Article details: 2013-0037	
Title	**Active surveillance for low-risk prostate cancer compared with immediate treatment: a Canadian cost comparison**
Authors	Alice Dragomir, Fabio Cury, Armen Aprikian
Reviewer 1	**Laurence Klotz**
Institution	Sunnybrook and Women's College Health Sciences Centre
General comments	This is an important and well done paper which confirms what many believe and some have reported in the US, namely that surveillance has economic benefits compared definitive intervention. Active surveillance has been widely adopted in Canada, and this paper reinforces the benefits of that approach. I don't see any significant defects in the manuscript. Suggest it be published.
Reviewer 2	**Kirk A Keegan**
Institution	Brooke Army Medical Center, Department of Urologic Surgery
General comments	The authors have presented a well-written, thoughtful analysis regarding the costs of Active Surveillance within the Canadian province of Quebec. As have several previous studies, they note an impressive cost savings to the system, even with the incorporation of the added costs of delayed active treatment after a period of active surveillance. The modeling assumptions are generally sound, but may require further elaboration in the final manuscript. The current analysis expands on previous models via the incorporation of death data in their Markov analyses and apparent information regarding recurrence. The analysis reports the theoretical cost of initial prostate cancer treatments and anticipated expenditures over 5 years of follow-up for the most common treatment modalities. Costs associated with delayed treatment for those initially treated with Active Surveillance are also noted. The introduction is well-written and provides good background. Given manuscript word count limitations, it may benefit from editing in order to elaborate more fully on the methods section. It is important to note the appropriateness of any model is largely based upon its assumptions. Additionally, the quality as well as the accuracy of those assumptions may yield radically different calculations. The suppositions within this manuscript are further confounded by the thorny issue of how to truly define healthcare costs, particularly in comparison to widely disparate healthcare systems. Nonetheless, the authors have done a respectable job. Upon review of the methods section, several points merit clarification. For those not familiar, the manuscript would benefit from a brief description of the protocol described by Klotz. It appears that the calculated costs would include a confirmatory biopsy. However, because the costs of Active Surveillance are largely driven by the costs and frequency of biopsy, a clearer description of this regime would be beneficial for the reader. The introduction of death data provides novel information compared to prior models, however, it introduces several concerning assumptions. Why was the patient age of 65 and older chosen? This has considerable influence on the total number of individuals in the cohort and therefore underestimates the true costs and benefits of an Active Surveillance paradigm. Additionally, it significantly influences the assumptions regarding patient death. In this reviewer's opinion, a more appropriate theoretical cohort would be the total number of incident very-low and low-risk cases diagnosed in Canada, rather than solely 12,750 patients used in the authors' analysis. This may provide a more informed estimate of true Active Surveillance costs and benefits to the Canadian health system as a whole. While the authors have decided to include death data in their Markov analysis, the 5-year cancer specific survival for men diagnosed with very-low and low-risk prostate cancer is greater than 99% and remain so even at 15 years. If the author's intent is to describe total healthcare costs of prostate cancer treatment in Canada, then the use of overall survival and death data provide an important addition to the model. However, given the high rates of both cancer-specific and overall-survival, as well as equivalent rates of death between treatment arms, it could safely be assumed that the effect of death within the model would be realized equally across treatment arms. If parsimony is the goal of any model, it is unclear if death calculations have significant effect or provide much information on cost comparisons between treatments. If the authors continue to use death data in their model, the median age of those with an incident diagnosis of low and very-low risk prostate cancer cases, rather than those 65 and older, may provide a more accurate assumption or at least form the basis of a sensitivity analysis.

