What do urologists think patients need to know when starting on androgen deprivation therapy? The perspective from Canada versus countries with lower gross domestic product

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Background: Androgen deprivation therapy (ADT) side effects are numerous and negatively impact prostate cancer patients' quality of life. There is considerable discrepancy though among Canadian urologists regarding what ADT side effects and side effect management strategies. Little is known about global differences in ADT patient education.

Methods: International respondents were recruited via online posting and at an international urology conference. Hypotheses suggest that economic and cultural differences influence patient education practices; therefore, international respondents were divided into 3 categories (high, medium, and low gross domestic product).

Results: No differences were found between responses from Canadian urologists and high GDP countries. Compared to responses from low GDP countries, Canadian urologists are more likely to endorse informing patients about: osteoporosis, loss of muscle mass, weight gain, fatigue/sleep disturbance, relationship changes, cognitive changes, and loss of body hair. Infertility was the only side effect more often disclosed by urologists in low GDP counties. Recommended management strategies for hot flashes are more likely to be pharmaceutical in Canada, and behavioral in low GDP countries. Management strategies for gynecomastia are emphasized more in low GDP countries. Physical exercise is endorsed consistently more often by Canadian urologists.

Conclusions: ADT educational practices vary greatly between Canada and lower GDP countries. Factors that could contribute to differences include economics (e.g., ADT drug costs), differences in side effect presentation due to different ADT drugs used, racial differences in perceived side effect burden, disease status at ADT commencement, and cultural differences in patient-physician shared-decision making.

Keywords: Androgen deprivation therapy (ADT); informed consent; patient education; prostate cancer; hormone therapy

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Introduction

With increased use of prostate specific antigen (PSA) testing, men are being diagnosed with prostate cancer at increasingly younger ages and the incidence of the disease has been rising in recent decades (1-4). In the North American context, biochemical failure (i.e., a rising PSA after a potentially curative treatment, such as a radical prostatectomy) spurs many men to start on androgen deprivation therapy (ADT) even without overt signs of the disease. In the past, prostate cancer patients typically did not begin ADT until they showed signs of advanced disease, such as bone pain associated with metastasis. With men starting ADT earlier in the disease progression, they are on that treatment for a longer time. An extended duration on ADT increases the risk of adverse effects (e.g., cardiovascular disease, diabetes, bone loss, etc.) and men on ADT for longer periods of time must cope with side effects for a longer duration. Thus the need for educating patients about ways to manage the more debilitating side effects is more important than ever before. Here we explore what physicians believe patients need to be most educated about, when starting on ADT.

ADT is most commonly administered in the form of luteinizing hormone releasing hormone agonists (LHRHa) and is associated with many adverse effects that reduce the quality of life of prostate cancer patients (5-11). Our previous research has indicated a gap in patient knowledge about these adverse effects (12), which can influence patients' ability to implement management strategies to mitigate these side effects. Tran et al. (12) examined the perspectives of Canadian uro-oncologists on patient education about ADT side effects. They found considerable diversity among treating physicians about which side effects they felt were essential to inform patients about. So, for example, less than 60% of physicians agreed that patients should be informed about increased risk for depression, diabetes, high cholesterol and anemia, the occurrence of genital shrinkage, and difficulties with orgasm. In contrast, there was strong agreement about informing patients about the following side effects: osteoporosis, erectile dysfunction, hot flashes, loss of libido, and loss of muscle mass. Respondents were also surveyed about side effect management strategies [reviewed in (13)] they recommended to patients (12) and a lack of concordance was also observed for management strategies.

Given the relative lack of agreement in the Canadian context, we sought to explore whether similar perspectives

on educational practices with patients starting on ADT exist for urologists treating prostate cancer patients in other countries. It is likely that there are cultural and/or geographical differences in opinions about what knowledge is essential to disseminate in different clinical settings. In order to explore this question, our analysis focused on countries with lower Gross Domestic Product (GDP) than that of Canada. We hypothesized that variation in access to healthcare, the stage at which the cancer is diagnosed, agents used for ADT, and cultural differences in physicianpatient relationships would be manifested in differences between uro-oncologists in Canada versus other countries. Here we identify such diversity and explore how these differences might influence what information physicians in the two settings feel their patients need to know.

Materials and methods

Urologists were anonymously surveyed about their perspectives on patient education regarding ADT adverse effects. Ethics approval was obtained from the Conjoint Health Research Ethics Board in Calgary, Alberta. Respondents represented a wide range of countries (n=28). Healthcare systems vary widely around the world and how medicine is practiced can be greatly influenced by economic factors. As such, countries were sorted into top, middle and bottom groups based on their per capita GDP (14); the top GDP countries (with number of responses in brackets) included: United States [4], Netherlands [1], Australia [3], Denmark [1], Ireland [1], Canada [4], Germany [4], United Kingdom [3] and France [1]. Countries classified as middle GDP included: Japan [4], Taiwan [1], Portugal [4], Poland [1], Latvia [1], Turkey [1], Malaysia [1], Argentina [1], Serbia [1] and Brazil [2]. The bottom GDP countries included: South Africa [3], China [1], Egypt [1], Indonesia [1], Philippines [1], Iraq [2], Nigeria [2], Ghana [2] and Kenva [1]. Not including the 4 Canadian responses, these tallied as 18, 17 and 14 respondents for high, middle, and lower GDP countries respectively.

