No clear evidence that decline in HRT use linked to fall in breast cancer

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There is no clear evidence that the decline in the use of hormone replacement therapy (HRT) is linked to a reported fall in the numbers of new cases of breast cancer, as has been claimed, suggests a study in the *Journal of Family Planning and Reproductive Health Care*.

The stats and time trends neither back up nor refute the claim, so no firm conclusions can be drawn, say the authors in the last of a series of five critiques of the published data in three major studies on HRT.

A trio of studies - the Collaborative Reanalysis (CR); the Women's Health Initiative (WHI); and the Million Women Study (MWS) - prompted the use of HRT to tumble, starting in 2002, after they concluded that it causes breast cancer.

Two subsequent studies published in 2006 and 2007 suggested that the drop-off in HRT use was directly linked to a decline in breast cancer rates, a claim that has gained considerable currency.

One of these studies tracked new cases of breast cancer between 1975 and 2004, from nine US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) registries.

This showed that between 2002 and 2003, the numbers of new cases fell by 6.7%. Between 2001 and 2004, the incidence among 50 to 69 year old women fell by 11.8% and by 11.1% among those aged 70 and above.

The second study used pharmacy data from the Kaiser-Permanente-Northern California (KPNC) health plan to look at HRT use between 1994 and 2004 and rates of breast cancer among women between the ages of 50 and 74.

This showed that the rates of single and combined HRT fell by 58% and 38%, respectively, between 2001 and 2003, while new breast cancer cases fell by around 11% in 2003.

The authors of the current analysis point out that in both studies the fall in breast cancer incidence started in 1999, three years before the sharp fall in HRT use began.

Between 1999 and 2002, the use of HRT fell by 1% every quarter, which would not have had any noticeable impact on breast cancer rates, they say. Between 2002 and 2004 it fell by 18%, after which it levelled off.

In the SEER study, the declines in breast cancer were similar for both early stage and advanced cancers. This suggests that advanced cancers would have rapidly shrunk very soon after HRT discontinuation, which is "unlikely," say the authors.

Similarly, the KPNC study claim, that HRT discontinuation might have prompted the 11% fall in breast cancer in 2003 "is not credible," say the authors: the WHI study published in 2002, so advanced cancers would have had to have regressed in six months, say the authors.

They go on to cite various methodological flaws in the studies that could have skewed the findings, including detection bias - where the study group does not reflect the population; and confounding - where major influential factors are not accounted for.

And they looked at breast cancer rates in 11 countries, which show that

it is impossible to establish a causal link between the declines in HRT use and breast cancer.

DNA damage to breast tissue takes at least a decade before cancer becomes detectable, say the authors, and if there was a causal link, HRT discontinuation would be expected to have conferred a reduction in new cases of cancer over a period of several years. But this is not what the data show, say the authors.

"Based on the observed trends in the incidence of breast cancer following the decline in HRT use, the ecological evidence is too limited either to support or refute the possibility that HRT causes cancer," they conclude.

In an accompanying commentary, Nick Panay of London's Queen Charlotte's & Chelsea and Chelsea and Westminster Hospitals, and chair of the British Menopause Society, points out that the WHI study was designed 20 years ago and looked at HRT as one entity.

But HRT now is often prescribed in lower doses, as skin patches, and more closely matches the make-up of the body's own hormones, so could have a completely different risk profile, he argues.

Even in 2002, the relative risk of breast cancer associated with HRT, the WHI study found, was small: 1 extra case per 1000 women a year, he says. And more recent research indicates that if started soon after menopause, HRT "seems to confer many benefits and has few risks," he writes.

"The arguments regarding the validity of the CR, WHI, MWS and breast cancer rate studies could rage on for years," he says, adding that a definitive trial with sufficient power to draw some firm conclusions might help to settle the issues.

In the meantime, he says, many women who could benefit from HRT are not using it. "If there is a risk, the risk is small, and the benefits of HRT can be life altering; it is vital that we keep this in perspective," he concludes.

More information: Does hormone replacement therapy (HRT) cause breast cancer? An application of causal principles to three studies Part 5. Trends in breast cancer incidence in relation to the use of HRT, doi 10.1136/jfprhc-2012-100508

Does hormone replacement therapy cause breast cancer? Commentary on Shaprio et al papers, Parts 1-5, doi 10.1136/jfprhc-2012-2013-100578

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