Long term use of combined HRT doubles cancer risk

David Spurgeon *Quebec*

Women over the age of 65 who take combined oestrogen and progestogen hormone replacement therapy (HRT) for five to 15 years or more face a 100% increase in the risk of developing breast cancer, regardless of their pattern of progestogen use, says a new study (*JAMA* 2003;289:3254-63).

Although it had been shown previously—with the early closing of an arm of the Women's Health Initiative study—that women taking the combined therapy have an increased risk of breast cancer (*BMJ* 2002;325:61), data on the long term use of the therapy and on the risks associated with patterns of use have been lacking.

The new study was undertaken to fill that gap. It involved 975 women aged 65 to 79 who had been given a diagnosis of inva-

sive breast cancer between 1 April 1997 and 31 May 1999 in three counties in western Washington state.

Dr Christopher Li, the lead author and an assistant member of the public health sciences division of the Fred Hutchinson Cancer Research Center, Seattle, said, "We found that long term use of combined oestrogen and progestin hormone replacement therapy not only doubles cancer risk but that the magnitude of this risk increases with duration of use."

"Few studies have assessed whether sequential progestin use is related to breast cancer risk, although some studies have suggested that continuous use of progestin is more strongly associated with breast cancer risk than sequential use. In this study we found that both regimens

were associated with similar increases in breast cancer risk. There does not seem to be any advantage to sequential progestin use compared to continuous progestin use with respect to reducing this risk."

The researchers assessed the effect of combined hormone replacement therapy on the risk of specific types of breast cancer. Among their findings was that the risk of invasive lobular breast cancer increased by 170%. This is the second most common histological type of breast cancer, affecting the lobes in the breast that contain milk producing glands. Lobular cancer accounts for 10% to 15% of cancer cases, and its incidence has increased by 65% in the United States during the last 12 years, which Dr Li says may be partly accounted for by greater use of combined hormone replacement therapy. The risk of ductal breast cancer increased by 50%. This type, involving the ducts that carry milk from the lobules to the nipple, accounts for about 80% of all cases of breast cancer.

Women who took the combined therapy had twice the risk of hormone receptor positive breast cancer, which requires oestrogen or progesterone to grow. About two thirds of all breast cancers are either oestrogen receptor positive or progesterone receptor positive.

Dr Li said that the study's finding that combined hormone replacement therapy increased only the risk of hormonally positive tumours shows the importance of progesterone in the development of breast cancer.

"It appears that hormone replacement therapy must contain progesterone to promote breast cancer growth and that it may act through stimulation of both oestrogen and progesterone receptors, not just one or the other," he said.

A potential clinical implication is the need for development of chemotherapeutic agents that target progesterone receptors—similar to the way that tamoxifen is used to treat oestrogen receptor positive tumours by blocking the oestrogen pathway. □

Prostate cancer drug may be useful for prevention

Janice Hopkins Tanne *New York*

The American Cancer Society and the National Cancer Institute have hailed the trial of a drug for prostate cancer as a milestone for cancer prevention, although the treatment can increase the aggressiveness of the cancer in some cases. And some commentators have questioned its use as a preventive, given the trial results.

Finasteride (Proscar), which is manufactured by Merck, reduced the incidence of prostate cancer by nearly 25% in a large, randomised, controlled trial and reduced symptoms of benign prostatic hypertrophy.

But prostate cancers that developed during the course of the trial were more aggressive in the treatment group than in the placebo group, says the study, which is released early online by the *New England Journal of Medicine* (www.nejm.org) and will be published in the 17 July issue. The

study also showed that, in the control group, the number of cancers detected was four times higher than expected.

These two factors, says Dr Peter Scardino, head of urology at Memorial Sloan-Kettering Cancer Center, New York, in an accompanying editorial, raise serious concern about the clinical significance of the cancers detected and the reduction achieved with the treatment. He said that "disturbing findings in the report argue that it [finasteride] should not" be used to lower the risk of prostate cancer.

Finasteride lowers concentrations of androgens, which are involved in the development of prostate cancer. Androgen deprivation

is one treatment for prostate cancer. Finasteride inhibits 5 α -reductase, reducing conversion of testosterone to dihydrotestosterone, the main androgen in the prostate.

The study enrolled 18 882 men aged 55 years or more whose results of manual rectal examination were normal and who had a prostate specific antigen concentration of ≤ 3.0 ng/ml. The men were to be followed for seven years, but the study ended early when it was found that finasteride reduced the incidence of prostate cancer in 9060 men by 24.8% (95% confidence interval 18.6% to 30.6%; $P < 0.001$).

Although men who took finas-

teride had fewer prostate cancers, men who did develop prostate cancer while taking finasteride were more likely to have aggressive cancer—defined as a Gleason score of 7 to 10—than the men in the placebo group (P for difference < 0.001). However, the Gleason score is based on a pathologist's visual inspection of prostate cancer cells, and finasteride affects the appearance of the cells, perhaps leading to a false estimate of the score. Or the drug might have eliminated less serious cancers, while allowing more serious ones to grow.

Finasteride reduced the risk of prostate cancer in all risk groups. It also reduced urinary tract symptoms of benign prostatic hypertrophy. However, men taking finasteride had more sexual side effects.

The study protocol called for a biopsy in all men who hadn't had a diagnosis of prostate cancer by the end of the study. This meant that men who would not normally have had a biopsy did have one. The surprising finding was that high risk cancers (according to the Gleason score) were as common in men with very low prostate specific antigen concentrations as in men with high concentrations. □

Light micrograph of a carcinoma of the male prostate gland

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