Recruitment strategies included online invitations posted by professional associations to their members, and in-person recruitment at an international urology conference held in Vancouver, BC in the fall of 2013 (i.e., 33rd Congress of the Société Internationale d'Urologie). The majority of international respondents were recruited in person at the aforementioned urology congress. Of those approached, approximately 50% agreed to participate. The most common reason for declining was a lack of efficiency

in English. Online invitations were successful for Canadian respondents and 4 international respondents only. The four additional Canadian responses collected at this conference, were added to the large sample of urologists who had previously completed the same survey in the Tran *et al.* (12) study. This yielded a tally of n=42 Canadian responses. The countries from the middle and low GDP groups were combined for a total of 31 responses (referred to here as "lower GDP countries"). Our subsequent data analysis compared these two samples.

A rationale for using Canada as the contrasting group is that Canada is one of the top ranking GDP countries with universal healthcare, so options for managing ADT side effects in Canada are not typically limited by patients' individual ability to pay for services. Furthermore, Canada's universal healthcare practices are largely similar to that of the countries in our top GDP category (e.g., United Kingdom, Germany, with the exception of USA). In fact, the same analyses described below, were conducted on the Canadian *vs.* other high GDP countries, and no significant differences were found.

The same survey used by Tran *et al.* (12) was implemented. The survey included three parts: (I) a list of commonly reported side effects associated with ADT; (II) a list of management strategies for ADT side effects (15) (identified by the ADT Working Group); and (III) a brief case scenario that exemplified a typical ADT patient (i.e., a 65-yearold married man, commencing ADT after failing primary prostate cancer treatment, who was previously sexually active using a phosphodiesterase type 5 inhibitor to treat erectile dysfunction; see Online Supplement 1). Demographic variables of the respondents were also collected (e.g., gender, age, years in practice, rural *vs.* urban).

The first two sections of the survey contained two ranking exercises. The "categories of importance" scale was used to rate how essential physicians considered it to inform patients about specific side effects, and the "side effect management" scale was used to rate how frequently physicians endorsed a specific management strategy. Four categories were used to rate the importance of informing patients about specific side effect: "essential", "important", "not important/no opinion" and "avoid". For statistical analysis the two categories of "essential" and "important" were collapsed into a single category: "inform". similarly, "not important/no opinion" and "avoid" were combined into the single category: "not inform".

To quantify the size of the difference of importance ranking for each individual side effect, an additional comparison was performed by applying a scoring system of 1 through 4 to each aforementioned ranking category, (i.e., "essential" =1, "important" =2, "not important" =3, and "avoid" =4), thus lower scores indicate higher importance.

Four categories were used to rate the endorsement of each management strategy and included: "always", "often", "sometimes/rarely" and "never". These categories were also dichotomized, "always" and "often" categories were combined into the single category: "endorse". Similarly "sometimes/rarely" and "never" were combined into the single category: "not endorse".

Statistical analyses

A series of chi-square tests were performed (16) in order to identify statistically significant differences between the two groups of respondents using a conservative P value cutoff of 0.01 for significance in recognition of our multiple comparisons.

To statistically evaluate the difference between the two groups of urologists in the importance they gave to telling patients about specific side effects a series of Mann-Whitney U tests were performed, using a P value of 0.01.

A chi-square test was run to determine if there was a significant difference between the number of side effects ranked as important or essential (<2) by the two groups of urologists. Significance was determined at P value of 0.05.

Results

Surveyed urologists from Canada ranged in age from 33 to 86 years (mean \pm SD =51.3 \pm 12.1). All 41 respondents were male. The average length of practice was 18.8 years (SD =11.3; range, 1–40). The average number of patients the physicians started on ADT per year was 6.9 (SD =4.9; range, 1–20).

The urologists from lower GDP countries ranged in age from 30 to 70 years (50.2 ± 10.9); 28 were male and 3 were female. The average length of practice was 20.6 years (SD =11.1; range, 3–40). The average number of patients the physicians started on ADT per year was 7.8 (SD =10.5; range, 2–58).

Statistical differences between the two samples were not significant for age, length of practice, or average number of patients started on ADT per year, but were significant for gender, with 3 female urologists from lower GDP countries and none from Canada (P=0.042). Excluding these three individuals did not change the patterns of significance for any



ADT side effects

Figure 1 Comparison of the perceived importance of informing patients of specific ADT side effects between a sample of Canadian urologists (n=42) and a sample of urologists from lower GDP countries (n=31). The side effects are arranged left to right in order from those that Canadian urologists consider most important to least important to discuss with patients starting on ADT. Side effects rated as essential or important are depicted above zero on the x-axis and those rated as not important, or a topic to be avoided, are depicted below the x-axis. The biggest differences between the two populations are found for weight gain, loss of muscle mass, relationship changes, cognitive changes, fatigue/sleep disturbances and osteoporosis (all P<0.001). ADT, androgen deprivation therapy.

of the following analyses, so they were retained in the sample.

Of those in the lower GDP category, LHRHa were listed as the most commonly used method of ADT by 54.8% of the sample (representing Portugal, Brazil, Poland, Taiwan, Malaysia, Iraq, Kenya, Turkey, China Argentina, Indonesia, South Africa and Ghana). An additional 29.0% indicated LHRHa was common, but so too were oral estrogens, antiandrogens, or surgical castration.

Part 1: what ADT side effects do urologists consider essential to inform the patients about?

The side effects that urologists in Canada considered most important to inform their patients about, in decreasing order, were: osteoporosis (100% ranked it essential or important), hot flashes (97.6%), erectile dysfunction (97.6%), loss of libido (94.9%) and gynecomastia (90.2%). Less than 50% of Canadian urologists thought it was important to inform their patients about 5 (out of 19) side effects: elevated cholesterol (46.2%), genital shrinkage (45.9%), delayed orgasm (39.5%), loss of body hair (23.7%) and infertility (10%). These and all other side effects examined are plotted in *Figure 1*.

