

# BMJ Open Association between ischaemic bowel syndromes and androgen deprivation therapy in patients with prostate cancer: a retrospective cohort study

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## ABSTRACT

**Objective:** This study investigated the risk of ischaemic bowel syndrome (IBS) in androgen deprivation therapy (ADT) users to explore the long-term outcomes of patients with prostate cancer (PC) receiving ADT treatment.

**Methods:** We performed a population-based retrospective cohort study. All the clinical information of the study participants were acquired from the Longitudinal Health Insurance Database for Catastrophic Illness Patients in Taiwan. We extracted data for all the patients newly diagnosed with prostate malignancy (ICD-9-CM 185 or C61 in ICD-10-CM) from 2000 to 2008. The patients were then divided into two groups: 7160 male ADT cohort receiving ADT and 7160 male non-ADT comparison group frequency matched by age and index year of ADT treatment of the ADT group. Cox proportional hazard regression was used to estimate the adjusted HR and 95% CIs of the IBS risk.

**Results:** No significant difference was noted in the overall incidence rate for IBS between the ADT and non-ADT cohorts (0.86 and 0.89 per 1000 person-year, respectively,  $p=0.89$ ). Even after adjusting for potential risk factors, a 1.06-fold risk of IBS (95% CI 0.62 to 1.82,  $p=0.82$ ) was observed in the ADT cohort relative to the non-ADT cohorts. Moreover, we stratified the ADT cohort by time point of ADT treatment after PC diagnosis. Different IBS incidence rates were observed among the early ADT, late-ADT and non-ADT users at 0.77, 1.23 and 0.89 per 1000 person-years, respectively; nonetheless, the difference was not statistically significant. Moreover, no difference was found between the ADT treatment types and IBS risk, including sole orchiectomy, sole luteinising-hormone-releasing hormone and both.

**Conclusions:** Results showed that ADT treatment in patients with PC is not an independent factor for IBS incidence. Large sample sizes for patients with IBS with patients with PC who had received ADT treatment are needed for further study.

## INTRODUCTION

Although Asian populations record a relatively low incidence and mortality rate in

## Strengths and limitations of this study

- Nationwide population and complete medical history were analysed using claims data from the Taiwan National Health Institutes.
- Certain lifestyle-related data, such as smoking status or cancer stage and grade, were not available and not adjusted in the analysed model.
- Small numbers of ischaemic bowel syndrome incidences resulted in a wide CI for the HRs.

prostate cancer (PC), this cancer type has become highly common among male cancers. This trend may be related to the enhanced detection and westernisation.<sup>1</sup> Androgen deprivation therapy (ADT) is a reasonable treatment option for patients with high-risk disease, very-high-risk localised disease and metastatic disease.<sup>2</sup> ADT options mainly include operative castration with orchiectomy and chemical castration with luteinising-hormone-releasing hormone (LHRH) agonists.<sup>3</sup> ADT has been reported to be associated with adverse effects on bone, old age, cognitive health and body composition.<sup>4</sup>

Ischaemic bowel syndrome (IBS) is a heterogeneous disorder that represents ischaemic damage to different portions of the bowel; the disease is associated with variable clinical symptoms and outcomes.<sup>5 6</sup> IBS may be caused by impaired blood perfusion to the small or large bowel, including acute arterial mesenteric ischaemia, acute venous mesenteric ischaemia, non-occlusive mesenteric ischaemia, ischaemia/reperfusion injury and ischaemic colitis.<sup>7</sup> The risk factors of IBS include old age, thromboembolic events, arrhythmia, low ejection fraction, congestive heart failure, asthma, chronic obstructive pulmonary disease (COPD), cardiomyopathy, recent myocardial infarction, ventricular aneurysm, aortic insufficiency and renal and

**Table 1** Distribution of baseline characteristics between patients with prostate malignancy with and without ADT treatment

	ADT N=7160		Non-ADT N=7160		p Value
	N	Per cent	N	Per cent	
Age, year					0.99
<65	932	13.0	932	13.0	
65–69	1008	14.1	1008	14.1	
70–74	1659	23.2	1659	23.2	
75–79	1849	25.8	1849	25.8	
80+	1712	23.9	1712	23.9	
Mean (SD)	74.2	(8.16)	74.2	(8.11)	0.95
Comorbidity					
CAD	2674	37.4	3085	43.1	<0.0001
Diabetes	1771	24.7	1913	26.7	0.007
Stroke	1822	25.5	2031	28.4	<0.0001
Hypertension	4698	65.6	4884	68.2	0.001
Hyperlipidaemia	2148	30.0	2132	29.8	0.77
Lower leg fracture or surgery	451	6.30	377	5.27	0.008
Asthma	985	13.8	1006	14.1	0.61
COPD	3638	50.8	4028	56.3	<0.0001
Treatment					
Prostatectomy	3	0.04	1	0.01	0.32
Radiotherapy	2905	40.6	2637	36.8	<0.0001
Antiandrogens	6743	94.2	5513	77.0	<0.0001
Duration from prostate cancer diagnosed to receiving ADT, year (SD)	0.76	(1.51)	0.73	(0.64)	0.07

