

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Androgen deprivation therapy and the risk of diabetes in men with prostate cancer

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-045797
Article Type:	Original research
Date Submitted by the Author:	15-Oct-2020
Complete List of Authors:	Drevinskaite, Mingaile; Nacionalinis vėžio institutas, Laboratory of cancer epidemiology; Vilnius University, Faculty of medicine Patasius, Ausvydas; Nacionalinis vėžio institutas, Laboratory of cancer epidemiology; Vilniaus Universitetas, Faculty of Medicine, Institute of Health Sciences Kincius, Marius; Nacionalinis vėžio institutas, Laboratory of Clinical Oncology Urbonas, Vincas; Nacionalinis vėžio institutas, Laboratory of cancer epidemiology Smailyte, Giedre; National Cancer Institute, Laboratory of Cancer Epidemiology; Vilniaus Universitetas, Faculty of Medicine, Institute of Health Sciences
Keywords:	Prostate disease < UROLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, Epidemiology < ONCOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **Androgen deprivation therapy and the risk of diabetes in men with**
4 **prostate cancer**
5
6
7
8

9 Mingaile Drevinskaite ^{1,3} Ausvydas Patasius ^{1,4}, Marius Kincius ², Vincas Urbonas ², Giedre
10 Smailyte ^{1,4}
11
12
13
14

15 ¹ Laboratory of Cancer Epidemiology, National Cancer Institute, Vilnius, Lithuania

16 ² Laboratory of Clinical Oncology, National Cancer Institute, Vilnius, Lithuania

17 ³ Faculty of Medicine, Vilnius University, Vilnius, Lithuania

18 ⁴ Institute of Health Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
19
20
21
22
23
24

25 Corresponding author: Mingaile Drevinskaite

26 Email.: mingaile.drevinskaite@nvi.lt

27 P.Baublio 3b, Vilnius, LT-08406, Lithuania

28 Tel.: +37052190911
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

Objectives: To examine the risk of type 2 diabetes in prostate cancer patients and its association with androgen deprivation therapy.

Design and participants: Patients diagnosed with prostate cancer in the Lithuanian male population between January 1, 2003 and December 31, 2012 were identified through the Lithuanian Cancer registry. All prostate cancer cases were linked to the National Health Insurance Fund (NHIF) database to obtain information regarding the diagnosis of diabetes mellitus and information on prescriptions of antiandrogens and gonadotropin-releasing hormone (GnRH) agonists. Prostate cancer patients were followed up until the diagnosis of type 2 diabetes, or December 31, 2017, or date of death, whichever came first. Cox proportional hazard models were used to estimate the risk of type 2 diabetes in prostate cancer patients with or without ADT exposure.

Results: 27 580 men were diagnosed with prostate cancer, out of whom 14 502 (52.58%) did not receive ADT and 13 078 (47.42%) were treated with ADT. The incidence of type 2 diabetes for all prostate cancer patients was 7.4/1000 person-years, for men on GnRH agonists 9.0/1000 person-years and 5.8/1000 person-years for men on antiandrogens. There was an increased risk of developing type 2 diabetes comparing androgen deprivation therapy users and non-users (HR = 1.49, 95% CI = 1.34 to 1.66).

Conclusion: This study showed an increased risk of diabetes in prostate cancer patients treated with ADT in comparison to ADT-free patient cohort. GnRH agonist users showed higher susceptibility, while the group on antiandrogen monotherapy showed no such increase.

Strengths and limitations

- Large cohort size, population-based design and long observation time (up to 15 years) are strengths of our study.
- Lack of clinical information regarding treatment modality, applied for patients in combination with ADT, especially information on surgical castration.
- Differences in ADT treatment groups could be influenced by selection bias, as GnRH agonists are used for treatment of metastatic disease, however differences in ADT treatment groups remains after adjusting to stage of disease.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing interests

The authors declare no conflict of interest.

Abbreviations:

AA – antiandrogens

ADT – androgen deprivation therapy

CI – confidence interval

GnRH - gonadotropin-releasing hormone

HR - Hazard ratio

NHIF - National Health Insurance Fund

SE – standard error

1. Introduction

Prostate cancer is one of the most prevalent malignancies and the second leading cause of cancer-related deaths in men worldwide [1]. The growth of prostate cancer cells is dependent on androgens; therefore, androgen deprivation therapy (ADT) is recommended treatment in men with metastatic prostate cancer. ADT is also used in clinically locally advanced prostate cancer in conjunction with radiotherapy as either adjuvant or neoadjuvant therapy [2].

ADT results in a rapid decrease in serum concentrations of testosterone to castration level by reducing testicular androgens secretion or by inhibiting the androgen receptors. Androgen deprivation can also be achieved with surgery (orchiectomy) or medications (gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists or oral antiandrogens (AA)). In addition, complete androgen blockade using combination of GnRH analogues and antiandrogens can also be used in some clinical cases [3]. If prostate cancer patients progress to castrate resistance state, it is recommended to continue ADT [4].

1
2
3 Hypogonadism produced by ADT leads to adverse effects, such as increased risk of
4 cardiovascular disease and metabolic syndrome, anaemia, sexual dysfunction, decreased
5 genital size, gynaecomastia, diminished quality of life, cognitive lesion, hot flushes and
6 reduced bone mineral density [5–8]. One of the newest long-term effect observed in other
7 studies is ADT increasing insulin resistance and having an impact on type 2 diabetes
8 development [5,9–12].
9

10
11 In our large population-based cohort study, we examined the risk of type 2 diabetes in
12 prostate cancer patients and its association with ADT.
13

14 15 16 17 18 **2. Research Design and Methods**

19 20 21 **Study population**

22
23 Patients diagnosed with prostate cancer in the entire Lithuanian male population between
24 January 1, 2003 and December 31, 2012 were identified through the Lithuanian Cancer
25 registry. The database includes information about the date of diagnosis, age at diagnosis,
26 tumour stage (classified by TNM), cause and date of death. Lithuanian data on cancer
27 incidence is included Cancer Incidence in Five Continents, a longstanding collaboration
28 between the International Agency for Research on Cancer and the International Association
29 of Cancer Registries, which serves as a unique source of cancer incidence data from high-
30 quality population-based cancer registries around the world [13].
31

