BMJ Open

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

Journal:	*BMJ Open*
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 Epiemiology; Vilniaus Universitetas, Faculty of Medicine, Institute of Health Sciences
Keywords:	Prostate disease < UROLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, Epidemiology < ONCOLOGY

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.

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

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

Abstract

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

Strenghts 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 – adrogen 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].

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

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

2. Research Design and Methods

Study population

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

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

In total between January 1, 2003 and December 31, 2012 29247 cases of prostate cancer were identified. Prostate cancer patients with date of prostate cancer diagnosis equal to the date of death (607 cases) and patient with diabetes mellitus diagnosis before prostate cancer diagnosis (1060 cases), where excluded from the analysis. 27580 prostate cancer patients were included in this study.

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 involment

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).**

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

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

4. Discussion

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

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

Keating et al. found that the treatment with GnRH agonists is associated with an increased risk of type 2 diabetes compared to ADT non-users (HR for GnRH agonists versus no ADT: 1.44, 95% CI: 1.34 – 1.55) [5]. *Crawley et al.* evaluated the risk of type 2 diabetes for the patients treated with GnRH agonists or antiandrogens. They found that GnRH agonists

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

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

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

Large cohort size, population-based design and long observation time (up to 15 years) are strengths of our study. Main limitation of our study is lack of clinical information regarding treatment modality, applied for patients in combination with ADT, especially information on surgical castration. This type of ADT is not common in clinical practice, therefore inclusion of those cases in non-ADT patients group has no substantial effect on diabetes risk evaluation. Another limitation is that 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.

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-Axelson 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.

13. Bray F, Ferlay J, Laversanne M, Brewster DH, Gombe Mbalawa C, Kohler B, et al. Cancer Incidence in Five Continents: Inclusion criteria, highlights from Volume X and the global status of cancer registration. Int J Cancer. 2015 Nov 1;137(9):2060–71.

14. Navickas R, Visockienė Ž, Puronaitė R, Rukšėnienė M, Kasiulevičius V, Jurevičienė E. Prevalence and structure of multiple chronic conditions in Lithuanian population and the distribution of the associated healthcare resources. Eur J Intern Med. 2015 Apr;26(3):160–8.

15. Huggins C, Stevens RE, Hodges CV. STUDIES ON PROSTATIC CANCER: II. THE EFFECTS OF CASTRATION ON ADVANCED CARCINOMA OF THE PROSTATE GLAND. Arch Surg. 1941 Aug 1;43(2):209–23.

16. Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. Urology. 2004 Apr;63(4):742–5.

17. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab. 2006 Apr;91(4):1305–8.

18. Bosco C, Crawley D, Adolfsson J, Rudman S, Van Hemelrijck M. Quantifying the evidence for the risk of metabolic syndrome and its components following androgen deprivation therapy for prostate cancer: a meta-analysis. PLoS ONE. 2015;10(3):e0117344.

19. Tunn UW, Canepa G, Kochanowsky A, Kienle E. Testosterone recovery in the off-treatment time in prostate cancer patients undergoing intermittent androgen deprivation therapy. Prostate Cancer Prostatic Dis. 2012 Sep;15(3):296–302.

20. Rezaei MM, Rezaei MM, Ghoreifi A, Kerigh BF. Metabolic syndrome in patients with prostate cancer undergoing intermittent androgen-deprivation therapy. Can Urol Assoc J. 2016;10(9–10):E300–5.

21. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, et al. Intermittent versus Continuous Androgen Deprivation in Prostate Cancer. New England Journal of Medicine. 2013 Apr 4;368(14):1314–25.

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:	*BMJ Open*
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 Epiemiology; 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

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.

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

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

Abstract

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

Design and participants: We performed a retrospective cohort study of patients diagnosed with prostate cancer in the Lithuanian male population between January 1, 2003 and December 31, 2012 who 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 (52.6%) did not receive ADT and 13 078 (47.4%) 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.

Strenghts and limitations

- Large cohort size, population-based design and long observation time (up to 15 years) are strenghts 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.

Abbreviations:

AA – antiandrogens

ADT – adrogen 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].

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

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

2. Research Design and Methods

Study population

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

All prostate cancer cases were linked to the National Health Insurance Fund (NHIF) database in order to obtain information regarding the diagnosis of diabetes mellitus and information on prescriptions of antiandrogens and GnRH agonists. Data linkage between databases was based on the personal identification code, which is unique to each resident in Lithuania. The National Health Insurance Fund (NHIF) database contains demographic data and entries on the primary and secondary healthcare services provided, emergency and hospital admissions and prescriptions of reimbursed medications. Data from the Lithuanian NHIF database encompasses about 98% of inpatient cases and 90% of outpatient visits (up to 100% of primary health care visits) in Lithuania, covering the entire territory of the country [14]. Male patients, who in NHIF database were registered with type 2 diabetes (International Classification of Diseases (ICD)-10 code E11) were considered diabetic. Men who received GnRH agonists or antiandrogens for at least six months were defined as ADT users.