$\chi^2$  and t-test.

ADT, androgen deprivation therapy; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease.

hepatic diseases, as well as certain medications, such as bevacizumab.<sup>8–11</sup>

Previous studies showed a correlation between metabolic syndrome, diabetes, cardiovascular events and ADT.<sup>12–13</sup> O'Farrell *et al*<sup>14</sup> reported that ADT would increase the risk of thromboembolic disease. Considering that IBS is common in men with cardiovascular and thromboembolic problems, we evaluated whether IBS is also related to ADT. Several studies have addressed the relationship between ADT and subsequent risk of IBS. Thus, we conducted a population-based retrospective cohort study to explore whether ADT treatment in patients with PC would increase the risk of IBS.

## MATERIALS AND METHODS

### Data source

The Longitudinal Health Insurance Database for Catastrophic Illness Patient was used in this retrospective cohort study. LHID-CIP was set up by Taiwan National Health Insurance (NHI) Administration Ministry of Health and Welfare and maintained by the National Health Research Institute. This database included all medical records for each catastrophic illness patient from 1996 to 2011. In Taiwan, patients would apply a catastrophic illness card to escape the copayment of inpatient or outpatient care. These patients must acquire a physician's certificate for catastrophic illness according to the Ministry of Health and Welfare guideline. On the

basis of the Personal Information Protection Act, patient identification was recorded by NHI.

### Study participants

We recruited 24 464 male patients newly diagnosed with PC by reviewing their medical records and using the code of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), 185 or C61 in ICD-10-CM during 2000–2008 in LHID-CIP database. Patients with the following criteria were excluded: (1) with ADT before the date for PC diagnosis; (2) other cancer history (ICD-9-CM 140–184 and 186–208); (3) with IBS history (IBS, ICD-9-CM 557); (4) with age <20 years old and (5) with duration between ADT and IBS <1 year. ADT included bilateral simple orchiectomy and administration of LHRH agonists containing leuprorelin (ATC code L02AE02), goserelin (L02AE03) and triptorelin (L02AE04).

Patients with PC were stratified into two groups on the basis of receipt of ADT. The non-ADT group was frequency matched by age strum (each 5-year strum, eg, 20–24, 25–29, 30–34 and so on) and by the index year of ADT treatment of the ADT group.

### Endpoint and comorbidity

All the study subjects were followed up from the index year of ADT treatment to IBS development. The subjects that did not develop IBS were followed up until the date

**Table 2** Comparison of incidence and HR for IBS between the ADT and non-ADT cohorts

	ADT		Non-ADT		Rate	Person-years	Person-years	Rate	IRR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
	Event no.	Person-years	Rate	Event no.								
Overall	25	28 959	0.86	35	39 163	0.89	0.97 (0.58 to 1.61)	0.89	1.08 (0.64 to 1.82)	0.78		
Age, year												
<70	5	8415	0.59	5	11 810	0.42	1.40 (0.41 to 4.85)	0.59	1.58 (0.39 to 6.36)	0.52		
70–79	14	14 629	0.96	15	20 036	0.75	1.28 (0.62 to 2.65)	0.51	1.37 (0.64 to 2.93)	0.41		
80+	6	5915	1.01	15	7317	2.05	0.49 (0.19 to 1.28)	0.15	0.54 (0.21 to 1.43)	0.22		

Adjusted for age, CAD, diabetes, stroke, hypertension, hyperlipidaemia, lower leg fracture or surgery, asthma, COPD, prostatectomy, radiotherapy and antiandrogen use. Rate, per 1000 person-years.