32
33 All prostate cancer cases were linked to the National Health Insurance Fund (NHIF) database
34 in order to obtain information regarding the diagnosis of diabetes mellitus and information on
35 prescriptions of antiandrogens and GnRH agonists. The National Health Insurance Fund
36 (NHIF) database contains demographic data and entries on the primary and secondary
37 healthcare services provided, emergency and hospital admissions and prescriptions of
38 reimbursed medications. Data from the Lithuanian NHIF database encompasses about 98%
39 of inpatient cases and 90% of outpatient visits (up to 100% of primary health care visits) in
40 Lithuania, covering the entire territory of the country [14].
41

42
43 In total between January 1, 2003 and December 31, 2012 29247 cases of prostate cancer were
44 identified. Prostate cancer patients with date of prostate cancer diagnosis equal to the date of
45 death (607 cases) and patient with diabetes mellitus diagnosis before prostate cancer
46 diagnosis (1060 cases), were excluded from the analysis. 27580 prostate cancer patients
47 were included in this study.
48
49
50
51
52
53
54
55
56
57
58
59
60

Statistical analysis

We analyzed risk of diabetes between men on ADT, and prostate cancer patients not treated with ADT. Identified patients were followed till the date of type 2 diabetes diagnosis, or December 31, 2017, or date of death, whichever came first.

In order to evaluate incidence of diabetes caused by ADT we calculated exact person-years at risk for each patient.

Cox proportional hazard models were used to estimate hazard ratios and their 95% confidence intervals to compare risk of diabetes in groups of prostate cancer patients by ADT exposure. Multivariate adjusted Cox proportional hazards models including age and stage at diagnosis were conducted to estimate the effect of ADT on diabetes risk. Association between duration of GnRH agonists use and diabetes risk was assessed by dividing duration into the following intervals: 0-1, 1-2, 2-3, 3-5 and more than 5 years.

All statistical analyses were carried out using STATA statistical software (version 15.1; College Station, TX, USA). The Vilnius Regional Biomedical Research Ethics Committee approved this study.

Patient and public involvement

This article does not contain any studies with human participants. No patients were involved in this study. Our study was based on retrospective data collected in national health insurance fund database.

3. Results

Table 1 presents baseline characteristics of 27 580 men who were diagnosed with prostate cancer, out of whom 14 502 (52.58%) did not receive ADT and 13 078 (47.42%) were treated with ADT. The vast majority of patients (92.25%) received GnRH agonists and 7.75% received antiandrogens.

During follow-up period there were 1371 prostate cancer patients diagnosed with type 2 diabetes. The incidence of type 2 diabetes for all prostate cancer patients (ADT users and ADT non-users) was 7.4/1000 person-years. For those who have never used ADT the incidence was 6.0/1000 person-years. Type 2 diabetes Incidence for ADT users was 8.8/1000 person-years, for men on GnRH agonists 9.0/1000 person-years and 5.8/1000 person-years for men on antiandrogens (**Table 2**).

1
2
3 There was a significantly increased risk of developing of type 2 diabetes comparing ADT
4 users with ADT non-users (HR = 1.49, 95% CI = 1.34 to 1.66) (**Table 3**). Adjusted hazards
5 models for patient's age and tumour's stage also showed a statistically higher risk of
6 developing type 2 diabetes (aHR = 1.47, 95% CI = 1.32 to 1.64) in ADT users group. As
7 compared to ADT non-users the usage of GnRH agonists was associated with an increased
8 risk of type 2 diabetes (HR = 1.53, 95% CI = 1.38 to 1.71), however, there was no significant
9 association between oral antiandrogen monotherapy and outcome.

10
11
12 **Table 4** reports diabetes risk in the group of GnRH agonists users. There were no significant
13 differences in risk by duration of GnRH agonists exposure duration.

20 21 **4. Discussion**

22
23 Our prostate cancer patient cohort study showed increased risk of diabetes in ADT users
24 compared to ADT-free patient cohort. In accordance with other studies, elevated risk was
25 found among GnRH agonist users, while in the antiandrogen monotherapy group no such
26 increase was observed.

27
28
29
30 ADT, which decreases serum testosterone levels by inhibiting testosterone production, has
31 been the first line treatment for men with locally advanced or metastatic prostate cancer since
32 1940 [15]. ADT can reduce circulating testosterone levels to castration levels, however,
33 previous studies have shown that low levels of testosterone might decrease lean body mass
34 growth and increase fat deposition, also might cause insulin resistance by reducing insulin
35 sensitivity [16,17]. The association between ADT users in prostate cancer patients and insulin
36 resistance was identified in *Basaria et al.* study. Patients who received ADT for at least 12
37 months had an increased risk of developing insulin resistance and hyperglycaemia. Forty-four
38 percents of ADT patients had glucose levels in the diabetic range and the duration of ADT
39 was linked to the severity of these metabolic abnormalities [9]. *Bosco et al.* meta-analysis
40 results suggested that ADT usage for prostate cancer patients increased risk of diabetes by
41 36% [18]. In our study we also observed that ADT usage increases the risk of diabetes
42 compared to ADT non-users (HR: 1.49 95% CI 1.34 to 1.66).

43
44
45
46
47
48
49
50
51
52
53 *Keating et al.* found that the treatment with GnRH agonists is associated with an increased
54 risk of type 2 diabetes compared to ADT non-users (HR for GnRH agonists versus no ADT:
55 1.44, 95% CI: 1.34 – 1.55) [5]. *Crawley et al.* evaluated the risk of type 2 diabetes for the
56 patients treated with GnRH agonists or antiandrogens. They found that GnRH agonists
57
58
59
60

1
2
3 increase the risk of type 2 diabetes. In contrast management with antiandrogens was not
4 associated with type 2 diabetes [12]. In our study we showed the highest risk of diabetes was
5 in GnRH agonists users group (HR: 1.53, 95% CI 1.38 to 1.71). This data is in line with
6 above mentioned studies.
7
8
9

10
11 The duration of ADT is a very important factor when trying to establish the link between type
12 2 diabetes and ADT. *Keating et al.* showed increase risk of type 2 diabetes for patients on
13 GnRH agonists, however, this study had a relatively short duration (up to 25 months) [5]. To
14 our knowledge *Crawley et colleagues* were the first that evaluated different types of ADT and
15 the effect of treatment duration. They examined the risk of type 2 diabetes with up to ten
16 years of exposure. In their study they revealed that patients on GnRH agonists during the first
17 3 years (2 – 2.5 years of exposure HR: 1.68, 95% CI 1.40 to 2.02) had the highest risk of
18 developing type 2 diabetes [12]. Similarly, we showed that the highest incidence of diabetes
19 was in the 3-year-exposure group (HR: 1.77, 95% CI 1.44 to 2.18), however, the risk was
20 also significantly elevated in other categories.
21
22
23
24
25
26
27
28

