REVIEW ARTICLE

Decline in Hormone Replacement Prescription and Fall in Breast Cancer Incidence

An Epidemiological Discourse

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SUMMARY

Introduction: Between 2002 and 2003 the incidence of invasive breast cancer among women aged 50 to 69 years declined considerably in the US. This decline was accompanied by a substantial fall in prescription rates of estrogen-progestin (EG-HRT).

Methods: Selective literature search in PubMed from 01/2003 to 12/2007 using the key words "hormone replacement therapy," "incidence," and "breast cancer."

Results: The parallel decline in EG-HRT and breast cancer suggests a causal link. Up to now, alternative explanations for the decline of the incidence can either be refuted or revealed as implausible.

Discussion: Detailed incidence trend analyses in the coming years and a close monitoring of EG-HRT prescription rates in and beyond the US. promise important insights. If EG-HRTs are carcinogenic, the extent of this effect remains unclear. If cessation of EG-HRT therapy only delays the appearance of detectable breast cancer, a long-term increase in incidence would be expected in women of age 50 and older, even with low prescription rates. However, if cessation of EG-HRT also stops tumor growth, the anticipated incidence will be permanently lower in the future.

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The incidence of breast cancer in the United States is falling, according to Ravdin et al., speaking at the San Antonio Breast Cancer Symposium in den US in December 2006 (1). A worldwide discussion ensued on the incidence of breast cancer, which rose by 40% between 1980 and 1998 (2). Since 1999 the incidence has been falling continually, and notably so between 2002 and 2003. These observations have prompted a debate about whether the drop in incidence is an artifact or – if it is not – which causes might be underlying the decline. Siegmund-Schulze et al. (3) have recently debated the fall in breast cancer incidence in this journal from a clinical perspective. This article summarizes the current discussion from an epidemiological perspective.

Decline in prescription of postmenopausal hormone replacement therapy

Trends in incidence and postmenopausal HRT prescriptions in the US

Clarke et al. in 2006 published data from an insurance sample in northern California (4). Between 2001 and 2003 they observed a drop in prescriptions of postmenopausal hormone replacement therapy (HRT) by 68% for combinations of estrogens and progestin (EG-HRT) and by 36% for estrogen monopreparations (E-HRT) in women aged 50 to 74. Over the same time period, the incidence of breast cancer fell by 11% (*figure 1*).

Because of the coincidence of the drastic reductions in HRT prescriptions and breast cancer incidence, the authors speculated that the drop in incidence might be causally related to the drop in prescriptions (4). Shortly afterwards, Ravdin et al. evaluated the cancer registry data from the US SEER (Surveillance, Epidemiology, and End Results) program (1). The SEER program collects data from US cancer registries. For detailed analyses regarding hormone receptor status (estrogen receptor: ER+, ER-; progesterone receptor: PR+, PR-) they investigated the diagnosis years 2000 to 2004. From 2001 to 2004, the incidence of breast cancer fell by 11.8% in women aged 50 to 69 and by 11.1% in women aged 70 or older. In the age group 50 to 69, the incidence fell by 14.7% in ER+ breast cancers. For

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FIGURE 1

Prevalence of HRT prescription (estrogen monotherapy and combination therapies) and incidence of invasive breast cancers in the insurance sample of the Kaiser Permanente Program in the region Northern California from 1994 to 2004; from Clarke CA, Glaser SL, Uratsu CS, Selby JV, Kushi LH, Herrinton LJ: Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. *J Clin Oncol* 2006; 24: e49, with permission from the American Society of Clinical Oncology

ER⁻ cancers, no notable change was seen. Quarterly incidence analyses for ages 50 and older found that the drop started in mid-2002 and ended in mid-2003. No change in trend was seen for ER⁻ breast cancers. The drop in incidence in 50 to 69 year old women was 11.3% for localized cancers and 13.6% for advanced cancers.

The decline in incidence coincided with an enormous drop in the number of prescriptions of HRT in the US. The two most commonly prescribed preparations in the US are Premarin (conjugated estrogens) and Prempro (conjugated estrogens plus medroxyprogesterone acetate); both were prescribed more rarely especially in 2002 and 2003 (figure 2). Ravdin et al. explain the fall in prescriptions with the publication of the Women's Health Initiative (WHI) in the summer of 2002 (1). Results from this study showed that the risk of breast cancer rose by 24% in postmenopausal women receiving conjugated estrogens and medroxyprogesterone acetate (5).