ADT, androgen deprivation therapy; IBS, ischaemic bowel syndrome; IRR, incidence rate ratio.

of withdrawal from the NHI programme or the end of 2011, whichever came first. Baseline comorbidity included coronary artery disease (CAD; ICD-9-CM 410–414), cardiovascular disease (CVD; ICD-9-CM 430–438), diabetes mellitus (ICD-9-CM 250), hypertension (ICD-9-CM 401–405), hyperlipidaemia (ICD-9-CM 272), lower leg fracture or surgery (ICD-9-CM 820, 821 and 823 and operation code 81.51–81.54), asthma (ICD-9-CM code 493) and COPD (ICD-9-CM 491, 492 and 496). During analysis, we also considered different treatments, such as prostatectomy (operation code 79403B, 79410B, 79404B and 79405B); radiotherapy (36009B and 36012B) and antiandrogen therapy, such as bicalutamide (ATC code L02BB03), flutamide (ATC code L02BB01) and cyproterone (ATC code G03HA01) treatments.

### Statistical analysis

All statistical analyses were performed using SAS software V.9.4 (SAS Institute, Cary, North Carolina, USA). The significance level was set at  $p < 0.05$  by using two-tailed testing. We used  $\chi^2$  test to observe the difference in age distribution (<65, 65–69, 70–74, 75–79 and 80+ years old) and the baseline comorbidity between the ADT and non-ADT groups. The differences in age and duration (from PC diagnosis and ADT treatment) between the ADT and non-ADT groups were evaluated using the t-test. The incidence density of IBS (per 1000 person-years) in the two groups was calculated. Poisson regression was used to assess the incidence rate ratio (IRR) in the ADT group compared with that of the non-ADT group. Cox proportional hazard regression was used to estimate the adjusted HR and 95% CIs of IBS after adjustment for age and all baseline comorbidities. We also estimated the association between IBS and the time point for ADT treatment (early and late treatments). Patients with ADT treatment within 180 days after PC diagnosis were defined as the early group, and the patients given ADT treatment for more than 180 days after PC diagnosis were defined as the late group. The association between IBS and different ADT treatment stages (early/late) was also assessed.

### RESULT

We selected 7160 patients with PC with ADT treatment and 7160 patients without ADT treatment. The mean ages in the ADT and non-ADT cohorts were ~74 years (table 1). No significant difference in age and duration (from PC diagnosis and ADT treatment) was observed for the two groups. Compared with the non-ADT group, the ADT group was likely to present a low baseline comorbidity, including CAD (37.4% vs 43.1%), diabetes (24.7% vs 26.7%), stroke (25.5% vs 28.4%), hypertension (65.6% vs 68.2%) and COPD (50.8% vs 56.3%). However, the ADT cohort achieved a higher prevalence of lower leg fracture or surgery (6.30% vs 5.27%), as well as radiotherapy (40.6% vs 36.8%) and antiandrogen therapy (94.2% vs 77%), than the non-ADT cohort.

**Table 3** Incidence and HRs for IBS in the patients who underwent different durations between the onset of prostate malignancy and ADT treatment relative to those of the non-ADT cohort

	N	Event no.	Person-years	Rate	HR (95% CI)			p Value
					Crude	Adjusted	p Value	
Non-ADT	7160	35	39 163	0.89	1.00		1.00	
ADT								
Early	5351	18	23 266	0.77	0.87 (0.49 to 1.53)	0.62	0.95 (0.53 to 1.70)	0.85
Late	1809	7	5692	1.23	1.38 (0.61 to 3.10)	0.44	1.59 (0.69 to 3.66)	0.28

Adjusted for age, CAD, diabetes, stroke, hypertension, hyperlipidaemia, lower leg fracture or surgery, asthma, COPD, prostatectomy, radiotherapy and antiandrogen use.

Early: duration between the date of onset of prostate cancer and ADT treatment  $\leq$ 180 days.

Late: duration between the date of onset of prostate cancer and ADT treatment >180 days.

Rate, per 1000 person-years.

ADT, androgen deprivation therapy; IBS, ischaemic bowel syndrome.

During follow-up from 2000 to 2011, 25 and 35 patients developed IBS in the ADT (28 959 person-years) and non-ADT cohorts (39 163 person-years) (table 2). For the ADT and non-ADT cohorts, the average follow-up years of ADT treatment and IBS incidence were 3.48 (incident rate: 0.86 per 1000 person-years) and 4.24 years (incident rate: 0.89 per 1000 person-years), respectively. Compared with the non-ADT cohort, the IBS risk in the ADT cohort was 0.97 (95% CI 0.58 to 1.61) and 1.06 (95% CI 0.62 to 1.82) in the crude and adjusted Cox model, respectively. Regardless of age group, no significant difference in IBS incidence was observed between the two cohorts.