	More specifically within the manuscript, it is not clear if the billing costs of the 3 CPT codes associated with the transrectal ultrasound and biopsy were included in the analysis, nor if TRUS and fiducial placement were included in IMRT cost calculations. Moreover, are the costs of initial diagnosis, initial urology consultation, TRUS, and pathology included in all treatment modalities? The authors note their series differs in the calculation of recurrence information, however, the assumptions, calculations, and costs associated with recurrence are not presented within the methods and are solely noted within Table 3. The manuscript would benefit from elaboration on these data or omission altogether. The allocation of delayed treatments is presented within the Interpretation, but may be more appropriately noted within the Methods. Regarding Figure A1, it is unclear to the reviewer why the initial costs of ADT are so high and decrease over time. The Interpretation provides a thoughtful summary. Given the apparent lower costs associated with Active Surveillance in the Canadian model, the costs of delayed active treatment are also reduced, as the marginal costs of deferred treatment are predicated on the costs and time spent on Active Surveillance. However, it is important to note, regardless of which healthcare system is being described, that the costs of treatment, with the exception of ADT, are largely initial costs. Therefore, any paradigm that includes two initial treatment modalities, such as delayed active treatment (or multimodal treatment…), will accrue significantly increased management costs due to both the initial costs associated with Active Surveillance as well as the expenditures associated with their delayed treatment. In this era of comparative effectiveness, where treatment choices should be allocated to the most effective, least costly management strategy, it is incumbent on providers to rapidly identify those patients within an Active Surveillance paradigm who are destined to progress to more advanced disease and therefore require additional treatment.
Reviewer 3	**Anthony Venyo**
Institution	North Manchester General Hospital, Department of Urology
General comments	This is a well written manuscript which can be published as it stands. However, in my opinion one important clarification is necessary to avoid doubt in the minds of readers as follows: Page Total cost estimation This value is explained by a total of $104.4 million savings obtained by avoiding the treatment in 17.3% of cases who died before requiring treatment [THIS STATEMENT SHOULD ME MADE IN SUCH A WAY AS TO CLARIFY WHETHER OR NOT THE 17.3% of the cases died of other unrelated causes or some died as a result of their prostate cancer. I would assume they died of other causes rather than prostate cancer.] If there were any prostate cancer deaths in this group that would raise a question regarding the ability of active surveillance picking up progress of some cases of localized prostate cancer in some cases and then leading to death.
Author response	We appreciate the careful review of our manuscript ''Active Surveillance for low-risk Prostate Cancer Compared with Immediate Treatment: A Canadian cost comparison''. We hope that we have adequately addressed the comments and revisions recommend by the editor and the reviewers, and we feel these changes have improved the quality of our manuscript. We look forward to seeing our work published in CMAJ Open. Below we outline the reviewers' suggestions and our revisions and response. Revisions are highlighted in text by track changes function. We would be pleased to provide any further clarifications. Introduction 1. Please provide your rationale for conducting a cost analysis, as opposed to a cost-effectiveness analysis. Authors' Response: In page 3, 2nd para of the manuscript it was cited Hayes et al. study (1), which evaluated quality-adjusted life expectancy (QALE) of patients on active surveillance versus patients receiving treatment. Their results showed that QALE associated with active surveillance is essentially equivalent with QALE associated with treatment (AS: 11.07 QALE, brachytherapy: 10.57 QALE, IMRT: 10.51 QALE, and RP: 10.23 QALE). In addition, a second study (2) (cited in page 3, para 2) has shown that the initial treatment with radiation therapy has an slight advantage of approximately 0.4 QALE over watchful waiting, but no benefit in the case of radical prostatectomy (9.4 QALE for both radical prostatectomy and watchful waiting). As per Drummond et al. (3), a cost

	analysis ''represents a partial form of economic appraisal, unless it can be independently shown that the consequences of the programmes or treatments being considered are broadly equivalent''. Finally, our study was designed to understand the magnitude of the cost savings potentially achievable with an active surveillance strategy rather than estimating cost-effectiveness ratio of these management strategies. 2. The second paragraph is quite detailed. This could be streamlined a bit. Authors' Response: The second paragraph has been streamlined as per your suggestion. 3. In the third paragraph, you state that about 75% of patients with prostate cancer received active treatment from 1995 to 2002. You add that "... most of these patients did not require active treatment..." Is it possible to quantify "most"? Authors' Response: As reveled by several studies, more than 50% of incident cases of prostate cancer are low and very-low risk ((4)). In addition, in Canada in 2012 more than 41% of patients newly diagnosed patients were 70 years and older (5). The mean age of patients included in the Canadian study between 1995 to 2002 was 69 years old (6). Based on these data we expect that more than 60% of patients be eligible for active surveillance. Finally, we estimated that more than half of patients having received treatment had not required this treatment. The text has been revised to address your comment (page 4, para 1). Methods 4. Please elaborate as to the methods used to estimate costs. Authors' Response: The disease-related method (7) has been used to estimate costs of treatments and active surveillance. The cost components and the quantities of resources used were based on specific protocols used at the McGill University Health Center; however, these protocols are similar to those described in Keegan et al (8). The cost components, the unit costs and data sources are presented in Table 1. Cost of treatments and active surveillance were estimated by summing the quantities of resources use times unit cost of each cost component. The active surveillance protocol was derived from Klotz et al. (9). This consists in: 1) PSA test performed every 3 months for 2 years and then every 6 months in stable patients, and 2) Initial biopsy and confirmatory biopsy performed 6 to 12 months after the initial biopsy, and then every 3 to 4 years. To reflect the time value of money, a standard discount rate of 5% was used (10). The text has been revised to address your comment (page 5 para 1). 5. As mentioned by Reviewer 2, please provide a clearer description on the active surveillance regime evaluated in your analysis. Authors' Response: Please see the response provided above. 6. Please use the subheading "Statistical analysis" and include under it the text currently appearing under "Cost analysis" and "Sensitivity analysis." Authors' Response: The text has been revised to address your comment. Results 7. Please provide a brief description of the results of your sensitivity analysis in the text (Table 5). Authors' Response: A brief description of the sensitivity analysis results has been added in the text to address your comment (page 7, para 5 and page 8, para 1). 8. Please use the past tense when describing results pertaining to your study (in the main text and in the abstract). Authors' Response: The text has been revised to address your comment. 9. In the third paragraph, please confirm the value $13,066. It is $13,166 in Table 3. Authors' Response: We confirm the correct value is $13,166. The text was revised accordingly (page 6, para 4). Interpretation

