Lifetime implications and cost-effectiveness of using finasteride to prevent prostate cancer
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined the use of the 5-alpha-reductase inhibitor finasteride (5 mg/day) for the prevention of prostate cancer.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The model analysed data for a hypothetical cohort of men aged 55 years who commenced chemoprophylaxis with finasteride. The data were derived from another study that enrolled 18,882 men aged 55 years of age and older without prostate cancer (Thomson et al. 2003). Inclusion criteria were a normal digital rectal examination, and a prostate-specific antigen (PSA) level of 3.0 ng/mL or lower. The participants agreed to be screened annually and undergo an end-of-study biopsy after 7 years.

Setting
The setting was primary care. The economic study was conducted in the USA.

Dates to which data relate
The input parameters used in the model were gathered from electronic sources and studies published between 1994 and 2003. The cost data were taken from published and electronic sources relating to 1995 to 2003. The costs were adjusted to 2003 prices.

Source of effectiveness data
The estimates for the final outcomes were derived from a synthesis of published studies.

Modelling
A decision analysis model was used to estimate the costs and benefits associated with finasteride and no treatment. The model incorporated a Markov process with a cycle length of 1 year. The drug costs were accrued from 55 to 85 years of age, or the onset of prostate cancer. The cost of care and the benefits were estimated over a lifetime. The five health states used in the model were cancer-free, low-grade prostate cancer, high-grade prostate cancer, death due to prostate cancer and death due to other causes. The model made several assumptions:

finasteride did not effect survival other than through a reduction in prostate cancer incidence;
men who experience side effects from finasteride would discontinue its use soon after noticing symptoms of side
effects;

for the base-case analysis, the proportion of cases with high-grade prostate cancer that would be expected among men
eligible for prevention would be similar to the interim diagnosed cases observed in the placebo group of the PCPT.

**Outcomes assessed in the review**
The authors did not specify whether a systematic or an ad hoc review of the literature was undertaken to identify the
model parameters. The outcomes assessed included:

- the number of true high-grade prostate cancer cases among the finasteride trial arm;
- the proportion of untreated men diagnosed with high-grade prostate cancer disease;
- the increase or decrease in observed Surveillance, Epidemiology and End Results registry (SEER) incidence of prostate
cancer (overall);
- the prevalence of benign prostatic hyperplasia requiring care among those aged younger than 65 years;
- the prevalence of benign prostatic hyperplasia requiring care among those aged 65 years and older;
- the relative effect of finasteride on the prevalence of benign prostatic hyperplasia;
- the mean disutility of prostate cancer (all grades); and
- the proportion of men estimated to be non-compliant with finasteride treatment due to side effects.

**Study designs and other criteria for inclusion in the review**
No specific criteria for inclusion in the review were reported. However, the finasteride effectiveness evidence was
derived from the PCPT (Thomson et al. 2003), a large randomised trial conducted between January 1994 and May
1997. The cancer incidence data were obtained from a national cancer surveillance registry, based on 1998 - 2000 data
(SEER 2003, see 'Other Publications of Related Interest' below for bibliographic details). Prostate cancer-specific
survival was also obtained from SEER statistics.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
No criteria were used to ensure the validity of the primary studies.

**Methods used to judge relevance and validity, and for extracting data**
No methods were used to judge the relevance and the validity of the extracted data.

**Number of primary studies included**
The values for the parameters in the model were obtained from 14 published studies and 2 electronic sources.

**Methods of combining primary studies**
A narrative explanation of how the study results were combined was provided.
Investigation of differences between primary studies
The authors did not investigate possible differences between the primary studies.

Results of the review
The following parameters were used in the model:

- the number of true high-grade prostate cancer cases among the finasteride trial arm was 90 (range: 38, 50, 90);
- the proportion of untreated men diagnosed with high-grade prostate cancer disease was 9% (range: 4.9 - 12);
- the increase or decrease in observed SEER incidence of prostate cancer (overall) was 1.0 (range: 0.75 - 1.25);
- the prevalence of benign prostatic hyperplasia requiring care among those aged younger than 65 years was 0.15% (range: 0.10 - 0.20);
- the prevalence of benign prostatic hyperplasia requiring care among those aged 65 years and older was 0.22% (range: 0.14 - 0.30);
- the relative effect of finasteride on the prevalence of benign prostatic hyperplasia was 0.6 (range: 0.5 - 1.0); and
- the proportion of men estimated to be non-compliant with finasteride treatment due to side effects was 18.3%.

Measure of benefits used in the economic analysis
The summary measures of health benefit used were the life-years gained (LYG) and the quality-adjusted life-years (QALYs) gained. These were obtained from the model. Health state valuations were obtained from the literature. Estimates for the reduction in quality of life associated with benign prostatic hyperplasia symptoms and prostate cancer were taken from prior studies that utilised the Health Utilities Index. These utility values were based on a general community-based sample and a prostate cancer patient sample. An additional reduction in health state utility for prostate cancer represented erectile dysfunction as a consequence of surgery or radiation therapy. An annual discount rate of 3% was applied to the benefits.

Direct costs
The authors did not report whose costs were considered. Only the direct costs of medical care were included in the analysis. These were the cost of finasteride, initial prostate cancer treatment and ongoing annual average care costs, and treatment costs associated with benign prostatic hyperplasia. The drug costs were derived from electronic and published sources. All other costs came from 3 published studies. The cost estimates were reported separately from other model parameters. Discounting was applied at an appropriate annual rate of 3%. The costs were adjusted to 2003 prices, although the method used was not reported. The average total discounted cost per person was reported.