29 Intermittent ADT treatment was suggested as alternative treatment to continuous ADT with
30 possibly fewer complications and better quality of life [19]. *Rezaei et al.* study's results
31 showed that in short-term treatment with intermittent ADT there was no difference in fasting
32 blood glucose, which suggests lower risks of diabetes mellitus in this group of patients [20].
33 Thus, difference in diabetes risk increase between non-users and ADT users could be
34 mitigated by the proportion of intermittent ADT user in our cohort, whom we could not
35 identify from our database. However, according to general used prostate cancer treatment
36 guidelines intermittent ADT could be applicable only for very small and well-informed
37 fraction of prostate cancer patients [21]. Therefore, we consider that this should not influence
38 the final results of our study.
39
40
41
42
43
44
45

46 Large cohort size, population-based design and long observation time (up to 15 years) are
47 strengths of our study. Main limitation of our study is lack of clinical information regarding
48 treatment modality, applied for patients in combination with ADT, especially information on
49 surgical castration. This type of ADT is not common in clinical practice, therefore inclusion
50 of those cases in non-ADT patients group has no substantial effect on diabetes risk
51 evaluation. Another limitation is that differences in ADT treatment groups could be
52 influenced by selection bias, as GnRH agonists are used for treatment of metastatic disease,
53 however differences in ADT treatment groups remains after adjusting to stage of disease.
54
55
56
57
58
59
60

5. Conclusion

This study showed that there is increased risk of diabetes in prostate cancer patients treated with ADT in comparison with ADT-free patient cohort. GnRH agonist users showed higher susceptibility while the group on antiandrogen monotherapy showed no such increase.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019 Jan;69(1):7–34.
2. Parker C, Gillessen S, Heidenreich A, Horwich A, ESMO Guidelines Committee. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015 Sep;26 Suppl 5:v69-77.
3. Jhan J-H, Yeh H-C, Chang Y-H, Guu S-J, Wu W-J, Chou Y-H, et al. New-onset diabetes after androgen-deprivation therapy for prostate cancer: A nationwide propensity score-matched four-year longitudinal cohort study. *J Diabetes Complicat*. 2018;32(7):688–92.
4. Lycken M, Garmo H, Adolfsson J, Stattin P, Holmberg L, Bill-Axelsson A. Patterns of androgen deprivation therapies among men diagnosed with localised prostate cancer: a population-based study. *Eur J Cancer*. 2014 Jul;50(10):1789–98.
5. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol*. 2006 Sep 20;24(27):4448–56.
6. Choo R, Chander S, Danjoux C, Morton G, Pearce A, Deboer G, et al. How are hemoglobin levels affected by androgen deprivation in non-metastatic prostate cancer patients? *Can J Urol*. 2005 Feb;12(1):2547–52.
7. Nguyen PL, Alibhai SMH, Basaria S, D'Amico AV, Kantoff PW, Keating NL, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol*. 2015 May;67(5):825–36.
8. Rhee H, Gunter JH, Heathcote P, Ho K, Stricker P, Corcoran NM, et al. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. *BJU Int*. 2015 Apr;115 Suppl 5:3–13.
9. Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. *Cancer*. 2006 Feb 1;106(3):581–8.
10. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J Natl Cancer Inst*. 2010 Jan 6;102(1):39–46.
11. Lage MJ, Barber BL, Markus RA. Association between androgen-deprivation therapy and incidence of diabetes among males with prostate cancer. *Urology*. 2007 Dec;70(6):1104–8.
12. Crawley D, Garmo H, Rudman S, Stattin P, Häggström C, Zethelius B, et al. Association between duration and type of androgen deprivation therapy and risk of diabetes in men with prostate cancer. *Int J Cancer*. 2016 Dec 15;139(12):2698–704.

- 1
2
3 13. Bray F, Ferlay J, Laversanne M, Brewster DH, Gombe Mbalawa C, Kohler B, et al. Cancer
4 Incidence in Five Continents: Inclusion criteria, highlights from Volume X and the global status
5 of cancer registration. *Int J Cancer*. 2015 Nov 1;137(9):2060–71.
6
- 7
8 14. Navickas R, Visockienė Ž, Purnaitė R, Rukšėnienė M, Kasiulevičius V, Jurevičienė E. Prevalence
9 and structure of multiple chronic conditions in Lithuanian population and the distribution of
10 the associated healthcare resources. *Eur J Intern Med*. 2015 Apr;26(3):160–8.
11
- 12 15. Huggins C, Stevens RE, Hodges CV. STUDIES ON PROSTATIC CANCER: II. THE EFFECTS OF
13 CASTRATION ON ADVANCED CARCINOMA OF THE PROSTATE GLAND. *Arch Surg*. 1941 Aug
14 1;43(2):209–23.
15
- 16 16. Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for
17 prostate cancer. *Urology*. 2004 Apr;63(4):742–5.
18
- 19 17. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for
20 prostate cancer. *J Clin Endocrinol Metab*. 2006 Apr;91(4):1305–8.
21
- 22 18. Bosco C, Crawley D, Adolphsson J, Rudman S, Van Hemelrijck M. Quantifying the evidence for the
23 risk of metabolic syndrome and its components following androgen deprivation therapy for
24 prostate cancer: a meta-analysis. *PLoS ONE*. 2015;10(3):e0117344.
25
- 26 19. Tunn UW, Canepa G, Kochanowsky A, Kienle E. Testosterone recovery in the off-treatment
27 time in prostate cancer patients undergoing intermittent androgen deprivation therapy.
28 *Prostate Cancer Prostatic Dis*. 2012 Sep;15(3):296–302.
29
- 30 20. Rezaei MM, Rezaei MM, Ghoreifi A, Kerigh BF. Metabolic syndrome in patients with prostate
31 cancer undergoing intermittent androgen-deprivation therapy. *Can Urol Assoc J*. 2016;10(9–
32 10):E300–5.
33
- 34 21. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, et al. Intermittent versus
35 Continuous Androgen Deprivation in Prostate Cancer. *New England Journal of Medicine*. 2013
36 Apr 4;368(14):1314–25.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1 Baseline characteristics of men with prostate cancer by ADT use.

