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Declining breast cancer incidence and decreased HRT use

Breast cancer is the most common cancer in women worldwide, comprising 23% of all cancers, with more than 1 million new cases per year.¹ The main risk factors are related to the female sex hormones with oestrogenic and progestagenic activity either produced within the body or given as hormonal contraceptives or hormone-replacement therapy (HRT). Changes in reproductive factors, use of postmenopausal HRT, mammographic screening, and lifestyle factors associated with affluence have been contributing to the increase in breast cancer witnessed during the past few decades in women aged 50 years or older from developed countries.

Karen Canfell and co-workers² recently examined the association between trends in HRT use and incidence of breast cancer in Australia. In the period after the rapid fall in HRT use beginning in 2001, the researchers found a decline in breast cancer incidence in women aged 50 years or older, but not in those younger than 50 years. Similar trends have been observed in the USA,^{3,4} New Zealand,⁵ Canada,⁶ Germany,⁷ and France.⁸

The long-term effect of HRT has been debated for decades. Despite possible adverse effects, HRT became increasingly popular among women in developed countries during the 1990s. Results during the late 1990s from two important studies about possible adverse effects

did little to affect the increasing popularity.^{9,10} However, results from the Women's Health Initiative's randomised trial in July, 2002, provoked a rapid fall in sales.¹¹ This study estimated an absolute excess risk of adverse events of 19 per 10 000 person-years of use. Women who used HRT were at increased risk of developing breast cancer, heart disease, stroke, and thrombosis. The researchers recommended that HRT should not be continued or started for primary prevention of coronary heart disease.

The incidence of breast cancer has been decreasing in women aged 50 years and older in many developed countries in the past few years, but whether this decline has been caused by the falling prevalence in use of HRT or by a reduction in the prevalence of mammographic screening attendance is controversial. A reduction in the prevalence of mammographic screening results in a reduction in the incidence of breast cancer in the short term, because mammography screening brings forward the diagnosis of breast cancer. To exclude changes in screening, Kerlikowska and co-workers³ restricted analyses to 603 411 women aged 50–69 years, all of whom had been screened from 1997 to 2003, inclusively. Their results suggested that the fall in HRT use was the main contributing factor to the decline in incidence of breast cancer seen in the USA since 2002.

In Norway, the incidence of breast cancer for women aged 50–69 years increased throughout the 1990s and reached a plateau in 2002–03 (figure).^{12,13} Since then, the incidence of breast cancer in women aged 50–69 years, but not in younger women, has declined. Two events might have contributed to the changes in incidence: implementation of the Norwegian Breast Cancer Screening Programme, and the rise and fall in HRT use. This screening programme was rolled out in 1996–2004 for women aged 50–69 years.¹⁴ Use of HRT increased rapidly during the 1990s, peaking in mid-2001. However, a 48% reduction in HRT use has been registered between 2002 and 2007.¹²

To assess whether HRT use or screening with mammography was the most important contributor to the rise in incidence of breast cancer in Norway in the 1990s, Bakken and co-workers¹⁵ used data from the Norwegian women and cancer study. They showed that, in Norwegian women aged 50–64 years, current HRT use doubled the risk of breast cancer whether or not they had been screened (relative risk for current use vs never use of HRT 2·2 without mammography, and 2·4 with mammography). In never users of HRT, the risk of breast cancer was broadly similar in women who were screened and in those who were not (1·2 and 1·0, respectively). They concluded that HRT use was thus a more important factor than screening as an explanation for the rise in incidence of breast cancer in Norway during the 1990s.

Although the drop in HRT use in Norway was previously reported not to be followed by a reduction in the incidence of breast cancer,¹⁶ the most up-to-date Norwegian national statistics show a decline in the incidence in women 50 years and older, but not in those who are younger (figure). Breast cancer trends in Norway are thus broadly similar to those in the USA, New Zealand, Canada, Germany, France, and Australia. In all these countries, postmenopausal women had a high prevalence of HRT use before 2002, with use almost halving in the next few years. In most of these countries, screening practices changed little after 2002.