In total between January 1, 2003 and December 31, 2012 29247 cases of prostate cancer were identified. Prostate cancer patients with date of prostate cancer diagnosis equal to the date of death (607 cases) and patient with diabetes mellitus diagnosis before prostate cancer diagnosis (1060 cases), where excluded from the analysis. 27580 prostate cancer patients were included in this study.

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 risk of developing diabetes among ADT users in prostate cancer patients' cohort 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. GnRH agonists' users to the duration group were assigned by cumulative exposure.

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 involment

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 (52.6%) did not receive ADT and 13 078 (47.4%) were treated with ADT. The vast majority of patients (92.2%) received GnRH agonists and 7.8% received antiandrogens. There were significant differences between ADT free cohort and ADT users according the mean age and stage distribution.

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).**

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

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

4. Discussion

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

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

Keating et al. found that the treatment with GnRH agonists is associated with an increased risk of type 2 diabetes compared to ADT non-users (HR for GnRH agonists versus no ADT: 1.44, 95% CI: 1.34 – 1.55) [5]. *Crawley et al.* evaluated the risk of type 2 diabetes for the patients treated with GnRH agonists or antiandrogens. They found that GnRH agonists increase the risk

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

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

Intermittent ADT treatment was suggested as alternative treatment to continuous ADT with possibly fewer complications and better quality of life [19]. *Rezaei et al.* study's results showed that in short-term treatment with intermittent ADT there was no difference in fasting blood glucose, which suggests lower risks of diabetes mellitus in this group of patients [20]. Thus, difference in diabetes risk increase between non-users and ADT users could be mitigated by the proportion of intermittent ADT user in our cohort, whom we could not identify from our database. However, according to general used prostate cancer treatment guidelines intermittent ADT could be applicable only for very small and well-informed fraction of prostate cancer patients [21]. Therefore, we consider that this should not influence the final results of our study. Large cohort size, population-based design and long observation time (up to 15 years) are strenghts of our study. Main limitation of our study is lack of clinical information regarding treatment modality, applied for patients in combination with ADT, especially information on surgical castration. This type of ADT is not common in clinical practice, therefore inclusion of those cases in non-ADT patients group has no substantial effect on diabetes risk evaluation. Another limitation is that 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.

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.

Ethics approval

This research was approved by Vilnius regional bioethics committee (Nr. 158200-16-879-388). Bioethics committee waived off informed consent.

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.

Contributorship statement

Conceptualization, Mingaile Drevinskaite, Ausvydas Patasius and Giedre Smailyte; Planning, Auvydas Patasius, Marius Kincius, Vincas Urbonas, Giedre Smailyte; Data curation, Giedre Smailyte; Formal analysis, Ausvydas Patasius and Giedre Smailyte; Methodology, Ausvydas Patasius and Giedre Smailyte; Project administration, Giedre Smailyte; Resources, Giedre Smailyte; Supervision, Giedre Smailyte; Writing – original draft, Mingaile Drevinskaite; Writing – review & editing, Ausvydas Patasius, Marius Kincius, Vincas Urbonas and Giedre Smailyte; Conception and design, Marius Kincius, Vincas Urbonas, Giedre Smailyte.

Data availability

Data are available upon reasonable request.

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-Axelson 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.

13. Bray F, Ferlay J, Laversanne M, Brewster DH, Gombe Mbalawa C, Kohler B, et al. Cancer Incidence in Five Continents: Inclusion criteria, highlights from Volume X and the global status of cancer registration. Int J Cancer. 2015 Nov 1;137(9):2060–71.

14. Navickas R, Visockienė Ž, Puronaitė R, Rukšėnienė M, Kasiulevičius V, Jurevičienė E. Prevalence and structure of multiple chronic conditions in Lithuanian population and the distribution of the associated healthcare resources. Eur J Intern Med. 2015 Apr;26(3):160–8.

15. Huggins C, Stevens RE, Hodges CV. STUDIES ON PROSTATIC CANCER: II. THE EFFECTS OF CASTRATION ON ADVANCED CARCINOMA OF THE PROSTATE GLAND. Arch Surg. 1941 Aug 1;43(2):209–23.

16. Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. Urology. 2004 Apr;63(4):742–5.

17. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab. 2006 Apr;91(4):1305–8.

18. Bosco C, Crawley D, Adolfsson J, Rudman S, Van Hemelrijck M. Quantifying the evidence for the risk of metabolic syndrome and its components following androgen deprivation therapy for prostate cancer: a meta-analysis. PLoS ONE. 2015;10(3):e0117344.

19. Tunn UW, Canepa G, Kochanowsky A, Kienle E. Testosterone recovery in the off-treatment time in prostate cancer patients undergoing intermittent androgen deprivation therapy. Prostate Cancer Prostatic Dis. 2012 Sep;15(3):296–302.

20. Rezaei MM, Rezaei MM, Ghoreifi A, Kerigh BF. Metabolic syndrome in patients with prostate cancer undergoing intermittent androgen-deprivation therapy. Can Urol Assoc J. 2016;10(9–10):E300–5.

21. Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, et al. Intermittent versus Continuous Androgen Deprivation in Prostate Cancer. New England Journal of Medicine. 2013 Apr 4;368(14):1314–25.

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%)	

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

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

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

* adjusted for age and stage

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
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

* adjusted for age and stage

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]**

		(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.