	10. Please structure the Interpretation section (discussion) into the following 4 main headings (i.e. insert the headings themselves): "Main findings" (this should begin with a brief summary of the key finding of your study, discussing implications, not a repetition of results),"Comparison with other studies", "Limitations", and "Conclusions" (including implications for practice and future research). Authors' Response: The Interpretation section has been structured as suggested. 11. As mentioned by Reviewer 2, the use of a cohort of patients over the age of 65 is a limitation that should be discussed in the Interpretation section. Authors' Response: Please see the authors' response to the 3rd question of Reviewer 2. 12. Please avoid reporting detailed results in this section. The first two paragraphs, and the paragraph on limitations, contain findings not mentioned elsewhere in the Results section. Authors' Response: The results mentioned in Interpretation section are now presented in the Results section. The text has been revised to address your comment (page 7 para 2 and 4, page 8 para 2, and page 10 para 1). Figures and Tables: 13. In the legend of Figure A1, you state "** in Canadian dollars". The ** symbol does not appear in either figure. Please clarify. Authors' Response: The ** symbol has been added to figure A1, in title ''Canadian cost estimates by treatment type and time to treatment initiation**'' 14. Figure 1 is not editable electronically. Please provide the original figure (not an embedded image). Authors' Response: The Figure 1 was provided in PowerPoint format. Abstract: 15. Please include the structured abstract in the Word file of your manuscript. Authors' Response: The structured Abstract has been included in the Word file of the manuscript. 16. The Background section should comprise two sentences: Explain the problem or issue (the reason you decided to conduct your study) in the first sentence. State the objective of your study (the question you set out to answer) in the second sentence. Authors' Response: The text has been revised to address your comment. 17. The Interpretation section of the abstract also should comprise two sentences: The first needs to answer your research question (What did the study show?). The second sentence should be a brief statement about implications for practice or research (What do the findings mean?). Avoid speculation and generalization. Authors' Response: The text has been revised to address your comment. References 18. Please number the references in the order in which they are cited, including references cited in tables and figures. For example, references 28–32 are cited in Table 1, but the table is first mentioned in the text after reference 22. Authors' Response: The text has been revised to address your comment. 19. For references 1 and 6, are there URLs or catalogue numbers for these documents? Authors' Response: The following URLs addresses have been added to these references: http://www.cancer-asian.com/images/news/Canadian_Cancer%20Statistics_2011_English.pdf