	All Patients	ADT Free Cohort	ADT users	AA	GnRH
n (%)	27580 (100%)	14502 (52.58%)	13078 (47.42%)	1014 (7.75%)	12064 (92.25%)
Mean follow up time, years (SE)	6.74 (3.64)	6.54 (3.56)	6.97 (3.73)	7.12 (4.34)	6.95 (3.68)
Age					
Mean age at diagnosis, years (SE)	67.81 (8.61)	68.71 (10.05)	66.81 (6.53)	66.10 (6.50)	66.87 (6.53)
<65	9327 (33.82%)	5120 (35.31%)	4207 (32.17%)	374 (36.88%)	3833 (31.77%)
65-74	12441 (45.11%)	4715 (32.51%)	7726 (59.08%)	580 (57.20%)	7146 (59.23%)
>75	5812 (21.07%)	4667 (32.18%)	1145 (8.76%)	60 (5.92%)	1085 (9.00%)
Stage					
I	1913 (6.94%)	1380 (9.52%)	533 (4.08%)	25 (2.47%)	508 (4.21%)
II	11986 (43.46%)	6660 (45.92%)	5326 (40.72%)	460 (45.36%)	4866 (40.34%)
III	7157 (25.95%)	2671 (18.42%)	4486 (34.30%)	214 (21.10%)	4272 (35.41%)
IV	1461 (5.06%)	663 (4.57%)	798 (6.10%)	105 (10.36%)	693 (5.74%)
Unknown	5063 (18.36%)	3128 (21.57%)	1935 (14.80%)	210 (20.71%)	1725 (14.30%)

Table 2 Incidence of type 2 diabetes per 1000 person-years in prostate cancer patients by ADT use

	Number of patients	Number of events	Incidence rate
All patients	27580	1371	7.4
ADT non-users	14502	570	6.0
ADT users	13078	801	8.8
GnRH agonists users	12064	759	9.0
Antiandrogen users	1014	42	5.8

Table 3 Hazard ratios (HR) for type 2 diabetes in prostate cancer by use of ADT.

	HR	95% CI	aHR*	95% CI
ADT free cohort	ref.	-	ref.	
ADT users	1.49	1.34 to 1.66	1.47	1.32 to 1.64
GnRH agonists users	1.53	1.38 to 1.71	1.51	1.35 to 1.69
Antiandrogen users	1.02	0.75 to 1.40	1.02	0.74 to 1.39

Table 4 Hazard ratios (HR) for type 2 diabetes in men with prostate cancer on GnRH agonists for different periods of exposure.

Years of exposure	Number of events	Number of patients	HR	95% CI	aHR*	95% CI
0–1	369	6800	1.41	1.23 to 1.61	1.38	1.21 to 1.58
1–2	139	2177	1.60	1.33 to 1.93	1.59	1.32 to 1.92
2–3	105	1330	1.77	1.44 to 2.18	1.76	1.42 to 2.17
3–5	96	1151	1.74	1.40 to 2.16	1.73	1.42 to 2.17
>5	50	606	1.58	1.18 to 2.11	1.57	1.17 to 2.10

BMJ Open

A retrospective cohort study of androgen deprivation therapy and the risk of diabetes in men with prostate cancer in Lithuania

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-045797.R1
Article Type:	Original research
Date Submitted by the Author:	09-Mar-2021
Complete List of Authors:	Drevinskaite, Mingaile; Nacionalinis vėžio institutas, Laboratory of cancer epidemiology; Vilnius University, Faculty of medicine Patasius, Ausvydas; Nacionalinis vėžio institutas, Laboratory of cancer epidemiology; Vilniaus Universitetas, Faculty of Medicine, Institute of Health Sciences Kincius, Marius; Nacionalinis vėžio institutas, Laboratory of Clinical Oncology Urbonas, Vincas; Nacionalinis vėžio institutas, Laboratory of cancer epidemiology Smailyte, Giedre; National Cancer Institute, Laboratory of Cancer Epidemiology; Vilniaus Universitetas, Faculty of Medicine, Institute of Health Sciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Urology
Keywords:	Prostate disease < UROLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, Epidemiology < ONCOLOGY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 A retrospective cohort study of androgen deprivation therapy and the risk 2 of diabetes in men with prostate cancer in Lithuania

3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Mingaile Drevinskaite ^{1,3} Ausvydas Patasius ^{1,4}, Marius Kincius ², Vincas Urbonas ², Giedre Smailyte ^{1,4}

¹ Laboratory of Cancer Epidemiology, National Cancer Institute, Vilnius, Lithuania

² Laboratory of Clinical Oncology, National Cancer Institute, Vilnius, Lithuania

³ Faculty of Medicine, Vilnius University, Vilnius, Lithuania

⁴ Institute of Health Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

Corresponding author: Mingaile Drevinskaite

Email.: mingaile.drevinskaite@nvi.lt

P.Baublio 3b, Vilnius, LT-08406, Lithuania

Tel.: +37052190911

42 Abstract

43 **Objectives:** To examine the risk of type 2 diabetes in prostate cancer patients and its
44 association with androgen deprivation therapy.

45 **Design and participants:** We performed a retrospective cohort study of patients diagnosed
46 with prostate cancer in the Lithuanian male population between January 1, 2003 and December
47 31, 2012 who were identified through the Lithuanian Cancer registry. All prostate cancer cases
48 were linked to the National Health Insurance Fund (NHIF) database to obtain information
49 regarding the diagnosis of diabetes mellitus and information on prescriptions of antiandrogens
50 and gonadotropin-releasing hormone (GnRH) agonists. Prostate cancer patients were followed
51 up until the diagnosis of type 2 diabetes, or December 31, 2017, or date of death, whichever
52 came first. Cox proportional hazard models were used to estimate the risk of type 2 diabetes in
53 prostate cancer patients with or without ADT exposure.

54 **Results:** 27 580 men were diagnosed with prostate cancer, out of whom 14 502 (52.6%) did
55 not receive ADT and 13 078 (47.4%) were treated with ADT. The incidence of type 2 diabetes
56 for all prostate cancer patients was 7.4/1000 person-years, for men on GnRH agonists 9.0/1000
57 person-years and 5.8/1000 person-years for men on antiandrogens. There was an increased risk
58 of developing type 2 diabetes comparing androgen deprivation therapy users and non-users
59 (HR = 1.49, 95% CI = 1.34 to 1.66).

60 **Conclusion:** This study showed an increased risk of diabetes in prostate cancer patients treated
61 with ADT in comparison to ADT-free patient cohort. GnRH agonist users showed higher
62 susceptibility, while the group on antiandrogen monotherapy showed no such increase.