Statistical analysis of costs
No statistical analysis of the costs was conducted.

Indirect Costs
The indirect costs were not included. It was unclear whether this was appropriate as the study perspective was not stated.

Currency
US dollars ($).

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Sensitivity analysis
A sensitivity analysis was conducted to investigate the robustness of the results to the uncertainty surrounding the parameters of the model. One-way sensitivity analyses of all input variables were undertaken using 95% confidence intervals, when available, or triangular distributions across plausible ranges. In alternative scenarios, drug costs were accrued only for 7 or 15 years with the same lifetime treatment effects. The discount rate for the costs and benefits was varied between 1 and 5%. A probabilistic sensitivity analysis was also conducted for each input parameter to explore three potential effects of finasteride. Specifically, excess high-grade disease, no impact on high-grade disease, and the prevention of both high-grade and low-grade disease.

Estimated benefits used in the economic analysis
Chemoprophylaxis with finasteride provided an additional 6 LYG per 1,000 men and 46 QALYs per 1,000 men, compared with no treatment. The benefits were discounted and their duration was calculated over the patient's lifetime. The side effects of treatment (primarily erectile dysfunction) were addressed in the finasteride non-compliance rate and the adjusted disutility values for surgery and radiation therapy.

Cost results
The average total discounted cost per man was $17,700 for those treated with finasteride and $7,300 for those not treated with finasteride.

Synthesis of costs and benefits
The costs and benefits were summarised in the form of an incremental cost-effectiveness ratio (ICER), by dividing the incremental costs by the incremental benefits.

The ICER for finasteride versus no treatment was $1,660,000 for each additional LYG and $200,000 for each QALY gained. The costs and benefits were discounted at a rate of 3%.

The LYG were most sensitive to assumptions about high-grade cancer: as their proportion increased, the survival gains associated with finasteride decreased due to the greater relative risk of high-grade cancer observed in the original trial (Thomson et al. 2003). The QALYs gained were sensitive to the effect of finasteride on benign prostatic hyperplasia, the discount rate and the price of finasteride. The probabilistic sensitivity analysis revealed that cost-effectiveness is improved if finasteride is not associated with excess high-grade disease. Limiting the drug costs to periods of 7 or 15 years decreased the cost per LYG, whereas limiting treatment to men aged from 65 to 85 years greatly increased the cost per LYG.

Authors' conclusions
The benefits associated with finasteride chemoprophylaxis were small and were only realised many years after treatment was initiated. However, the costs of finasteride were high. Assuming a cost-effectiveness threshold of $100,000 per quality-adjusted life-year (QALY) gained, the use of finasteride for chemoprophylaxis of prostate cancer is unlikely to be acceptable. To achieve this cost-effectiveness threshold, the wholesale price of finasteride would need to be reduced by 50%, and the drug's efficacy at preventing high-grade disease would have to be proven.

CRD COMMENTARY - Selection of comparators
The current study extrapolated data from a previous study and used the same comparator. You should decide if the option of no treatment represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The study used a decision analysis model with a Markov process, which was appropriate given the study question. It was unclear whether a systematic review of the literature was undertaken. However, the effectiveness evidence was primarily derived from one large randomised trial. This was supplemented by epidemiological data from a national
cancer surveillance registry and recently published studies. Therefore, it is likely that the effectiveness model input parameters were valid estimates. The estimates of effectiveness were combined in narrative. One-way sensitivity analyses were conducted on all of the model parameters and, in general, a justification was given for the ranges over which the parameters were investigated. In addition, probabilistic sensitivity analyses were employed to examine further the effect of uncertainty in the input parameters.

Validity of estimate of measure of benefit
The summary measures of benefit were survival (LYG) and health utility (QALYs). These were obtained from the model. Non-compliance with finasteride and adjustment to health utilities reflected the effect of adverse effects of treatment. The authors commented that the QALY analysis was limited by the availability in the literature of health state utilities for prostate-related conditions.

Validity of estimate of costs
The study perspective was not stated. Consequently, it was not possible to determine whether all the relevant categories of costs were included in the analysis. The medical costs were reported separately to other model parameters, but were presented in an aggregated manner. This will limit the reproducibility of the study in other settings. The costs were treated deterministically, but the robustness of the estimates used was investigated in a sensitivity analysis and by the use of alternative scenarios. Discounting was applied, which was appropriate given the time horizon of the study. Costs, rather than charges, were reported. The cost data were adjusted to a single price year, although the method used was not described.

Other issues
The authors did not compare their findings with those from other studies, so it is not known to what extent their results agreed with published studies. The issue of the generalisability of the results to other settings was not directly addressed. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.

The authors acknowledged three limitations of their study. First, it is not known whether the 7-year prevalence rates from the PCPT accurately represent lifetime changes in incidence rates. Second, survival for other-cause and prostate-specific by grade were assumed to be the same for treated and untreated men. Finally, cancer survival estimates were based on data prior to PSA testing and may not be valid for men diagnosed with prostate cancer now and in the future.

Implications of the study
The authors stated that, while the adoption of finasteride chemoprophylaxis would have a substantial impact on health care costs, it is likely to have only a limited effect on prostate cancer mortality. Further research is needed to investigate the increased number of high-grade tumours observed with finasteride in the original trial, and to determine whether these tumours are associated with more aggressive disease and shorter survival. Studies of other chemoprevention agents for prostate cancer are currently underway, and it is imperative that the cost-effectiveness of these is assessed prior to the implementation of any intervention.

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Other publications of related interest


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