	http://publications.gc.ca/collections/Collection/H21-136-1998E.pdf 20. Please verify the document cited in reference 30. Is it a single document? Is there a URL and access date? Please give more details. Authors' Response: The text has been revised to address your comment (page 12): †unpublished data. Details on collected variables can be found at: http://www.informa.msss.gouv.qc.ca/Details.aspx?Id=OLgRnU5HvPw= Other points: 21. Please avoid using abbreviations and acronyms and instead spell them out in full at each occurrence in the main text and the abstract. CMAJ Open makes exceptions for only the most familiar and broadly recognized abbreviations (e.g., 95% CI, SD, OR, RR, HR), and even for these, please spell them out at first mention and include the abbreviation in parentheses. Authors' Response: The text has been revised to address your comment. 22. Please avoid claims of precedence. One such claim is made in the conclusion ("To the best of our knowledge, this is the first economic evaluation..."). Authors' Response: The text has been revised to address your comment (page 10, para 2). Reviewers' Comments to Author: Reviewer 1: Laurence Klotz Comments to the Author This paper confirms what many believe and some have reported in the US, namely that surveillance has economic benefits compared definitive intervention. Active surveillance has been widely adopted in Canada, and this paper reinforces the benefits of that approach. Authors' Response: Thank you for your comment. Reviewer 2: Kirk A. Keegan Comments to the Author The authors have presented a thoughtful analysis regarding the costs of Active Surveillance within the Canadian province of Quebec. As have several previous studies, they note an impressive cost savings to the system, even with the incorporation of the added costs of delayed active treatment after a period of active surveillance. The modeling assumptions are generally sound, but may require further elaboration in the final manuscript. The current analysis expands on previous models via the incorporation of death data in their Markov analyses and apparent information regarding recurrence. The analysis reports the theoretical cost of initial prostate cancer treatments and anticipated expenditures over 5 years of follow-up for the most common treatment modalities. Costs associated with delayed treatment for those initially treated with Active Surveillance are also noted. The introduction is well-written and provides good background. Given manuscript word count limitations, it may benefit from editing in order to elaborate more fully on the methods section. Authors' Response: Thank you for your comment. Please see the authors' response provided above at the point 4). It is important to note the appropriateness of any model is largely based upon its assumptions. Additionally, the quality as well as the accuracy of those assumptions may yield radically different calculations. The suppositions within this manuscript are further confounded by the thorny issue of how to truly define healthcare costs, particularly in comparison to widely disparate healthcare systems. Nonetheless, the authors have done a respectable job. Authors' Response: Thank you for your comment. Upon review of the methods section, several points merit clarification.

	1. For those not familiar, the manuscript would benefit from a brief description of the protocol described by Klotz. Authors' Response: Please see the authors' response provided at the point 4) above. 2. It appears that the calculated costs would include a confirmatory biopsy. However, because the costs of Active Surveillance are largely driven by the costs and frequency of biopsy, a clearer description of this regime would be beneficial for the reader. Authors' Response: Please see the authors' response provided at the point 4) above. 3. The introduction of death data provides novel information compared to prior models, however, it introduces several concerning assumptions. Why was the patient age of 65 and older chosen? This has considerable influence on the total number of individuals in the cohort and therefore underestimates the true costs and benefits of an Active Surveillance paradigm. Additionally, it significantly influences the assumptions regarding patient death. In this reviewer's opinion, a more appropriate theoretical cohort would be the total number of incident very-low and low-risk cases diagnosed in Canada, rather than solely 12,750 patients used in the authors' analysis. This may provide a more informed estimate of true Active Surveillance costs and benefits to the Canadian health system as a whole. Authors' Response: In response to the reviewer's 1st concern, the number of individuals simulated through the model do not influence the mean cost of active surveillance and IT. Consequently, these estimates are valid. In contrast, the total number of individuals influences the total cost of patients under active surveillance and immediate treatment strategies and cost savings that can potentially be obtained with active surveillance at the Canadian level (Table 4). In addition, the patient age of 65 and older has no influence on the cost estimates of active surveillance and immediate treatment (average cost and total cost), as the number of 12,750 patients candidates to active surveillance was estimated based on the fact that 50% of newly diagnosed prostate cancer cases are low-risk patients and that 25,500 Canadian men are annually diagnosed with prostate cancer (page 5, para 2). The information about patients' age was removed from the text (page 5, para 2). Furthermore, two additional sensitivity analyses have been performed to test the impact of rate of low-risk prostate cancer among newly diagnosed men. The text in page 6 para 1 has been completed with: ''Finally, we assumed that 40% and 60% of yearly incident cases are eligible to active surveillance, which yield a number of 10,200 and 15,300 patients, respectively.'' In addition, the results were presented in page 7, para 4: ''When the rate of patients eligible to active surveillance was set to 40% and 60%, the total cost estimates were $76.9 million, and $115.3 million, respectively (data not shown).'' While the authors have decided to include death data in their Markov analysis, the 5-year cancer specific survival for men diagnosed with very-low and low-risk prostate cancer is greater than 99% and remains so even at 15 years. If the author's intent is to describe total healthcare costs of prostate cancer treatment in Canada, then the use of overall survival and death data provide an important addition to the model. However, given the high rates of both cancer-specific and overall-survival, as well as equivalent rates of death between treatment arms, it could safely be assumed that the effect of death within the model would be realized equally across treatment arms. If parsimony is the goal of any model, it is unclear if death calculations have significant effect or provide much information on cost comparisons between treatments. If the authors continue to use death data in their model, the median age of those with an incident diagnosis of low and very-low risk prostate cancer cases, rather than those 65 and older, may provide a more accurate assumption or at least form the basis of a sensitivity analysis. Authors' Response: The one-year death probability of 3.8% was derived from the Canadian study on active surveillance by Klotz et al. (9). The information was mentioned in manuscript at page 4, para 4 and footnote in Figure 1. This study reported a 10-year overall survival of 68% for a cohort with a median age of 70.3 years. Furthermore, the annual probability of death in general population reported by Statistics Canada is quite similar: 3.9% for a population of 65 years and older. As described in the footnote of Figure 1, the rate of death is the same in both active surveillance and immediate treatment groups. Finally, there are two main reasons of including the rate of death into the Markov model: 1) we wanted to design a model that follows the course of low-risk prostate cancer patients treated with active surveillance as observed in Klotz et al. (9) (which reflect real-life data); and 2) to demonstrate that the economic benefits of