A gap was noticed between the side effects that were considered important and not important by urologists in the low GDP countries. Only 4 side effects were consistently considered important to inform the patients about, by both groups of urologists: hot flashes (93.5% ranked it essential or important), erectile dysfunction (90.3%), loss of libido (90.3%) and gynecomastia (90.3%). The remaining side effects were predominantly considered not important to discuss with patients by 58% or more of urologists. This

Table 1	Comparison	of perceived	importance	of side effects
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Side offect	Urologists ir	n Canada (%)	Urologists in lower	. 2			
Side ellect	Essential/important Not important/avoid		Essential/important	Not important/avoid	χ	Р	
Hot flashes	97.6	2.4	93.5	6.5	0.712	0.399	
Gynecomastia	90.2	9.8	90.3	9.7	< 0.001	0.991	
Weight gain	77.5	22.5	16.1	83.9	26.317	< 0.001	
Loss of muscle mass	87.5	12.5	19.4	80.6	33.239	< 0.001	
Erectile dysfunction	97.6	2.4	90.3	9.7	1.763	0.184	
Loss of libido	94.9	5.1	90.3	9.7	0.539	0.463	
Delayed orgasm	39.5	60.5	22.6	77.4	2.243	0.134	
Genital shrinkage	45.9	54.1	25.8	74.2	2.943	0.086	
Loss of body hair	23.7	76.3	6.5	93.5	3.783	0.052	
Infertility	10.0	90.0	32.3	67.7	5.466	0.019	
Relationship changes	50.0	50.0	3.2	96.8	18.344	< 0.001	
Cognitive changes	60.0	40.0	16.1	83.9	13.912	< 0.001	
Fatigue/sleep disturbances	72.5	27.5	12.9	87.1	24.936	< 0.001	
Depression	56.4	43.6	16.1	83.9	11.828	0.001	
Osteoporosis	100.0	0.0	32.3	67.7	37.742	< 0.001	
Cardiovascular disease	76.3	23.7	41.9	58.1	8.472	0.004	
Anemia	53.8	46.2	16.1	83.9	10.524	0.001	
Diabetes type 2	51.3	48.7	32.3	67.7	2.552	0.110	
Elevated cholesterol	46.2	53.8	25.8	74.2	3.063	0.080	

Chi-Square test (χ^2); df=1; significance at P<0.01.

ranking was a significantly different between the two groups of urologists (P=0.003). The perceived importance of informing patients about specific ADT side effects is summarized in *Table 1*.

Differences in importance ranking for each individual side effect, are shown in *Table 2*. Lower scores indicate higher importance. The largest difference in importance was observed for osteoporosis, followed by loss of muscle mass, weight gain, fatigue/sleep disturbance, relationship changes, cognitive changes and loss of body hair (all P<0.001).

A comparison of the overall number of side effects determined important to tell patients about was also conducted. A total of 8 out of 19 side effects were given a summative ranking of <2 (essential or important) by Canadian urologists, but only 4 out of the 19 side effects where ranked similarly (<2) by urologists in lower GDP countries. The difference in rankings borders on significant (P=0.020).

Interestingly, only one side effect, infertility, was given an importance rating of larger than 3 by Canadian urologists, denoting that on average they categorize it as a topic on which to outright avoid discussion with patients. In the lower GDP countries however, 9 out of 19 ADT side effects were given an importance score of 3 or higher by the urologists. This ranking was also significantly different between the two groups of urologists (P=0.008) and indicated a strong propensity for urologists in our sample from lower GDP countries to avoid discussing almost half of the ADT side effects with their patients.

Part 2: what management strategies do urologists endorse for these side effects?

Table 3 and Figure 2 show ADT side effect management strategies in which significant differences in endorsement were found between urologists in Canada and urologists in lower GDP countries. Seven side effects had one or more management strategies that differed significantly between Canada and lower GDP countries (*Figure 2*).

Although urologists in both groups rated hot flashes as an adverse effect that is essential to discuss with patients, they do not agree on what patients might do to reduce the burden of this side effect. For hot flashes, most

according to perceived importance for discussion with patients. The lower the score the higher the perceived importance.

s in	Canada	Urologists in lower	Urologists in lower GDP countries		Differences in scores		
	Importance score	Side effect	Importance score	Side effect	Difference	Mann-Whitney U	Р
	1.31	Erectile dysfunction	1.61	Osteoporosis	1.50	60.00	<0.0001
	1.34	Hot flashes	1.65	Loss of muscle mass	1.20	168.50	<0.0001
	1.37	Loss of libido	1.71	Weight gain	1.11	191.50	<0.0001
	1.44	Gynecomastia	1.84	Fatigue/Sleep disturb	0.78	279.00	<0.0001
	1.61	CV disease	2.65	Relationship changes	0.75	299.00	<0.0001
S	1.83	Osteoporosis	2.81	Cognitive changes	0.72	322.00	<0.0001
	1.95	Genital shrinkage	2.90	Delayed/absent orgasm	0.68	339.50	0.002
	2	Infertility	2.97	Loss of body hair	0.68	287.00	<0.0001
	2.28	Depression	2.97	Cardiovascular disease	0.65	346.50	0.002
С	2.28	Diabetes	2.97	Anemia	0.65	369.50	0.004
	2.44	Cognitive changes	3.00	Diabetes type 2	0.53	418.50	0.022
	2.46	Loss of muscle mass	3.03	Depression	0.51	368.50	0.003
	2.51	Elevated cholesterol	3.03	Elevated cholesterol	0.49	417.00	0.021
	2.54	Weight gain	3.06	Hot flashes	0.31	464.00	0.025
ısm	2.58	Fatigue/sleep disturb	3.06	Genital shrinkage	0.31	446.00	0.098
	2.59	Anemia	3.16	Loss of libido	0.27	463.00	0.060
s	2.6	Delayed/absent orgasm	n 3.26	Erectile dysfunction	0.24	511.50	0.104
	2.84	Relationship changes	3.35	Gynecomastia	0.23	504.00	0.095
	3.15	Loss of body hair	3.52	Infertility	0.18	571.00	0.535*

is given higher importance in low GDP countries than in Canada.