In countries such as the Netherlands, where HRT had not been widely used by postmenopausal women, few breast cancers in women aged 50 years and older would be because of such hormonal therapy, and so changes in use of HRT would not have much effect on trends in breast cancer.¹⁷ In England, where screening practices altered substantially after 2002, the effects of changes

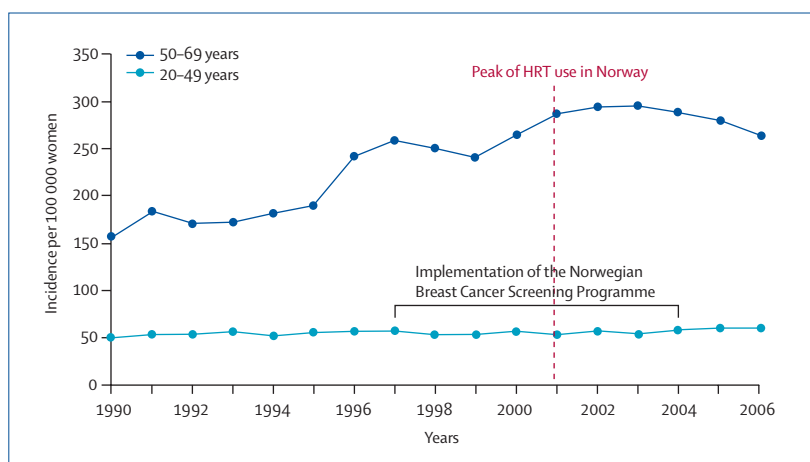


Figure: Age-standardised incidence of breast cancer in Norwegian women, 1990–2006
Data from references 12 and 13.

in HRT use and changes in screening on trends in breast cancer are impossible to disentangle. Up till 2002, the programme invited women aged 50–64 years and offered double-view mammography in the first round and single view in subsequent screenings. In 2002, the programme was extended from age 64 years to 70 years and a two-view mammography was offered in both first and subsequent screening rounds.¹⁸

Undoubtedly, there is a striking correlation between the fall in HRT use and the decline in incidence of breast cancer in women aged older than 50 years in many developed countries. These trends are in line with the well-established finding that the increased risk of breast cancer associated with HRT disappears within a few years of ceasing use.⁹ Correlation is not the same as causation, but few other factors could result in such a rapid change in the incidence of breast cancer. Changes in screening practices are by far the most important alternative explanation, but changes in screening have been shown not to explain the recent fall in incidence of breast cancer in the USA and Australia.^{2,3}

Since 2002, regulatory bodies have continued to recommend that HRT can be used to treat menopausal symptoms only and for as short a time as possible. This advice contributed to substantial declines in HRT use by postmenopausal women. With the growing number of consistent reports of recent falls in the incidence of breast cancer in women aged older than 50 years, the advice for cautious use of HRT seems to have already prevented substantial numbers of breast cancers worldwide. For the safety of women, recommendations about HRT use

should continue to be for the treatment of menopausal symptoms only and for as short a time as possible.

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Antiepileptic drug withdrawal in seizure-free patients

The ultimate goal of epilepsy treatment is to become seizure free and live a healthy life without the need to take antiepileptic drugs, which cause several inconvenient and sometimes serious side-effects.¹ Although about 70% of all patients with newly diagnosed epilepsy become seizure free with such drugs,² many seizure-free patients (and their physicians) prefer to continue medication, mainly for fear of seizure relapse.

Why is withdrawal so controversial? What is the evidence to guide physicians and patients? Surprisingly, there is no class I evidence that is based on randomised double-blind trials for withdrawal of antiepileptics in adults who become seizure-free while taking such drugs. The best evidence comes from a large unblinded randomised trial in patients who became seizure-free on treatment,³ and several useful but non-randomised observations.^{4–6} It is therefore a pleasure to comment on the first randomised double-blind trial on the consequences of withdrawal of an antiepileptic in seizure-free patients.⁷

In this benchmark study, the Akershus study, Morten Lossius and colleagues randomised adult patients, who were seizure-free for more than 2 years on

a single antiepileptic drug, to withdrawal (n=79) and no withdrawal (n=81). The patients were followed up for 12 months or until seizure relapse. The authors reported a statistically non-significant difference of seizure relapse of 15% in the withdrawal group and in 7% in the no-withdrawal group (relative risk 2.46, 95% CI 0.85–7.08, p=0.095). The effect difference was 9% (0.00–0.20). After withdrawal, seizure relapse rates were 27% after a median of 41 months off medication.

The question is, of course, how did the no-withdrawal group do at longer follow-up? This question cannot be answered because almost all patients (except eight) in the no-withdrawal group preferred to withdraw after the study period of 12 months, and their seizure outcome is not known. A normal result to all 15 neuropsychological tests improved from 11% to 28% in those withdrawing from treatment. By contrast, the proportion of normal tests decreased from 11% to 9% in those remaining on treatment. However, the risk was not statistically significant. Withdrawal did not affect quality of life and EEG. Predictors for remaining seizure-free after drug withdrawal over