	active surveillance can be maintained over a long period of time. As mentioned in page 8, 2nd para, over a 15 years of follow-up there were 41.2% of patients who died under AS. This helps to understand that finally, at the end of 15-year period there will be only 24% of patients still on active surveillance and potentially candidate to treatment, and not 65.5%, simulated by a model which not accounted for the mortality. 4. More specifically within the manuscript, it is not clear if the billing costs of the 3 CPT codes associated with the transrectal ultrasound and biopsy were included in the analysis, nor if TRUS and fiducial placement were included in IMRT cost calculations. Moreover, are the costs of initial diagnosis, initial urology consultation, TRUS, and pathology included in all treatment modalities? Authors' Response: The medical costs associated with initial diagnosis, initial urology consultation, transrectal ultrasound, and biopsy (including pathology), were counted in all treatment modalities. In addition, in the footnote of Table 1it is specified that the IMRT procedure includes cost of dosimetry (radiation therapist, planning system, information system), physics quality assurance (physicist, physics associates, specialised quality assurance equipment, planning system, information system) and treatment preparation & delivery (radiation therapy, linear accelerator, nurse, information system) equivalent of 38 fractions. This value does not includes overheads. 5. The authors note their series differs in the calculation of recurrence information, however, the assumptions, calculations, and costs associated with recurrence are not presented within the methods and are solely noted within Table 3. The manuscript would benefit from elaboration on these data or omission altogether. Authors' Response: We agree with the reviewer's comment. However, due to the words limit we had to move some parts of the methods in tables or figures. The information concerning the recurrence can also be found in Figure 1 (blue lines). The blue lines show the possible transitions based on treatment initially received. So, all the patients will receive ADT in case of recurrence, except for surgery, where the patients can receive ADT or IMRT. Despite this limited information, we kept the model including the recurrence for several raisons. First, we wanted to design a model consistent with the results reported by Klotz et al. (9). Their study reported that 13% of the overall cohort has recurred and has received additional treatment. Second, we felt that the cost associated with the recurrence could be significant, and we considered appropriate to include them in the calculation. Indeed, the mean cost in active surveillance and immediate treatment groups were approximately $1,600 lower when we did not accounted for the recurrence requiring additional treatment, with values of $4,611 for AS, and $12,177 for IT, respectively. Finally, we expected that the cost associated with recurrence be different depending on the treatment initially received, and so, we considered that ignoring this cost, may affect the accuracy of our cost estimates based on the treatment initially received. Effectively, the cost associated with recurrence accounted for 27.8%, 25% and 19% of the 5-year cost of treatment in patients receiving delayed treatment of brachytherapy, surgery, and IMRT plus ADT, respectively. The text has been revised to address your comment on elaboration on these data: page 6 para 4 and page 7 para 2. 6. The allocation of delayed treatments is presented within the Interpretation, but may be more appropriately noted within the Methods. Regarding Figure A1, it is unclear to the reviewer why the initial costs of ADT are so high and decrease over time. Authors' Response: We agree with the reviewer's comment. However, the allocation of delayed treatments was mainly performed to compare our results with those obtained in other studies, particularly Keegan's et al. study (8). For this reason and because of the limited space, this analysis was integrated in Interpretation section. Furthermore, the values represented at the time 0 represent the cost cumulated over the initial and 5-year follow-up period. For ADT this represent $28,338 ($5,136+$23,202) which is far higher than the cost of the other treatments over the same period (as presented in Table 2). The decrease in time is explained by the fact that the cost of ADT over the 5-year period of follow-up is high and each 1-year delay will decrease by $4,640 ($23,202 divided by 5 years) the cost over the 6-year period. In contrast, the initial cost of all the other treatments is much higher than the cost associated with the 5-year period of follow-up (Table 2). Table 2: Initial and 5-year cost of treatments and active surveillance (2012 Canadian $) Treatment type Initial 5-year period of follow-up