		Urologists in Canada (%)		Urologists	in low GDP		
Side effect	Management strategy			count	ries (%)	$-\chi^2$	Р
	0 00	Always	Sometimes	Always	Sometimes	,,,	
		or often	or never	or often	or never		
Hot flashes	SSRI	22.0	78.0	10.3	89.7	1.611	0.204
	Transdermal estrogen	2.6	97.4	11.1	88.9	2.047	0.152
	Megestrol	25.0	75.0	14.8	85.2	0.267	0.605
	Diaphragmatic breathing	4.9	95.1	74.2	25.8	37.420	<0.001
	Lifestyle accommodations	57.5	42.5	51.6	48.4	0.244	0.621
Gynecomastia	Radiotherapy	5.0	95.0	10.3	89.7	0.715	0.398
	Binding	7.7	92.3	74.2	25.8	32.716	<0.001
	Estrogen receptor modulators	7.7	92.3	71.0	29.0	30.119	<0.001
	Mastectomy	10.0	89.7	87.1	12.9	41.331	<0.001
	Acceptance	20.5	79.5	22.2	77.8	0.028	0.867
Weight gain	Aerobic exercise	85.4	14.6	51.7	48.3	9.420	0.002
	Dietary change	75.6	24.4	61.3	38.7	1.706	0.192
Loss of muscle mass	Physical activity	90.2	9.8	63.3	36.7	7.529	0.006
Infertility	Sperm banking	0.0	100.0	20.0	80.0	8.128	0.004
Osteoporosis	Avoid alcohol and tobacco	45.0	55.0	57.1	42.9	0.971	0.324
	Calcium	92.7	7.3	70.0	30.0	6.346	0.012
	Vitamin D	95.1	4.9	66.7	33.3	9.987	0.002
	Medication	51.2	48.8	46.7	53.3	0.144	0.705
	Regular exercise	87.5	12.5	40.7	59.3	16.378	<0.001
Cholesterol	Regular exercise	82.5	17.5	46.7	53.3	9.978	0.002
	Statin drugs	33.3	66.7	27.6	72.4	0.257	0.612
	Fish oil	18.9	81.1	21.4	78.6	0.063	0.802

Table 3	Management	strategies	endorsement	comparison
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Chi-Square test (χ^2); df=1; significance at P<0.01.

pharmaceutical options are not strongly recommended in either group. But, in the lower GDP countries, the behavioral intervention, which has no cost associated with it, i.e., diaphragmatic breathing, receives much more promotion than in Canada (74.2% vs. 4.9%). Canadian urologists do appear to endorse pharmaceuticals more than those in lower GDP countries, in the management of hot flashes (25.0% vs. 14.4% for Megestrol; 22.0% vs. 10.3% for selective serotonin reuptake inhibitors). This specific finding may reflect economic disparities. Though recommended strategies differ, recall that there is no difference between the two groups in how important it is to talk to patients about this side effect.

Gynecomastia is the one side effect where urologists in lower GDP countries endorsed more management strategies and offer more advice to patients, than do urologists in Canada. Specifically, binding the chest, prescribing selective estrogen receptor modulators, and mastectomy, are all endorsed as management strategies for gynecomastia by at least 71% of urologists in lower GDP countries and by only 10% or less of urologists in Canada. This suggests that gynecomastia is perceived as a more stigmatizing or burdensome condition for men in those countries than in Canada. However, it is also possible that the greater focus on gynecomastia in the lower GDP countries reflects a racial or regional difference in the prevalence of gynecomastia (and concomitant mastalgia) for men on ADT in those countries. There have been documented racial differences in the prevalence of hot flashes in menopausal women (17,18), though this has not yet been studied in an ADT population.

For side effects such as weight gain, loss of muscle mass, osteoporosis, and elevated cholesterol one management

■ Always or often □ Sometimes or never Solid colours = Canada; stripes = low GDP countries



Figure 2 Comparison of strategies recommended for managing side effects of ADT between Canadian urologists and urologists from lower GDP countries. Only side effects for which there was a significant differences at P<0.01 in recommended management strategies between the two groups of urologists are presented. The strategies are arranged left to right in order from those that Canadian urologists endorse most to least often. Strategies endorsed always or often are above zero on the x-axis and those endorsed sometimes/rarely or never are below zero. The biggest differences between the two populations are in management strategies recommended for gynecomastia, followed by hot flashes and osteoporosis.

strategy—increased physical exercise—is consistently endorsed by Canadian urologists, significantly more so than by urologists in lower GDP countries. Canadian urologists are more likely to endorse vitamin D (95.1%) and exercise (85.4%), for weight gain, for example, than are urologists in the sample of lower GDP countries (66.7%, 51.7%). Also, none of the Canadian urologists endorsed sperm banking as a management strategy for infertility, while 20% of urologists in lower GDP countries did. Gender biases (i.e., male *vs.* female urologists) in the recommendation for sperm banking were not found, possibly due to the small sample of females (n=3). With regards to sarcopenic obesity, Canadian urologists are far more likely to recommend exercise as a management strategy for the side effects of muscle loss and weight gain.