Jemal et al. conducted analyses of breast cancer incidence of the SEER program focusing on tumor size, stage, hormone receptor status, and the women's age (2). Between 1999 and 2003, the incidence of breast cancer fell from the age of 45 in each five-year group; the extent of the fall and the starting time varied between the age groups.

The fall between 1999 and 2003 was observed only for small tumors (≤ 2 cm) and localized or regionally

metastasized breast cancers. The incidence of in situ cancers plateaued between 1999 and 2003 after rising by 6.6% per year from 1981 to 1999. The incidence of ER⁺ and PR⁺ cancers rose from 1990 to 2000. Between 2002 and 2003, the incidence of these cancers declined enormously, by 9.1% (2).

Data analyses of an insurance sample in the Federal State of Oregon between 2001 and 2006 showed an annual decline by 2.7% in the incidence of ER⁺ breast cancers. The incidence of ER⁻ breast cancers, however, fell in 1999 to 2006 by 9.8% annually (6). The US Centers for Disease Control and Prevention (CDC), in a nearly population wide analysis of breast cancer incidence, evaluated data from 36 cancer registries and five SEER cancer registries. These registries cover some 86% of the entire US population (7). The incidence of invasive breast cancers fell steadily from 1999 to 2003. The biggest drop, by 6.1%, occurred between 2002 and 2003. The incidence of in situ cancers rose from 1999 to 2002 and then fell from 2002 to 2003, by 2.7%. The incidence of localized breast cancers fell most (6.9%), followed by cancers with regional metastases (4.7%) and cancers with distant metastases (1.8%) (7).

In a recent publication, Keegan et al. analyzed the incidence trend of breast cancer and HRT prescribing in the San Francisco region for 1988 to 2004, on the basis of cancer registry data. In the past, this region had had extremely high incidence rates of breast cancer. The results were similar to those of the SEER evaluations (8). Table 1 shows further details of the results of the US incidence trend analyses.

Incidence trends and postmenopausal HRT in other countries

In Canada, the incidence of breast cancer fell by 1.8% annually between 1999 and 2003. The biggest decrease (2.6%) was seen in women aged 75 or older (9). The temporal correlation with prescription rates of HRT was not investigated. Incidence rates of breast cancer in Norway and Sweden remained practically unchanged, although substantially less HRT was prescribed. In women aged 50 to 69, Norway posted a fall in HRT prescription rates that was similar to that in the US (10) (figure 3). Ravdin et al. countered this by pointing out that, unlike in the US, the main forms of HRT used in Norway were based on estradiol and not on conjugated estrogens and that the effect of HRT on the incidence of breast cancer may depend on the preparation used (11). In Germany, too, the most commonly prescribed HRT preparation is a combination of estradiol and norethisterone. Conjugated estrogens with medroxyprogesterone acetate are prescribed notably less (see drug prescription report) (12).

Data analyses from the cancer registry of Germany's northernmost state, Schleswig-Holstein, showed a clear temporal association between the decline in breast cancer incidence and the fall in prescriptions of EG-HRT, similar to the US. From 2002 to 2005, the incidence of breast cancer in women aged 50 to 69 fell by 8.8% and in women aged 70 and older,

by 8.1%. In this time period, the number of prescriptions of EG-HR in all age groups had fallen by 8.0% (13, 14).

Arguments in favor

The World Health Organization (WHO) has recently declared that there is sufficient evidence that combination HRT (estrogens and progestin, EG-HRT) causes breast cancer in postmenopausal women (15). Several observations seem to confirm that EG-HRT has a carcinogenic effect on breast cancer cells (16). This means that under the influence of EG-HRT, subclinical breast cancers become apparent in a shorter time interval as they would if no EG-HRT were taken. It may even be possible that subclinical breast cancers without HRT might never become clinically apparent. The following arguments favor this assumption:

- The rapid decline in the incidence of breast cancer was noted within the first few years after stopping EG-HRT prescribing that was noted in the Million Women Study (17).
- The analyses of regional breast cancer incidence rates and HRT prevalence rates in California. The breast cancer incidence in white women aged 45 to 74 and HRT prevalence rates showed that per 1% decline in HRT prevalence the incidence of breast cancer fell by 3.1/100 000 women (18).
- The comparison of incident breast cancers in the treatment and placebo groups in the WHI study. In women receiving EG-HRT, breast tumors were on average larger, more often node positive, and many were cancers with regional or distant metastases (5).

