

Are 5-ARIs suitable for prevention of prostate cancer?

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THE HOLY GRAIL IN MANAGING ANY CANCER IS OF COURSE PREVENTION, AND IF THIS CANNOT be achieved through lifestyle or dietary measures, the possibility of chemoprevention through the use of medication may become of interest. Prostate cancer is highly prevalent and is the most common cancer in men in the UK. In 2010, nearly 41,000 men were diagnosed with prostate cancer in the UK, and there were 10,721 deaths from the disease.¹ For many years it has been hypothesised that the 5-alpha reductase inhibitors (5-ARIs) represent potential chemopreventive agents for this common cancer.

In 2003, the Prostate Cancer Prevention Trial (PCPT) was published in the *New England Journal of Medicine*, looking at the potential of finasteride to reduce the incidence of prostate cancer.²

This seminal study reported that finasteride did indeed prevent prostate cancer, with a reduction in relative risk of almost 25% compared with the control group. However, this decrease was seen in low-grade cancer only, the very cancers that have created so much debate in terms of overdiagnosis and overtreatment.

More worryingly, there was a relative increase of 26.9% in the risk of high-grade cancers in the finasteride arm of PCPT. High-grade cancers were seen in 280 of 4,368 patients taking finasteride compared with 237 of 4,692 patients taking placebo. This finding has been analysed in great detail ever since publication, and although detection bias is thought to account, at least in part, for this increase in high-grade tumours, this has remained a concern.

A recent study, also published in the NEJM,³ is an update to the original PCPT data. It is a post hoc analysis, looking at the long-term outcomes in men who had been diagnosed with prostate cancer during the study, time to metastases and any differences in all cause and prostate cancer mortality between the finasteride and placebo arms of the study. The authors were also able to update the data of the original PCPT study with a further year of follow-up.

In terms of prostate cancer diagnosis, 989 of 9,423 men in the finasteride group (10.5%) were diagnosed

with prostate cancer, compared with 1,412 of 9,457 (14.9%) in the placebo arm – a relative risk (RR) of 0.70 (95% CI:0.65-0.76, $P < 0.001$). For high-grade prostate cancer the RR was 1.17 (95% CI:1.00-1.37, $P = 0.05$) with 3.5% of men in the finasteride group and 3.0% in the control group diagnosed with a cancer of Gleason grade 7-10.

There were 2,538 deaths in the finasteride group, compared with 2,496 in the placebo group – a 15-year survival rate of 78.0% and 78.2% respectively. For men with low-grade prostate cancer, the 10-year survival rate was 83.0% in the finasteride group versus 80.9% in the placebo group. For those with high-grade cancer, 10-year survival rates were 73.0% and 73.6% respectively.

Thus, as with the original PCPT study, the use of

a 5-ARI, in this case finasteride, was seen to reduce the incidence of prostate cancer by about a third. Although high-grade cancer was more common in the 5-ARI group, after 18 years of follow-up there was no significant difference in rates of prostate cancer specific survival or overall survival between the two groups.

What are the conclusions to be

drawn for primary care? First, that prescription of finasteride or dutasteride as a chemopreventive agent against prostate cancer cannot be justified on the available evidence. Second, if a patient is aware of the data on increased risk of high-grade cancer in men prescribed long-term 5ARIs, GPs can reassure them that risk difference is small and does not impact on the most important long-term outcome measure, i.e. survival.

REFERENCES

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