Part 3: do urologists modify their discussion with patients according to patients' characteristics?

The majority of urologists in both groups reported they would not change their responses based on patient's age, relationship status, previous sexual history, and if the patient were prescribed ADT as short term therapy in combination with external beam radiotherapy, or as an intermittent hormonal therapy for systemic disease. Differences were not significant between the two analyzed groups of urologists.

Do urologists routinely provide educational materials to patients on ADT?

In Canada, 73.2% of urologists reported they routinely provide educational material (such as booklets, books,

Table 4	Additional	screenings	and	referrals
		6		

	Urologists in Canada (%)		Urologists in lo			
Question: in the past 6 months have you			(2 ²	Р	
Question. In the past o months have you	Always	Sometimes	Always or	Sometimes or	λ	
	or often	or never	often	never		
screened for signs of grief and loss in patients?	29.3	70.7	40.0	60.0	0.892	0.345
screened for signs of grief and loss in partners?	12.5	87.5	29.6	70.4	3.025	0.082
recommended counseling to patients?	12.2	87.8	31.0	69.0	3.768	0.052
recommended counseling to partners?	7.3	92.7	25.9	74.1	4.494	0.034
recommended parenteral estrogen?	2.6	97.4	21.4	78.6	6.008	0.014
used teach back techniques?	7.7	92.3	17.9	82.1	1.602	0.206
made referral to clinical psychologists?	12.2	87.8	61.3	38.7	10.147	<0.001
made referral to counsellor?	5.0	95.0	3.4	96.6	0.097	0.755
made referral to sex therapist?	9.8	90.2	14.3	85.7	0.333	0.564
made referral to psychosexual counselling?	2.4	97.6	10.3	89.7	1.970	0.160
made referral to sexual medicine specialist?	17.1	82.9	77.4	22.6	26.220	<0.001
made referral to prostate cancer support group?	41.5	58.5	27.6	72.4	1.425	0.233
made referral to other services?	0.0	100.0	23.5	76.5	0.303	0.582

Pearson's Chi-Square test; df=1; significance at P<0.01.

websites, DVDs) to their patients on ADT compared to only 19.4% of urologists in lower GDP countries. Differences between the two groups were highly significant (P<0.001).

What additional screenings and referrals do urologists make?

Most urologists rarely screen their ADT patients or their partners for signs of grief and loss. Canadian urologists reported that they rarely refer their patients to counseling and, if they do, most (41.5%) refer their patients to a prostate cancer support group. Surprisingly, the data indicate that significantly more referrals are made by urologists in lower GDP countries to "clinical psychologists and sexual medicine specialists", than are referrals made by urologists in Canada. An overview of these findings is given in *Table 4*.

Conclusions

Throughout the world countries establish national guidelines for when to prescribe specific medications and there is a global consensus that some form of ADT is appropriate for treating systemic prostate cancer. To the best of our knowledge there are in contrast no "standards of care" concerning patient education about ADT adverse effects or ways to mitigate these adverse effects. The data show profound differences between the side effects that Canadian urologists consider important to discuss with patients compared to urologists in lower GDP countries.

Several factors may account for this overall difference, starting with the agents used to suppress testosterone. Though the most common pharmacological agents used for ADT among international respondents are LHRHa (85%), they are not used exclusively and different ADT agents have different side effect profiles. Across Canada, LHRH agonists are the most common form of ADT, with rising use of LHRH antagonists in recent years. These drugs induce both testosterone and estrogen deprivation and have different side effect profiles than drugs that do not cause estrogen deprivation. LHRH agonists and antagonists are among the most expensive drugs licensed in Canada and are out of economic reach for many patients in lower GDP countries. Cheaper alternative agents include the synthetic steroidal antiandrogen, cyproterone acetate, the synthetic non steroidal estrogen diethylstilbestrol, and even conjugated equine estrogen (commercially sold as Premarin; pers. comm., 2015). These cheaper agents all have estrogenic effects. Where physicians prescribe estrogenic

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agents for androgen suppression, gynecomastia would be expected to be a more common concern and therefore, more emphasized by the urologists. Similarly hot flashes and osteoporosis would be less frequent in their patients and thus less heavily emphasized in their discussions with those patients.

A second possibility is that there may, in fact, be substantial variation in the incidence or severity of specific side effects along both racial and regional (climatic) lines. Our data suggests that this could be relevant for the side effect of gynecomastia. These differences may also be present for bone density loss strategies, given the high incidence of vitamin D deficiency in Canada (associated with its high latitude global position). In comparison with lower GDP countries (which are largely more equatorial) citizens in those countries are more likely to have adequate sunlight exposure for the natural production of endogenous vitamin D. However at this time we are unaware of any studies documenting ADT side effect incidence and burden across racial or geographic lines.

Another variable may be that patients are more likely to present with more advanced disease in lower GDP countries (19). This, in turn, may reflect the health status of patients when they are first offered ADT as a treatment. The patient's life expectancy and morbidity would alter the perceived balancing between the cost and benefit of managing ADT side effects. In Canada, a large number of patients are regularly screened for prostate cancer and as a result are diagnosed at a relatively early stage in the disease trajectory (20). Patients diagnosed with prostate cancer are likely to be followed with repeated PSA tests and are more likely to start on ADT in the context of biochemical failure, before presenting with metastatic signs of systemic disease.