63 Strengths and limitations

- 64 • Large cohort size, population-based design and long observation time (up to 15 years)
65 are strengths of our study.
- 66 • Lack of clinical information regarding treatment modality, applied for patients in
67 combination with ADT, especially information on surgical castration.
- 68 • Differences in ADT treatment groups could be influenced by selection bias, as GnRH
69 agonists are used for treatment of metastatic disease, however differences in ADT
70 treatment groups remains after adjusting to stage of disease.

71

1
2
3 **72 Abbreviations:**
4

5 **73 AA** – antiandrogens
6

7 **74 ADT** – androgen deprivation therapy
8

9 **75 CI** – confidence interval
10

11 **76 GnRH** - gonadotropin-releasing hormone
12

13 **77 HR** - Hazard ratio
14

15 **78 NHIF** - National Health Insurance Fund
16

17 **79 SE** – standard error
18
19
20
21
22
23

24

25 **81 1. Introduction**

26 **82** Prostate cancer is one of the most prevalent malignancies and the second leading cause of
27 **83** cancer-related deaths in men worldwide [1]. The growth of prostate cancer cells is dependent
28 **84** on androgens; therefore, androgen deprivation therapy (ADT) is recommended treatment in
29 **85** men with metastatic prostate cancer. ADT is also used in clinically locally advanced prostate
30 **86** cancer in conjunction with radiotherapy as either adjuvant or neoadjuvant therapy [2].
31
32
33
34

35 **87** ADT results in a rapid decrease in serum concentrations of testosterone to castration level by
36 **88** reducing testicular androgens secretion or by inhibiting the androgen receptors. Androgen
37 **89** deprivation can also be achieved with surgery (orchiectomy) or medications (gonadotropin-
38 **90** releasing hormone (GnRH) agonists, GnRH antagonists or oral antiandrogens (AA)). In
39 **91** addition, complete androgen blockade using combination of GnRH analogues and
40 **92** antiandrogens can also be used in some clinical cases [3]. If prostate cancer patients progress
41 **93** to castrate resistance state, it is recommended to continue ADT [4].
42
43
44
45
46
47

48 **94** Hypogonadism produced by ADT leads to adverse effects, such as increased risk of
49 **95** cardiovascular disease and metabolic syndrome, anaemia, sexual dysfunction, decreased
50 **96** genital size, gynaecomastia, diminished quality of life, cognitive lesion, hot flushes and
51 **97** reduced bone mineral density [5–8]. One of the newest long-term effect observed in other
52 **98** studies is ADT increasing insulin resistance and having an impact on type 2 diabetes
53 **99** development [5,9–12].
54
55
56
57
58
59
60

1
2
3 100 In our large population-based cohort study, we examined the risk of type 2 diabetes in prostate
4 cancer patients and its association with ADT.
5 101

6 7 102 **2. Research Design and Methods**

8 9 103 **Study population**

10 104 We performed a retrospective cohort study of patients diagnosed with prostate cancer in the
11
12 105 entire Lithuanian male population between January 1, 2003 and December 31, 2012 who were
13
14 106 identified through the Lithuanian Cancer registry. The database includes information about the
15
16 107 date of diagnosis, age at diagnosis, tumour stage (classified by TNM), cause and date of death.
17
18 108 Lithuanian data on cancer incidence is included Cancer Incidence in Five Continents, a
19
20 109 longstanding collaboration between the International Agency for Research on Cancer and the
21
22 110 International Association of Cancer Registries, which serves as a unique source of cancer
23
24 111 incidence data from high-quality population-based cancer registries around the world [13].
25

26
27 112 All prostate cancer cases were linked to the National Health Insurance Fund (NHIF) database
28
29 113 in order to obtain information regarding the diagnosis of diabetes mellitus and information on
30
31 114 prescriptions of antiandrogens and GnRH agonists. Data linkage between databases was based
32
33 115 on the personal identification code, which is unique to each resident in Lithuania. The National
34
35 116 Health Insurance Fund (NHIF) database contains demographic data and entries on the primary
36
37 117 and secondary healthcare services provided, emergency and hospital admissions and
38
39 118 prescriptions of reimbursed medications. Data from the Lithuanian NHIF database
40
41 119 encompasses about 98% of inpatient cases and 90% of outpatient visits (up to 100% of primary
42
43 120 health care visits) in Lithuania, covering the entire territory of the country [14]. Male patients,
44
45 121 who in NHIF database were registered with type 2 diabetes (International Classification of
46
47 122 Diseases (ICD)-10 code E11) were considered diabetic. Men who received GnRH agonists or
48
49 123 antiandrogens for at least six months were defined as ADT users.

50 124 In total between January 1, 2003 and December 31, 2012 29247 cases of prostate cancer were
51
52 125 identified. Prostate cancer patients with date of prostate cancer diagnosis equal to the date of
53
54 126 death (607 cases) and patient with diabetes mellitus diagnosis before prostate cancer diagnosis
55
56 127 (1060 cases), were excluded from the analysis. 27580 prostate cancer patients were included
57
58 128 in this study.

59 129 **Statistical analysis**

60

1
2
3 130 We analyzed risk of diabetes between men on ADT, and prostate cancer patients not treated
4
5 131 with ADT. Identified patients were followed till the date of type 2 diabetes diagnosis, or
6
7 132 December 31, 2017, or date of death, whichever came first.

8
9 133 In order to evaluate risk of developing diabetes among ADT users in prostate cancer patients'
10
11 134 cohort we calculated exact person-years at risk for each patient.

12
13 135 Cox proportional hazard models were used to estimate hazard ratios and their 95% confidence
14
15 136 intervals to compare risk of diabetes in groups of prostate cancer patients by ADT exposure.
16
17 137 Multivariate adjusted Cox proportional hazards models including age and stage at diagnosis
18
19 138 were conducted to estimate the effect of ADT on diabetes risk. Association between duration
20
21 139 of GnRH agonists use and diabetes risk was assessed by dividing duration into the following
22
23 140 intervals: 0-1, 1-2, 2-3, 3-5 and more than 5 years. GnRH agonists' users to the duration group
24
25 141 were assigned by cumulative exposure.

26 142 All statistical analyses were carried out using STATA statistical software (version 15.1;
27
28 143 College Station, TX, USA). The Vilnius Regional Biomedical Research Ethics Committee
29
30 144 approved this study.

31 145 **Patient and public involment**

32
33
34 146 This article does not contain any studies with human participants. No patients were involved
35
36 147 in this study. Our study was based on retrospective data collected in national health insurance
37
38 148 fund database.