Table 3 presents the association between IBS and the time point for ADT treatment. The patients with late ADT treatment show a high IBS incidence than that of the non-ADT cohort (1.23 vs 0.89 per 1000 person-years) but the difference was not statistically significant.

The association between IBS and the different types of ADT treatment is shown in table 4. The IBS incidence values were 0.89, 0.92, 0.92 and 0.35 per 1000 person-years in the patients without ADT treatment, with orchiectomy, with LHRH agonist therapy and with both treatments, respectively. The patients who underwent orchiectomy or LHRH treatment showed higher IBS incidence, but the difference did not reach statistical significance.

## DISCUSSION

ADT could be beneficial to symptomatic advanced PC. The treatment may also serve as a neoadjuvant therapy

in patients with PC receiving radiotherapy and may be efficacious for metastatic disease; however, ADT is associated with certain adverse effects and complications.<sup>15</sup> These adverse effects include decreased bone mineral density, osteoporosis, weight gain, reduced muscle mass, aggravated insulin resistance, decreased libido, reduced sexual function, hot flushes, gynaecomastia, reduced testicular size, anaemia, depression, cognitive decline and fatigue.<sup>4</sup> Chung *et al* reported a significant relationship between ADT with gonadotropin-releasing hormone (GnRH) agonists and an increased pneumonia risk.<sup>3</sup> ADT is a well-established treatment for advanced and metastatic PC and is mainly administered with bilateral simple orchiectomy (surgical castration) or LHRH therapy (medical castration).<sup>16</sup> Oral antiandrogen is not usually used as monotherapy. We evaluated the medication history from our records and found that 94.2% and 77% of the patients with PC who received and did not receive ADT, respectively, also received antiandrogens. Thus, we mainly focused on LHRH in our study. Among 24 464 patients with PC, only 257 (1.05%) patients used LHRH agonists as single treatment. Therefore, we could not eliminate the patients treated with combined antiandrogens. Seaman *et al* compared the risk of venous thromboembolism among patients treated with different antiandrogens and LHRH agonists. The group found that venous thromboembolism was associated only with cyproterone acetate, whereas the other antiandrogens did not contribute to thromboembolic event.<sup>17</sup> In our series, ADT users presented a significantly higher percentage of lower leg fracture/surgery than the non-ADT

**Table 4** Incidence and HRs for IBS under different ADT treatments relative to those in non-ADT patients

	N	Event no.	Person-years	Rate	HR (95% CI)			p-value
					Crude	Adjusted	p-value	
Non-ADT	7160	35	39 163	0.89	1.00		1.00	
ADT treatment								
Orchiectomy	1754	7	7574	0.92	1.03 (0.46 to 2.33)	0.94	1.03 (0.45 to 2.35)	0.94
LHRH	4710	17	18 568	0.92	1.02 (0.57 to 1.83)	0.93	1.17 (0.64 to 2.15)	0.60
Both	696	1	2817	0.35	0.40 (0.05 to 2.90)	0.36	0.45 (0.06 to 3.30)	0.43

Adjusted for age, CAD, diabetes, stroke, hypertension, hyperlipidaemia, lower leg fracture or surgery, asthma, COPD, prostatectomy, radiotherapy and antiandrogen use.

ADT, androgen deprivation therapy; IBS, ischaemic bowel syndrome; LHRH, luteinising-hormone-releasing hormone.

users (6.30% vs 5.27%,  $p < 0.01$ ). This result is identical to that in previous literature.<sup>4 12 15</sup>

The cardiovascular effects of ADT have been reported by several studies, but the results are controversial.<sup>12</sup> Wall *et al*<sup>18</sup> observed that prolonged ADT is associated with accumulating CVD risk factors, such as reduced cardiorespiratory capacity and decreased resting metabolic rate. Short-term (3–6 months) ADT results in the development of hyperinsulinaemia, and long-term ADT ( $\geq 12$  months) yields a higher prevalence of diabetes and metabolic syndrome.<sup>19</sup> In men, testosterone is inversely correlated with the level of low-density lipoprotein cholesterol and positively correlated with the level of high-density lipoprotein (HDL) cholesterol.<sup>20</sup> Meanwhile, ADT is known to increase HDL and total cholesterol in patients with PC.<sup>21</sup> This aspect means that androgen suppression with ADT variably influences the HDL–testosterone correlation relative to those of non-diabetic men. Several studies also supported that ADT is associated with thromboembolic cardiovascular events, including aortic atherosclerosis, CAD, myocardial infarction and sudden cardiac death.<sup>22–24</sup> However, the studies where ADT exerted significantly negative cardiovascular effects mainly involved Caucasian population.<sup>25</sup> A recent study in Asia showed no increase in risk of coronary heart disease in the Chinese/Taiwanese patients with PC who received ADT.<sup>26</sup> The findings are supported by several other studies.<sup>13 27</sup> In the present study, we considered the abovementioned ADT-related risk factors in the models. However, ADT did not significantly increase IBS risk. In the present study, the mean age of the patients with PC was 74 years old, which is older than those in other countries, including Japan and in the Caucasian population.<sup>28</sup> Late age PC diagnosis in Taiwan could be blinding the ADT effects because the risks of CVD, stroke and diabetes increase with age.