In contrast, in lower GDP countries, where screening is far less common (19,21) patients are more likely to be diagnosed upon metastatic presentation. Mortality rates from prostate cancer in developing countries are twice that of mortality rates in developed countries (21). This difference may account for many of the noted differences in perspectives on management of ADT side effects. For example, osteoporosis is of far more concern to urologists in Canada than to urologists in the lower GDP countries. It is possible that for patients starting ADT in Canada, where the majority have a good life expectancy and minimal evidence of skeletal-related events, managing the risk of osteoporosis is a valid concern. In contrast, in low GDP countries, where patients first present with metastatic bone lesions and reduced life expectancy, the long term management of osteoporosis would appear to be less relevant as life expectancy is shorter.

Several other side effects, which Canadian urologists endorse as essential for discussion with patients, but urologists from lower GDP countries do not, similarly appear to reflect the typical disease status of the patients that they start on ADT. Results indicate that Canadian urologists are far more likely to recommend exercise as a management strategy for muscle loss and weight gain. This difference is statistically significant, but should be interpreted cautiously given the finding that there is less concern in general about these side effects in lower GDP countries. We suggest that the greater concern about loss of muscle mass and weight gain by Canadian urologists reflects the concern in more affluent countries about obesity in general. In lower GDP countries, where obesity is less common [although on the rise; see (22)] managing sarcopenic obesity would also be less common and thus would be seen as comparably less important by urologists prescribing ADT.

Furthermore, for patients with more advanced disease at first presentation, when overall life expectancy may be at best, only a few years, concerns about cardiovascular risk, cholesterol, type 2 diabetes, cognitive changes, depression, anemia, or the impact on relationships, all would seem to be of less relevance. That would appear to explain why management strategies to deal with those side effects are not rated as important in lower GDP countries as they are in Canada.

In contrast, patients showing no overt signs of systemic disease, and with good life expectancy, are more likely to be negatively impacted by the same adverse effects, and for a longer duration. Such patients may be more commonly found in Canada. As such, we would expect that Canadian urologists would rate those side effects as important to discuss with their patients. This is consistent with our findings. The management strategy most recommended by Canadian urologists, is physical exercise, which is in fact a well-documented intervention to collectively reduce the majority of ADT adverse effects (3,15,23,24).

Cultural factors may also play a role in education practices. There is cultural variation in the degree to which the patient versus the physician is responsible for the decision to treat with ADT. In general, Canadian urologists consider it important to discuss with patients far more side effects than do urologists in lower GDP countries (*Table 1*). A focus on shared-decision making and patientempowerment in Western medicine has largely come to replace more traditional or paternalistic model of the

doctor-physician relationship (25). This shift may reflect a fundamental difference between the extent to which the patient is informed about side effects, so that he can be part of the decision-making process.

In Canada, and the affluent world in general, there is a strong emphasis on independence and autonomy, such that it is largely accepted that patients must be well-informed about side effects in order to make informed decisions about their treatment. In westernized, English speaking countries, patients who are younger and have higher education, tend to prefer a more active role in treatment decision-making (26). Among other types of cancer patients (e.g., gynecological, lung and colorectal), American breast and prostate cancer patients tend to report the highest percentage of shared and active role preferences (27). Furthermore, consistent with this notion is the increased emphasis placed on individuals to take responsibility for their health; therefore, selfmanagement strategies that focus on lifestyle (i.e., diet and exercise) are more likely to be promoted.

In non-western cultures, there is an understanding that the responsibility for treatment decisions rests to a higher degree with the physician than with the patient (27-31). This may be even more so when the patient has advanced disease. As such, a need to discuss side effects at length with patients may be seen as less essential in these countries. In fact extensive discussion of ADT side effects may even be perceived of as unnecessarily distressing to patients. In this context, shared decision-making may be less commonly expected by both physician and patient, and therefore less emphasis may be placed on educating patients about ADT side effects. Trill and Holland (32) contrast the assumption in North American culture, that individuals are expected to gain mastery over their environment, whereas in Eastern cultures the value is for individuals to strive to live in harmony with their environment. They further argue that individuals in Eastern cultures have increased acceptance of illness. By extension, patients in lower GDP countries may be more accepting of adverse treatment effects, whereas Canadian patients may feel a greater need for managerial control over those same side effects.

In non-western countries, where the average patient starting on ADT may be more likely to have advanced disease, and physicians hold more power to make treatment decisions on behalf of their patients, information disclosure may be even more restricted. When patients have a terminal diagnosis, there is large cultural variability in the degree to which such information is shared with the patient, such that in many countries (e.g., Saudi Arabia, Egypt, Singapore, Japan, and China) there is a high degree of concealment of information from the patient [reviewed in (30-33)] and varied disclosure to their family. Even in some European countries (e.g., Italy, Spain, and Greece) a cancer diagnosis may not be disclosed directly to the patient [reviewed in (33)]. This is in stark contrast to Anglo-Saxon and Northern European countries where a more forthcoming communication style is preferred [reviewed in (34)].

Another influencing variable is likely to be divergent cultural, social, and religious beliefs around perceived masculinity. Such differences appear to be most relevant to a cluster of side effects that are considered more important for physicians within lower GDP countries to discuss with patients. These side effects include loss of libido, gynecomastia, genital shrinkage, and infertility. What is intriguing about this group of side effects is that they all relate to masculinity, male identity, and sexual performance.