39 40 149 **3. Results**

41
42 150 **Table 1** presents baseline characteristics of 27 580 men who were diagnosed with prostate
43
44 151 cancer, out of whom 14 502 (52.6%) did not receive ADT and 13 078 (47.4%) were treated
45
46 152 with ADT. The vast majority of patients (92.2%) received GnRH agonists and 7.8% received
47
48 153 antiandrogens. There were significant differences between ADT free cohort and ADT users
49
50 154 according the mean age and stage distribution.

51
52 155 During follow-up period there were 1371 prostate cancer patients diagnosed with type 2
53
54 156 diabetes. The incidence of type 2 diabetes for all prostate cancer patients (ADT users and ADT
55
56 157 non-users) was 7.4/1000 person-years. For those who have never used ADT the incidence was
57
58 158 6.0/1000 person-years. Type 2 diabetes Incidence for ADT users was 8.8/1000 person-years,
59
60 159 for men on GnRH agonists 9.0/1000 person-years and 5.8/1000 person-years for men on
160
160 160 antiandrogens (**Table 2**).

1
2
3 161 There was a significantly increased risk of developing of type 2 diabetes comparing ADT users
4 with ADT non-users (HR = 1.49, 95% CI = 1.34 to 1.66) (**Table 3**). Adjusted hazards models
5 162 for patient's age and tumour's stage also showed a statistically higher risk of developing type
6 163
7 164 2 diabetes (aHR = 1.47, 95% CI = 1.32 to 1.64) in ADT users group. As compared to ADT
8 165 non-users the usage of GnRH agonists was associated with an increased risk of type 2 diabetes
9 166 (HR = 1.53, 95% CI = 1.38 to 1.71), however, there was no significant association between
10 167 oral antiandrogen monotherapy and outcome.

11
12
13
14
15
16 168 **Table 4** reports diabetes risk in the group of GnRH agonists users. There were no significant
17 169 differences in risk by duration of GnRH agonists exposure duration.

18 19 20 170 **4. Discussion**

21
22
23 171 Our prostate cancer patient cohort study showed increased risk of diabetes in ADT users
24 172 compared to ADT-free patient cohort. In accordance with other studies, elevated risk was found
25 173 among GnRH agonist users, while in the antiandrogen monotherapy group no such increase
26 174 was observed.

27
28
29
30 175 ADT, which decreases serum testosterone levels by inhibiting testosterone production, has
31 176 been the first line treatment for men with locally advanced or metastatic prostate cancer since
32 177 1940 [15]. ADT can reduce circulating testosterone levels to castration levels, however,
33 178 previous studies have shown that low levels of testosterone might decrease lean body mass
34 179 growth and increase fat deposition, also might cause insulin resistance by reducing insulin
35 180 sensitivity [16,17]. The association between ADT users in prostate cancer patients and insulin
36 181 resistance was identified in *Basaria et al.* study. Patients who received ADT for at least 12
37 182 months had an increased risk of developing insulin resistance and hyperglycaemia. Forty-four
38 183 percents of ADT patients had glucose levels in the diabetic range and the duration of ADT was
39 184 linked to the severity of these metabolic abnormalities [9]. *Bosco et al.* meta-analysis results
40 185 suggested that ADT usage for prostate cancer patients increased risk of diabetes by 36% [18].
41 186 In our study we also observed that ADT usage increases the risk of diabetes compared to ADT
42 187 non-users (HR: 1.49 95% CI 1.34 to 1.66).

43
44
45
46
47
48
49
50
51
52
53 188 *Keating et al.* found that the treatment with GnRH agonists is associated with an increased risk
54 189 of type 2 diabetes compared to ADT non-users (HR for GnRH agonists versus no ADT: 1.44,
55 190 95% CI: 1.34 – 1.55) [5]. *Crawley et al.* evaluated the risk of type 2 diabetes for the patients
56 191 treated with GnRH agonists or antiandrogens. They found that GnRH agonists increase the risk

1
2
3 192 of type 2 diabetes. In contrast management with antiandrogens was not associated with type 2
4
5 193 diabetes [12]. In our study we showed the highest risk of diabetes was in GnRH agonists users
6
7 194 group (HR: 1.53, 95% CI 1.38 to 1.71). This data is in line with above mentioned studies.
8

9
10 195 The duration of ADT is a very important factor when trying to establish the link between type
11
12 196 2 diabetes and ADT. *Keating et al.* showed increase risk of type 2 diabetes for patients on
13
14 197 GnRH agonists, however, this study had a relatively short duration (up to 25 months) [5]. To
15
16 198 our knowledge *Crawley et colleagues* were the first that evaluated different types of ADT and
17
18 199 the effect of treatment duration. They examined the risk of type 2 diabetes with up to ten years
19
20 200 of exposure. In their study they revealed that patients on GnRH agonists during the first 3 years
21
22 201 (2 – 2.5 years of exposure HR: 1.68, 95% CI 1.40 to 2.02) had the highest risk of developing
23
24 202 type 2 diabetes [12]. Similarly, we showed that the highest incidence of diabetes was in the 3-
25
26 203 year-exposure group (HR: 1.77, 95% CI 1.44 to 2.18), however, the risk was also significantly
27
28 204 elevated in other categories.

29
30 205 Intermittent ADT treatment was suggested as alternative treatment to continuous ADT with
31
32 206 possibly fewer complications and better quality of life [19]. *Rezaei et al.* study's results showed
33
34 207 that in short-term treatment with intermittent ADT there was no difference in fasting blood
35
36 208 glucose, which suggests lower risks of diabetes mellitus in this group of patients [20]. Thus,
37
38 209 difference in diabetes risk increase between non-users and ADT users could be mitigated by
39
40 210 the proportion of intermittent ADT user in our cohort, whom we could not identify from our
41
42 211 database. However, according to general used prostate cancer treatment guidelines intermittent
43
44 212 ADT could be applicable only for very small and well-informed fraction of prostate cancer
45
46 213 patients [21]. Therefore, we consider that this should not influence the final results of our study.
47
48 214 Large cohort size, population-based design and long observation time (up to 15 years) are
49
50 215 strenghts of our study. Main limitation of our study is lack of clinical information regarding
51
52 216 treatment modality, applied for patients in combination with ADT, especially information on
53
54 217 surgical castration. This type of ADT is not common in clinical practice, therefore inclusion of
55
56 218 those cases in non-ADT patients group has no substantial effect on diabetes risk evaluation.
57
58 219 Another limitation is that differences in ADT treatment groups could be influenced by selection
59
60 220 bias, as GnRH agonists are used for treatment of metastatic disease, however differences in
221 ADT treatment groups remains after adjusting to stage of disease.

