.7%)	1 (1.4%)
Intermediate risk	47 (26.6%)	28 (26.9%)	19 (26.0%)
High risk	120 (67.8%)	67 (64.4%)	53 (72.6%)
Diabetes mellitus	11 (6.2%)	7 (6.7%)	4 (5.5%)

#Preoperative score in surgically treated patients (41% were reclassified after surgery, typically from intermediate to high risk). T stage and Gleason score in surgically treated patients were also registered preoperatively.

First, the groups of all 73 users of any examined drug or combination was compared to that of all 104 non-users, adjusted for age, prostate volume, diagnostic setting, T stage, Gleason score and presence of diabetes mellitus. The median PSA of drug users was 15.0 ng/ml, as reported in Table I, which also shows that the unadjusted absolute difference was 1.0 ng/ml. Even in the unadjusted analysis where drug users had unfavourable baseline characteristics, such as older age, almost 7% lower PSA was found. In the adjusted analysis, drug users had a 12% lower PSA (95% confidence interval (CI): 4-19%, p=0.01). Then 16 users of statins plus thiazide diurectics (with or without additional NSAIDs) were compared to all 104 non-users. The analysis was again adjusted for the potential confounders mentioned above. Drug users had a 25% lower median PSA (95% CI: 9-40%, p=0.03).

Compared to the original NCCN risk group assignment based on measured PSA levels, reassignment after correcting the PSA value for medication use by the percentage calculated in this study (12% irrespective of drug type) would result in 8 changes among 57 patients with low or intermediate risk (14%). Two patients would be upgraded from low to intermediate risk and six from intermediate to high risk. If one corrected by the drug-specific relative changes published by Chang *et al*. (1), *e.g*. 26% with thiazide diuretics as compared to 6% with NSAIDs, 6 out of 57 patients with low or intermediate risk would still be upgraded (11%). Two patients would be reassigned from the low- to the intermediate-risk group and four from the intermediate- to the high-risk group. The two low-risk patients who would be upgraded chose active surveillance as their initial approach. One of them continues to do so after three years of follow-up, the other one experienced PSA progression from 9.1 to 14.0 ng/ml after 11 months and started endocrine treatment.

Discussion

The present study is the first attempt to evaluate the intriguing impact of NSAIDs, statins and thiazide diuretics described by Chang *et al*. (1) in a cohort of men who were actually

Table II. *Use of NSAIDs, statins and thiazide diurectics (minimum 1 year).*

Medication	<60 years old (n=17)	60-69 years old (n=68)	≥70 years old (n=92)
None	15 (88.2%)	43 (63.2%)	46 (50.0%)
All three	0	4 (5.9%)	2 (2.2%)
Only NSAIDs	0	3 (4.4%)	6 (6.5%)
Only statins	0	4 (5.9%)	11 (12.0%)
Only thiazide diuretics	1 (5.9%)	2 (2.9%)	1 (1.1%)
NSAIDs + statins	1 (5.9%)	10 (14.7%)	15 (16.3%)
NSAIDs + thiazide diuretics	0	0	3 (3.3%)
Statins + thiazide diurectics	0	2 (2.9%)	8 (8.7%)

diagnosed with clinically localised prostate cancer. Therefore, this study aimed to follow the methods used by Chang *et al*. as closely as possible. However, it is acknowledged that these authors were able to perform and adjust their analyses in a more sophisticated fashion, simply as a result of their higher number of cases. The present study showed that these medications are commonly used among prostate cancer patients and that the oldest patients have the highest utilisation rates. The data also supported the hypothesis that patients treated with any of these drugs or a drug combination may have considerably lower serum PSA levels than controls without any use of NSAIDs, statins and thiazide diuretics. These analyses were corrected for age, prostate volume, Gleason score, T stage, diagnostic setting (symptomatic patients *versus* asymptomatic patients who chose to have their PSA value measured) and presence of diabetes mellitus. Associations between serum PSA value and NSAID use were also reported by Fowke *et al*. (4). Other data confirmed that statin use may reduce PSA levels (5-8). The potential mechanisms were discussed by Chang *et al*. (1) and will only be summarized briefly here. The effect may result from direct inhibition of angiogenesis, induction of apoptosis and reduction in cellular proliferation through several intracellular signaling pathways. A reduction in bioavailable testosterone may be involved in the PSA reduction seen with thiazide diuretic use. Recent data from the Finnish prostate cancer screening trial (23,320 men) showed that the overall prostate cancer incidence is reduced among statin users (hazard ratio: 0.75, 95% CI: 0.63-0.89) (9).