It is possible that these side effects are more stigmatizing in the lower GDP countries than they are in Canada. We speculate that gender role distinction, and in particular markers of masculinity may be more important for males in lower GDP countries, than for males in Canada. The only side effect that was ranked more often by lower GDP country respondents, than Canadian respondents as important, was infertility (see Table 2). With the mean age of prostate cancer diagnosis in the Canadian population now in the mid-60s, it makes intuitive sense that the effect of infertility may be seen as less important. This does not appear to hold though for lower GDP countries. It is possible that masculinity, fertility, genital size, and libido, may collectively be seen as more important for male selfesteem and well-being in lower GDP counties than in Canada, though this has not been documented in the literature.

Lastly, the finding that respondents from lower GDP countries were more likely than Canadian respondents to refer their patients to clinical psychologists and sex therapists was surprising. We speculate that the definition that is used for clinical psychologists is different in these countries as compared to Canada, as psychosocial oncology in general is a far newer field in less economically advanced countries. We would also assume that availability of these health care professionals would be scarcer. It is possible that the phrasing of the question lead to misleading findings, "In that past 6 months have you made a referral to..." reflects only an occasional referral, rather than a routine practice.

There are several obvious limitations to this study; the most outstanding is the small sample size. Because of that,

it is not possible to correlate in any meaningful way the specific agents recommended by the physicians for androgen deprivation with their particular answers to questions about side effects and their recommended management strategies. Also, generalizations cannot be made about responses from any particular country. Recruitment of international survey respondents was challenging and online invitations were largely unsuccessful. Future efforts in this area are likely to be most successful from face-to-face recruitment at international urology conferences.

All told, there are major differences about what urologists around the world think patients need to know about ADT side effects and how to manage them. Across different regions, variations in cultural ideologies (e.g., value of shared decision-making, patriarchal socialization) and health care systems (e.g., prostate cancer screening, privatized *vs.* universal health care) may strongly influence patient education practices. Recognizing these differences may help physicians treating patients from different cultures and countries attend to side effects of ADT that are likely to be most bothersome to their individual patients.

Recently the American Cancer Society published Prostate Cancer Survivorship Care Guidelines (35), which have now been formally endorsed by the American Society of Clinical Oncology (36). These guidelines include recommendations for managing many ADT side effects. Notably the guidelines focus on the physiological side effects of osteoporosis, cardiovascular risk, and sarcopenic obesity. Conversely they provide little attention to ADT side effects related to sexual performance or masculine identity. Although neither the ACS nor ASCO qualify their recommendations with a statement that they are specific to the USA or other high GDP countries, our data suggest that such a caveat is appropriate. Urologists from lower GDP countries are likely to find that the ACS guidelines do not reflect what they perceive of as the particular needs and concerns of their patients starting on ADT.

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Footnote

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Online supplement: ADT educational practices survey

Please read these instructions carefully:

The following is a list of potential side effects of androgen deprivation therapy (ADT) (left half) and potential management strategies for each side effect (right half). Please read the clinical scenario, and answer the following questions based on the prostate cancer patient presented in the scenario at the bottom of this page. Please fill out the survey in a **left-to-right fashion**, beginning with the side effect, and then the corresponding management strategies.

For the **side effects**, rate how important it is to inform patients of each of these potential side effects by checking it off as either "essential", "important", "not important/no opinion", or "avoid".

For the **management strategies**, rate the degree to which you would endorse each strategy by checking it off as either "mostly or always", "often", "sometimes", "rarely or never".

*Note:

- "essential" = it is absolutely necessary to inform patients of this side effect in almost all circumstances
- "important" = it is desirable, but if, for example, time is limited, informing patients of this side effect could be dropped
- "not important/no opinion" = it is not necessary to inform patients of this side effect, or either you don't have a strong opinion or you don't have any opinion at all about this

- "**avoid**" = it should definitely be avoided informing patients of this side effect in almost all circumstances (Adapted from Feldman-Stewart *et al.*, 1997)

Clinical scenario: A 65-year-old married man who has failed primary treatment for prostate cancer now has a rising prostate-specific antigen (PSA). He is previously sexually active using oral medications (PDE5i). You, the man, and his wife agree that commencing androgen deprivation therapy is the best course of action.