IBS is an abdominal emergency caused by impaired intestinal blood perfusion.<sup>7</sup> At present, mesenteric ischaemia presents a high mortality rate, ranging between 50% and 90%.<sup>29</sup> Thus, prompt diagnosis and risk factor identification are crucial for IBS management. The main predisposing factors for IBS are vascular factors and bowel factors. Hypoperfusion, vascular surgery requiring aortic clamping, vasospasm, vasoconstrictor drugs and thromboembolism from hypercoagulable states or cardiac emboli may lead to IBS.<sup>30</sup> O'Farrell *et al* assessed the risk of thromboembolic disease in patients with PC undergoing ADT. The group noted that the incidence of deep vein thrombosis and pulmonary embolism increases with prolonged ADT usage and recommended that only men with relevant indication should receive systemic ADT.<sup>14</sup> The study also showed an increased thrombotic risk in the patients who switched from antiandrogen therapy to GnRH agonist therapy, although these agonists were not considered in our present analysis.<sup>14</sup> Teoh *et al*<sup>31</sup> observed that ADT users presented an increased risk of ischaemic stroke relative to non-ADT users in patients with PC. Old age

(HR 1.13), hyperlipidaemia (HR 4.61) and ADT (HR 3.32) were associated with ischaemic stroke. Ultee *et al*<sup>32</sup> also reported an increased risk for bowel ischaemia in smokers, leading to COPD.<sup>11</sup> Longstreth *et al* found that acute large bowel ischaemia is independently associated with COPD (adjusted OR 3.13).<sup>10</sup> Thus, we considered the COPD variable in our adjusted models. Considering that ADT is reportedly associated with diabetes, dyslipidaemia and CVD, which are all related to thromboembolic events, we determined whether the ADT users presented a higher risk of IBS development. In general, patients with PC with good clinical conditions received ADT treatment. Therefore, the ADT group in the present study exhibited a lower prevalence of CAD, diabetes, stroke, hypertension and COPD. We then considered these factors in the multivariate regression models. Accordingly, no difference in IBS incidence was observed between the ADT and non-ADT users. Although the late-ADT users presented higher HRs of IBS compared with the early ADT and non-ADT users, a significant difference was not reached.

Although the data analysed in the study were obtained from the nationwide-based LHID-CIP, several limitations must be considered. First, the follow-up duration of study cohort was  $\sim 10$  years (2000–2011). Considering the medical and medication history, as well as frequency matching in the study design, we limited the ADT and non-ADT groups and IBS incidence to a small sample size in the present study. This aspect resulted in the wide CI for risk. Second, all the patients with PC in our study possessed an average age of 74 years and exhibited high mortality during follow-up (48.2% in the ADT group and 35.6% in the non-ADT group). Yu *et al*<sup>33</sup> reported that two genetic markers, namely, AKR1C3 rs12529 and AR-CAG repeat length, are significantly associated with PC-specific mortality. In addition, the genetic polymorphism of AKR1C3 rs12529 could also minimise ADT-related impact on quality of life in patients with PC.<sup>34</sup> The effect of the genetic variability on IBS risk was not considered in the present analysis. However, we further examined and found no violation for the assumption of the Cox proportional hazard regression ( $p = 0.87$ ). Finally, several important clinical variables, such as prostate serum antigen levels, cancer stage and grade and smoking habits, were not acquired from the LHID-CIP. For cigarette smoking, we attempted to use the COPD variables as proxy indicators for tobacco smoking and further adjusted the variable in the multivariable models. However, the association between ADT therapy and IBS risk remains statistically insignificant.

## CONCLUSION

No significant difference in HR for IBS was observed between ADT-treated and non-ADT-treated patients with PC. Large-scale studies of IBS events and other related clinical variables must be conducted to determine the association between ADT and IBS risk.

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