222 5. Conclusion

1
2
3 223 This study showed that there is increased risk of diabetes in prostate cancer patients treated
4 224 with ADT in comparison with ADT-free patient cohort. GnRH agonist users showed higher
5 225 susceptibility while the group on antiandrogen monotherapy showed no such increase.
6
7

8 9 226 **Ethics approval**

10
11 227 This research was approved by Vilnius regional bioethics committee (Nr. 158200-16-879-388).
12 228 Bioethics committee waived off informed consent.
13

14 15 229 **Funding**

16 230 This research received no specific grant from any funding agency in the public, commercial or
17 231 not-for-profit sectors.
18

19 232 **Competing interests**

20
21 233 The authors declare no conflict of interest.
22

23 234 **Contributorship statement**

24
25 235 Conceptualization, Mingaile Drevinskaite, Ausvydas Patasius and Giedre Smailyte; Planning,
26 236 Ausvydas Patasius, Marius Kincius, Vincas Urbonas, Giedre Smailyte; Data curation, Giedre
27 237 Smailyte; Formal analysis, Ausvydas Patasius and Giedre Smailyte; Methodology, Ausvydas
28 238 Patasius and Giedre Smailyte; Project administration, Giedre Smailyte; Resources, Giedre
29 239 Smailyte; Supervision, Giedre Smailyte; Writing – original draft, Mingaile Drevinskaite;
30 240 Writing – review & editing, Ausvydas Patasius, Marius Kincius, Vincas Urbonas and Giedre
31 241 Smailyte; Conception and design, Marius Kincius, Vincas Urbonas, Giedre Smailyte.
32
33

34 242 **Data availability**

35 243 Data are available upon reasonable request.
36
37
38
39
40
41
42
43
44
45
46
47

48 245 **References**

- 49
50 246 1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019 Jan;69(1):7–34.
51
52 247 2. Parker C, Gillessen S, Heidenreich A, Horwich A, ESMO Guidelines Committee. Cancer of the
53 248 prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.*
54 249 2015 Sep;26 Suppl 5:v69-77.
55
56 250 3. Jhan J-H, Yeh H-C, Chang Y-H, Guu S-J, Wu W-J, Chou Y-H, et al. New-onset diabetes after
57 251 androgen-deprivation therapy for prostate cancer: A nationwide propensity score-matched
58 252 four-year longitudinal cohort study. *J Diabetes Complicat.* 2018;32(7):688–92.
59
60

- 1
2
3 253 4. Lycken M, Garmo H, Adolfsson J, Stattin P, Holmberg L, Bill-Axelsson A. Patterns of androgen
4 254 deprivation therapies among men diagnosed with localised prostate cancer: a population-
5 255 based study. *Eur J Cancer*. 2014 Jul;50(10):1789–98.
- 6
7 256 5. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen
8 257 deprivation therapy for prostate cancer. *J Clin Oncol*. 2006 Sep 20;24(27):4448–56.
- 9
10 258 6. Choo R, Chander S, Danjoux C, Morton G, Pearce A, Deboer G, et al. How are hemoglobin levels
11 259 affected by androgen deprivation in non-metastatic prostate cancer patients? *Can J Urol*. 2005
12 260 Feb;12(1):2547–52.
- 13
14 261 7. Nguyen PL, Alibhai SMH, Basaria S, D'Amico AV, Kantoff PW, Keating NL, et al. Adverse effects
15 262 of androgen deprivation therapy and strategies to mitigate them. *Eur Urol*. 2015
16 263 May;67(5):825–36.
- 17
18 264 8. Rhee H, Gunter JH, Heathcote P, Ho K, Stricker P, Corcoran NM, et al. Adverse effects of
19 265 androgen-deprivation therapy in prostate cancer and their management. *BJU Int*. 2015 Apr;115
20 266 Suppl 5:3–13.
- 21
22 267 9. Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS. Hyperglycemia and insulin resistance in
23 268 men with prostate carcinoma who receive androgen-deprivation therapy. *Cancer*. 2006 Feb
24 269 1;106(3):581–8.
- 25
26 270 10. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during
27 271 androgen deprivation therapy: observational study of veterans with prostate cancer. *J Natl*
28 272 *Cancer Inst*. 2010 Jan 6;102(1):39–46.
- 29
30 273 11. Lage MJ, Barber BL, Markus RA. Association between androgen-deprivation therapy and
31 274 incidence of diabetes among males with prostate cancer. *Urology*. 2007 Dec;70(6):1104–8.
- 32
33 275 12. Crawley D, Garmo H, Rudman S, Stattin P, Häggström C, Zethelius B, et al. Association between
34 276 duration and type of androgen deprivation therapy and risk of diabetes in men with prostate
35 277 cancer. *Int J Cancer*. 2016 Dec 15;139(12):2698–704.
- 36
37 278 13. Bray F, Ferlay J, Laversanne M, Brewster DH, Gombe Mbalawa C, Kohler B, et al. Cancer
38 279 Incidence in Five Continents: Inclusion criteria, highlights from Volume X and the global status
39 280 of cancer registration. *Int J Cancer*. 2015 Nov 1;137(9):2060–71.
- 40
41 281 14. Navickas R, Visockienė Ž, Puronaitė R, Rukšėnienė M, Kasiulevičius V, Jurevičienė E. Prevalence
42 282 and structure of multiple chronic conditions in Lithuanian population and the distribution of
43 283 the associated healthcare resources. *Eur J Intern Med*. 2015 Apr;26(3):160–8.
- 44
45 284 15. Huggins C, Stevens RE, Hodges CV. STUDIES ON PROSTATIC CANCER: II. THE EFFECTS OF
46 285 CASTRATION ON ADVANCED CARCINOMA OF THE PROSTATE GLAND. *Arch Surg*. 1941 Aug
47 286 1;43(2):209–23.
- 48
49 287 16. Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for
50 288 prostate cancer. *Urology*. 2004 Apr;63(4):742–5.
- 51
52 289 17. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for
53 290 prostate cancer. *J Clin Endocrinol Metab*. 2006 Apr;91(4):1305–8.