		"Informi	ing patients is"				"I endo	rse this"	D 1
Side Effect	Essential	I Important	Not Important/No Opinion	Avoid	Management Strategies	Mostly or Always	Often	Sometimes	Rarely or Never
Hot flashes					SSRIs (e.g. venlafaxine)				
					Transdermal estradiol				
					Megestrol (Megace)				
					Diaphragmatic breathing/paced respiration				
					Lifestyle accommodations (e.g. use a cold compress, fan				
					yourself, drink cold water, etc.)				
					Other?				
growth) and mastodynia					Radiotherapy to prevent breast growth				
(breast pain)					Binding/camouflage				
					Selective estrogen receptor modulators (e.g. tamoxifen)				
					Mastectomy/liposuction				
					Acceptance and/or sexualization or autoeroticization of breasts				
					Other?				
Weight gain					Aerobic and resistance exercise				
					Dietary changes				
					Other?				
Loss of muscle mass					Increased physical activity/exercise				
					Other?				
Erectile dysfunction					Intracavernosal injections				
					Vacuum erection device				
					Penile implants				
					PDE5i				
					Masturbation				
					Redefinition or reframing of sexual activities (e.g.				
					nonpenetrative sexual activity such as oral sex, mutual masturbation, use of sex toys, etc.)				
					Other?				
Loss of sexual desire/libido					Bupropion				
					Special effort to enhance displays of physical affection				
					Counselling to recruit past sexual fantasies and explore				
					expanding erogenous zones (e.g. new breast sensitivity)				
Delayed or absent orgasm					The use of lubricants to permit increased penile				
					stimulation without skin irritation				
					The use of a vibrator or sex toys				
					Other?				
Genital shrinkage					Penile rehabilitation strategies to maintain blood flow to penile tissue (e.g. PDE5i, vacuum erection devices, etc.)				
					Other?				
Loss of body hair					Reassuring the patient that this is of no medical				
					Consequence Other?				
Infertility					Sperm banking				
·					Other?				
Relationship changes					Refer for counselling to aid couple's adjustment				
					Suggest patients increased effort toward displaying				
					emotional and physical connectedness				
					(e.g. potential to withdraw, moodiness, female partner				
					feeling less attractive, feelings of insecurity, feelings of doubt, etc.)				
					Other?				
Potential for cognitive					Management strategies for cognitive changes in the				
changes					elderly (e.g. computer games, etc.)				
Fatigue and sleep					Standard treatment for sleep disturbance in				
disturbances					oncology(including medication)				
					Psychotherapy				
					Aerobic and resistance exercise				
Dotardi 1: 1 1 1					Other?				
developing depression					Antidepressant medication				
					depression				
					Psychotherapy				
					Other?				
Increased risk of developing					Avoid alcohol and tobacco				
					Calcium supplements				
					Vitamin D				
					Medication (e.g. bisphosphonates, calcitonin,				
					Aerobic and resistance exercise				
					Other?				
Potential increased risk of					Fish oil				
developing cardiovascular disease					Avoid tobacco				
					Aerobic and resistance exercise				
					Other?				
Potential increased risk of					Aerobic and resistance exercise				
developing anemia					Other?				
Potential increased risk of					Regular exercise				
developing diabetes type II					Dietary changes				
					Other?				
Potential increased risk					Regular exercise				
or developing elevated cholesterol					Statin				
					Fish oil				
					Other?				

Would you change any of your replies above if the patient was...

- 55-years-old (rather than 65-years-old)?
 Yes I No
 If yes, please explain how:
- 75-years-old (rather than 65-years-old)?
 Yes I No
 If yes, please explain how:
- Single (rather than partnered)?
 Yes No
 If yes, please explain how:
- Previously not sexually active (rather than previously sexually active)?
 Yes I No
 If yes, please explain how:
- Prescribed Androgen deprivation therapy (ADT) for 3 years in combination with external beam radiotherapy (rather than prescribed ADT, alone, indefinitely)?
 Yes
 No
 If yes, please explain how:

For each question, please rate the degree to which each applies to you in the past 6 months, by checking off one of the boxes

In the past 6 months with regards to my Androgen deprivation therapy (ADT) patients, I have	Mostly or Always	Often	Sometimes	Rarely or Never
Screened for signs of grief and loss in patients				
Screened for signs of grief and loss in partners				
Recommended counseling resources to patients				
Recommended counseling resources to partners				
Recommended parenteral estrogen therapy (provided by transdermal estradiol patches or gel) as an alternative (or in addition to) LH-RH agonists				
Used teach-back techniques with my patients (the patient explains back to you the information you have just given)				
Made referrals to a:				
Clinical psychologist				
Counselor				
Sex therapist				
Psychosexual counseling				
Sexual medicine specialist				
Prostate cancer support group				
Other?				
Other?				

on the scale.

For each question in this last section, please rate the importance of each **to you** by checking **one** of the boxes on the scale.

How important is it for you to	Essential	Important	Not Important/ No opinion	Avoid
Attend a CME course on the management of ADT patients				
Read journal articles on ADT and its impact on patients and their partners?				
Attend conferences on the management of ADT patients?				
Have a set of clinical practice guidelines on the management of ADT patients?				
To have the partners present along when you discuss the side effects of LH-RH agonists?				
Other?				
Other?				

Do you routinely provide educational material(s) on androgen deprivation therapy to your patients?

☐ Yes ☐ No If yes, please list:

- o Booklets:
- o Books:
- o Websites:
- o DVDs:
- o Referral to educational classes on Androgen deprivation therapy (ADT) side effects and their management strategies:
- o Other:

Demographic Data

- What is your age?
- What is your sex? Please check one:
- Male Female Rather not say
- What is your professional discipline? Please check one:
 Urologist
 Medical Oncologist
 Radiation Oncologist
 Nurse
 Pharmacist
 Other:
- How many years have you been practicing in this profession?
- In what country are you currently practicing?
- How many prostate cancer patients do you start on androgen deprivation therapy in an average month?
- Which Androgen deprivation therapy (ADT) treatment do you recommend most often?
 - □ LH-RH agonists
 - □ Oral estrogens
 - □ Non-oral estrogens
 - □ Surgical castration
 - □ Anti-androgen monotherapy
 - GnRH (gonadotropin-releasing hormone) antagonists
 - \Box Other
- Which Androgen deprivation therapy (ADT) treatment do you recommend least often?
 - LH-RH agonists
 - □ Oral estrogens
 - □ Non-oral estrogens
 - \Box Surgical castration
 - □ Anti-androgen monotherapy
 - GnRH (gonadotropin-releasing hormone) antagonists
 - \Box Other
- What determines which treatment you recommend to a patient?
 - \Box Patient's disease status
 - □ Patient's financial resources
 - □ Patient's life expectancy
 - □ Patient's marital status
 - □ Institutional policy/guidelines
 - □ Other (please specify) ____
- Approximately, what proportion of your patients lives in a rural area? Please check one:
 □ < 25%

□ Between 25% and 50%

 \Box About 50%

□ Between 50% and 75%

□ > 75%