Erroneous PSA levels (reduced by medications) may influence NCCN risk group assignment and thus choice of treatment in 11-14% of patients, depending on the magnitude of changes induced by these drugs. Some patients would be reassigned from low to intermediate and others from intermediate to high risk. Overall, the present results extend the concerns about the impact of common medications on prostate cancer screening expressed by Chang *et al*. (1) to patients actually diagnosed with the disease. If erroneous NCCN risk group assignment and possible undertreatment occurs, outcomes including survival may be compromised, unless this effect is smaller than the positive biological impact of drug treatment on the cancer. Hamilton *et al*. (10) recently suggested that statin users treated with radical prostatectomy had a 30% lower risk of PSA recurrence (*i.e*. biochemical failure). Gutt *et al*. (11) made comparable observations regarding freedom from biochemical failure after radiotherapy for prostate cancer. Kollmeier *et al*. (12) found improved biochemical outcomes in high-risk patients on statins treated with radiotherapy as compared to non-statin users. However, Soto *et al*. (13) reported that statins did not influence biochemical outcomes after radiotherapy for localised prostate cancer and Krane *et al*. (6) came to the same conclusion in their study on surgically treated patients. Whether other relevant drugs influence any of these outcomes is at present unknown. Taken together, additional prospective studies are required to shed more light on this issue.

Further validation of the present results is necessary for several reasons. Firstly, the size of the patient population examined was limited and so was the statistical power of the study. The majority of the patients were elderly (median age, 70 years), had high-risk disease and were diagnosed after they had developed urinary symptoms. Therefore these results cannot be extrapolated to men with early-stage, predominantly screening-detected disease, who have much lower PSA levels than those measured in the patient group of this study. Despite adjusting for known imbalances, other sources of bias cannot be ruled out in a retrospective analysis such as this one. Due to the lack of information on BMI, this parameter was not included in the analysis. Previous studies found an inverse relationship between PSA concentration and BMI, which might be the result of a haemodilution effect (14). However, the magnitude of the difference was small. Thus, Loeb *et al*. suggested that adjusting PSA for BMI does not appear to be warranted (15). Another aspect that deserves discussion is that patients using NSAIDs, statins or thiazide diuretics, largely because of concomitant cardiovascular disease, likely consult their primary physician and/or cardiologist regularly or more often than control patients. By doing so, their urinary symptoms may be recognised earlier and further urological examination may be pursued (16, 17).

Even if these patients are classified as symptomatic at diagnosis, they may have less severe symptoms and lower cancer volume than patients consulting their physician for serious urinary problems. Surprisingly, drug users were less frequently asymptomatic at cancer detection (27% as compared to 37% of non-users). This study relied on the hospital EPR system for determining whether a patient used a given medication. No serum drug concentration measurements or pharmacy claims were evaluated. Thus, compliance may have differed from the EPR data. In addition, drug doses and duration of treatment were not considered, as long as a minimum treatment time of one year was recorded. Further studies with larger patient numbers are required to investigate such details or potential differences, *e.g.* between different NSAIDs.

The study recorded differences in PSA levels that were slightly lower than expected compared to the data provided by Chang *et al*. (1). Whether such disagreement results from different patient selection criteria (*e.g.* much higher baseline PSA levels or the presence *versus* absence of prostate cancer), from different duration of drug treatment, or from the small sample size is difficult to estimate. While future studies may determine the magnitude of changes more precisely, the data of the present study provided initial support to the hypothesis put forward by Chang *et al*., namely that common medications should no longer be ignored in this group of patients. Furthermore, data on less commonly prescribed medications should also be collected.

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