- 1
2
3 291 18. Bosco C, Crawley D, Adolfsson J, Rudman S, Van Hemelrijck M. Quantifying the evidence for the
4 292 risk of metabolic syndrome and its components following androgen deprivation therapy for
5 293 prostate cancer: a meta-analysis. PLoS ONE. 2015;10(3):e0117344.
6
7 294 19. Tunn UW, Canepa G, Kochanowsky A, Kienle E. Testosterone recovery in the off-treatment
8 295 time in prostate cancer patients undergoing intermittent androgen deprivation therapy.
9 296 Prostate Cancer Prostatic Dis. 2012 Sep;15(3):296–302.
10
11 297 20. Rezaei MM, Rezaei MM, Ghoreifi A, Kerigh BF. Metabolic syndrome in patients with prostate
12 298 cancer undergoing intermittent androgen-deprivation therapy. Can Urol Assoc J. 2016;10(9–
13 299 10):E300–5.
14
15 300 21. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, et al. Intermittent versus
16 301 Continuous Androgen Deprivation in Prostate Cancer. New England Journal of Medicine. 2013
17 302 Apr 4;368(14):1314–25.
18
19
20 303
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

304 **Table 1** Baseline characteristics of men with prostate cancer by ADT use.

	All Patients	ADT Free Cohort	ADT users	AA	GnRH	p value*
n (%)	27580 (100%)	14502 (52.6%)	13078 (47.4%)	1014 (7.8%)	12064 (92.2%)	
Mean follow up time, years (SE)	6.74 (3.64)	6.54 (3.56)	6.97 (3.73)	7.12 (4.34)	6.95 (3.68)	
Age						
Mean age at diagnosis, years (SE)	67.81 (8.61)	68.71 (10.05)	66.81 (6.53)	66.10 (6.50)	66.87 (6.53)	<0.001
<65	9327 (33.9%)	5120 (35.3%)	4207 (32.2%)	374 (36.9%)	3833 (31.8%)	
65-74	12441 (45.1%)	4715 (32.5%)	7726 (59.0%)	580 (57.2%)	7146 (59.2%)	
>75	5812 (21.0%)	4667 (32.2%)	1145 (8.8%)	60 (5.9%)	1085 (9.0%)	
Stage						
I	1913 (6.9%)	1380 (9.5%)	533 (4.0%)	25 (2.5%)	508 (4.2%)	<0.001
II	11986 (43.5%)	6660 (45.9%)	5326 (40.8%)	460 (45.3%)	4866 (40.4%)	
III	7157 (25.9%)	2671 (18.4%)	4486 (34.3%)	214 (21.1%)	4272 (35.4%)	
IV	1461 (5.3%)	663 (4.6%)	798 (6.1%)	105 (10.4%)	693 (5.7%)	
Unknown	5063 (18.4%)	3128 (21.6%)	1935 (14.8%)	210 (20.7%)	1725 (14.3%)	

305 * shows significance of differences between the ADT free cohort and ADT users

306

307

308

309

310

311 **Table 2** Incidence of type 2 diabetes per 1000 person-years in prostate cancer patients by ADT
 312 use

	Number of patients	Number of events	Person years	Incidence rate
All patients	27580	1371	185961,74	7.4
ADT non-users	14502	570	94866,21	6.0
ADT users	13078	801	91095,53	8.8
GnRH agonists users	12064	759	87683,91	9.0
Antiandrogen users	1014	42	3411,62	5.8

313

314 **Table 3** Hazard ratios (HR) for type 2 diabetes in prostate cancer by use of ADT.

	HR	95% CI	aHR*	95% CI
ADT free cohort	ref.	-	ref.	-
ADT users	1.49	1.34 to 1.66	1.47	1.32 to 1.64
GnRH agonists users	1.53	1.38 to 1.71	1.51	1.35 to 1.69
Antiandrogen users	1.02	0.75 to 1.40	1.02	0.74 to 1.39

315 * adjusted for age and stage

316

317 **Table 4** Hazard ratios (HR) for type 2 diabetes in men with prostate cancer on GnRH
 318 agonists for different periods of exposure.

Years of exposure	Number of events	Number of patients	HR	95% CI	aHR*	95% CI
ADT free cohort	570	14502	ref.	-	Ref.	-
0–1	369	6800	1.41	1.23 to 1.61	1.38	1.21 to 1.58
1–2	139	2177	1.60	1.33 to 1.93	1.59	1.32 to 1.92
2–3	105	1330	1.77	1.44 to 2.18	1.76	1.42 to 2.17
3–5	96	1151	1.74	1.40 to 2.16	1.73	1.42 to 2.17
>5	50	606	1.58	1.18 to 2.11	1.57	1.17 to 2.10

319 * adjusted for age and stage

320

321

322

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract [Page 1; lines 1-2] (b) Provide in the abstract an informative and balanced summary of what was done and what was found [Page 2; lines 42-62]
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported [Page 3-4, lines 87-107]
Objectives	3	State specific objectives, including any prespecified hypotheses [Page 4, lines 106-107]
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection [Page 4, lines 110-117]
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up [Page 4-5, lines 118-134] (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable [Page 5, 136-140]
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Exposed and Unexposed group [Page 5, lines 141-147]
Bias	9	Describe any efforts to address potential sources of bias [Page 2, lines 68-70]
Study size	10	Explain how the study size was arrived at [Page 4, lines 130-134]
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why [quantitative variable - age]
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding [Page 5, lines 141-147] (b) Describe any methods used to examine subgroups and interactions [Cox proportional Hazard] (c) Explain how missing data were addressed [not applicable] (d) If applicable, explain how loss to follow-up was addressed [not applicable] (e) Describe any sensitivity analyses [not applicable]
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed [Page 5, lines 156-160] (b) Give reasons for non-participation at each stage [not applicable] (c) Consider use of a flow diagram [not applicable]
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders [Page 5, lines 156-160] (b) Indicate number of participants with missing data for each variable of interest [not applicable]

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

(c) Summarise follow-up time (eg, average and total amount) [Page 2, lines 64-65]
[Page 6, lines 162-163]

Outcome data	15*	Report numbers of outcome events or summary measures over time [Page 6, lines 161-166]
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included [Page 6, lines 167-173 + Table 3. Adjusted to age and stage] (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period [not applicable]
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses [not applicable]
Discussion		
Key results	18	Summarise key results with reference to study objectives [Page 6-7, lines 177-227]
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias [Page 7-8, lines 220-227]
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence [Page 7-8, lines 177-227]
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based [Page 3, lines 72-74]

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.