Active surveillance $1,224 $1,767
Radical prostatectomy $7,428 $929
IMRT $12,261 $618
IMRT + ADT* $14,444 $618
Brachytherapy $8,455 $618
Primary ADT $5,136 $23,202

The Interpretation provides a thoughtful summary.

Authors' Response: Thank you for your comment.

1. Given the apparent lower costs associated with Active Surveillance in the Canadian model, the costs of delayed active treatment are also reduced, as the marginal costs of deferred treatment are predicated on the costs and time spent on Active Surveillance. However, it is important to note, regardless of which healthcare system is being described, that the costs of treatment, with the exception of ADT, are largely initial costs. Therefore, any paradigm that includes two initial treatment modalities, such as delayed active treatment (or multimodal treatment…), will accrue significantly increased management costs due to both the initial costs associated with Active Surveillance as well as the expenditures associated with their delayed treatment. In this era of comparative effectiveness, where treatment choices should be allocated to the most effective, least costly management strategy, it is incumbent on providers to rapidly identify those patients within an Active Surveillance paradigm who are destined to progress to more advanced disease and therefore require additional treatment.

Authors' Response: We totally agree with the reviewer's comment. However, our interpretation of cost associated with delayed treatment was done in the particularity of the Canadian health care system, where the initial as well as follow-up costs, for both active surveillance and treatments are much lower than in the US health care system. For this reason the impact of delaying treatment is not as important as it is in the US study. In addition, we discussed separately the case of ADT initiation.

Reviewer 3: Anthony Venyo
Comments to the Author

1. In my opinion, one important clarification is necessary to avoid doubt in the minds of readers as follows:

This value is explained by a total of $104.4 million savings obtained by avoiding the treatment in 17.3% of cases who died before requiring treatment [this statement should be made in such a way as to clarify whether or not the 17.3% of the cases died of other unrelated causes or some died as a result of their prostate cancer. I would assume they died of other causes rather than prostate cancer.] If there were any prostate cancer deaths in this group that would raise a question regarding the ability of active surveillance picking up progress of some cases of localized prostate cancer in some cases and then leading to death.

Authors' Response: Thank you for your comment. The text has been revised to address your comment (Page 7, para 4).

1. Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Stewart ST, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. JAMA. 2010;304(21):2373-80. Epub 2010/12/02.
2. Sommers BD, Beard CJ, D'Amico AV, Dahl D, Kaplan I, Richie JP, et al. Decision analysis using individual patient preferences to determine optimal treatment for localized prostate cancer. Cancer. 2007;110(10):2210-7. Epub 2007/09/26.
3. Drummond M, Sculpher MJ, Torrace GW, O'Brien BJ, Stoddart GL,. Methods for the Economic Evaluation of Health Care Programmes. Third edition ed: Oxford; 2005.
4. Andriole GL, Crawford ED, Grubb RL, 3rd, Buys SS, Chia D, Church TR, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst. 2012;104(2):125-32. Epub 2012/01/10.
5. Canadian Cancer Society. Canadian Cancer Statistics 2012. Statistics Canada; 2012.
6. Krahn MD, Zagorski B, Laporte A, Alibhai SM, Bremner KE, Tomlinson G, et al. Healthcare costs associated with prostate cancer: estimates from a population-based study. BJU Int. 2010;105(3):338-46. Epub 2009/07/15.

	7. Akobundu E, Ju J, Blatt L, Mullins CD. Cost-of-illness studies : a review of current methods. Pharmacoeconomics. 2006;24(9):869-90. Epub 2006/09/01. 8. Keegan KA, Dall'Era MA, Durbin-Johnson B, Evans CP. Active surveillance for prostate cancer compared with immediate treatment: an economic analysis. Cancer. 2012;118(14):3512-8. Epub 2011/12/20. 9. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol. 2010;28(1):126-31. Epub 2009/11/18. 10. Drummond M. SMJ, Torrance G.W., O'Brien B.J. Stoddart G.L.,. Methods for the Economic Evaluation of Health Care Programmes. third ed. New York: Oxford University Press; 2005.