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

I-Ni Chiang,1,2 Chao-Yuan Huang,2 Yeong-Shiau Pu,2 Chao-Hsiang Chang,3,4 Chih-Hsin Muo,5,6 Chi-Jung Chung,7,8 Ruey-Yun Wang,5 Tai-Horng Young1

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

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.2 5 6 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.7 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...
hepatic diseases, as well as certain medications, such as bevacizumab.8–11

Previous studies showed a correlation between metabolic syndrome, diabetes, cardiovascular events and ADT.12 13 O’Farrell et al14 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 leuprolrelin (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

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

<table>
<thead>
<tr>
<th></th>
<th>ADT N=7160</th>
<th>Non-ADT N=7160</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>932</td>
<td>932</td>
<td>0.99</td>
</tr>
<tr>
<td>65–69</td>
<td>1008</td>
<td>1008</td>
<td></td>
</tr>
<tr>
<td>70–74</td>
<td>1659</td>
<td>1659</td>
<td></td>
</tr>
<tr>
<td>75–79</td>
<td>1849</td>
<td>1849</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>1712</td>
<td>1712</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>74.2 (8.16)</td>
<td>74.2 (8.11)</td>
<td>0.95</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>2674</td>
<td>3085</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1771</td>
<td>1913</td>
<td>0.007</td>
</tr>
<tr>
<td>Stroke</td>
<td>1822</td>
<td>2031</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4698</td>
<td>4884</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>2148</td>
<td>2132</td>
<td>0.77</td>
</tr>
<tr>
<td>Lower leg fracture or surgery</td>
<td>451</td>
<td>377</td>
<td>0.008</td>
</tr>
<tr>
<td>Asthma</td>
<td>985</td>
<td>1006</td>
<td>0.61</td>
</tr>
<tr>
<td>COPD</td>
<td>3638</td>
<td>4028</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>3</td>
<td>1</td>
<td>0.32</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>2905</td>
<td>2637</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antiandrogens</td>
<td>6743</td>
<td>5513</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration from prostate cancer diagnosed to receiving ADT, year (SD)</td>
<td>0.76 (1.51)</td>
<td>0.73 (0.64)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

χ² and t-test.
ADT, androgen deprivation therapy; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease.

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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 410–414), 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 χ² 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.
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 1.70) 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 showed 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.15 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.4 Chung et al reported a significant relationship between ADT with gonadotropin-releasing hormone (GnRH) agonists and an increased pneumonia risk.13 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).16 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.17 In our series, ADT users presented a significantly higher percentage of lower leg fracture/surgery than the non-ADT users.

### 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

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Event no.</th>
<th>Person-years</th>
<th>Rate</th>
<th>Crude HR (95% CI)</th>
<th>p-value</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ADT</td>
<td>7160</td>
<td>35</td>
<td>39,163</td>
<td>0.89</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>ADT</td>
<td>Early</td>
<td>5351</td>
<td>18</td>
<td>23,266</td>
<td>0.77</td>
<td>0.87 (0.49 to 1.53)</td>
<td>0.62</td>
<td>0.95 (0.53 to 1.70)</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td>1809</td>
<td>7</td>
<td>5692</td>
<td>1.23</td>
<td>1.38 (0.61 to 3.10)</td>
<td>0.44</td>
<td>1.59 (0.69 to 3.66)</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

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

Rate, per 1000 person-years.

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

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

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.
The cardiovascular effects of ADT have been reported by several studies, but the results are controversial. Wall et al. 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 (≥12 months) yields a higher prevalence of diabetes and metabolic syndrome. 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. Meanwhile, ADT is known to increase HDL and total cholesterol in non-ADT users (6.30% vs 5.27%, p<0.01). This result is identical to that in previous literature.

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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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Contributors
C-JC, I-NC, C-YH, Y-SP, C-HC, R-YW and T-HY partly contributed to the conception and design of the work; C-JC, R-YW and C-HM contributed to the analysis of the data and wrote the manuscript; C-HM performed the data analysis. All authors have read the manuscript and approved the final version for submission to BMJ Open and those they accept responsibility for the manuscript’s contents.

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Competing interests
All authors have disclosed any potential competing financial interests regarding the submitted article.

Ethics approval
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Provenance and peer review
Not commissioned; externally peer reviewed.

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No additional data are available.

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REFERENCES
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