Arguments against

Bluming said that if HRT is carcinogenic then early stage breast cancers should become rarer if less HRT is prescribed (19). Ravdin et al., however, observed a fall in the incidence of advanced breast cancer of the same magnitude (1). Bluming also postulated that the observed decline in breast cancer incidence would be less pronounced with increasing age because older women are less often prescribed HRT (19). However, Ravdin et al. observed a comparable drop in incidence even in women older than 70. Analyses from the CDC contradict the latter argument – they show that the US breast cancer incidence in older women and at advanced cancer stages decreased less than in younger women and localized cancers (7).

Decline in participation in mammography screening

US data for 2000 to 2005 show that the proportion of women older than 40 who have had a mammography in the preceding two years fell from 76.4% to 74.6% (7, 20, 21).

Arguments in favor

The incidence of breast cancer in the US fell even before the sudden enormous drop in HRT prescriptions (1).

FIGURE 2

Quarterly incidence of breast cancer (per 100 000) in women aged 50 to 69, subdivided by estrogen receptor status and annual US wide numbers of prescriptions of HRT (Prempro and Premarin); from: Ravdin PM, Cronin KA, Howlader N et al.: The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med* 2007; 356: 1670–4, with permission from the Massachusetts Medical Society

Women who have regular mammograms have two to three times the detection rate of breast cancer as women who do not participate in screening (22). The proportion of women who regularly attend mammography screening obviously has an influence on breast cancer incidence.

In a context of declining mammography rates it would be plausible if especially the rates of in situ and early stage invasive tumors and ER⁺ cancers were to drop because screening particularly detects such tumors. CDC analyses show that the incidence of in situ cancers from 1999 to 2002 rose steadily and then fell. The fall in rates of localized breast cancers has

TABLE

Current changes in breast cancer incidence (invasive cancers) in the US

Cohort	Age (years)	Further subcategorization	Year of diagnosis	Relative change (percent)	Case numbers	95% confidence interval
Kaiser Permanente Program, Northern California (3)	50–74	Total incidence	2001–2003	–11	NA	NA
SEER-Programm. 9 Regionen (1)	< 50	Total incidence	2001–2004	+1.3	NA	–3.1; +5.8
	50–69	Total incidence	2001–2004	–11.8		–14.5; –9.2
	70+	Total incidence	2001–2004	–11.1		–14.2; –7.9
	50–69	ER+ cancers	2001–2004	–14.7		–17.4; –11.6
	50–69	ER– cancers	2001–2004	–1.7		–8.0; +4.6
	50–69	Localized cancers	2001–2004	–11.3		–14.6; –8.0
	50–69	Advanced cancers	2001–2004	–13.6		–17.9; –9.2
SEER program, 9 regions (2)	≥ 40	Tumor size ≤ 2 cm	1999–2003	–4.1	394 891*1	–7.8; –0.2
	≥ 40	Localized cancers	1999–2003	–3.1		–5.0; –1.2
	≥ 40	ER+ cancers	2002–2003	–9.1		NA
	≥ 40	ER– cancers	2002–2003	–4.8		NA
	≥ 40	PR+ cancers	2002–2003	–9.1		NA
	≥ 40	PR– cancers	2002–2003	–6.9		NA
	65–69	ER+ cancers	2002–2003	–20		NA
	65–69	ER– cancers	2002–2003	+2		NA
	65–69	PR+ cancers	2002–2003	–20		NA
	65–69	PR– cancers	2002–2003	–9		NA
Kaiser Permanente Program Oregon (5) *2	All	Total incidence	2001–2006	–4.3	7 386*2	–7.2; –1.1
	45–59	Total incidence	2000–2006	–4.9		–9.7; +0.1
	60+	Total incidence	2001–2006	–4.1		–7.9 –0.03
	All	ER+ cancers	2001–2006	–2.7		–6.4; +1.1
	All	ER– cancers	1999–2006	–9.8		–12.8; –6.6
68% of US population (6)	All	Total incidence	2002–2003	–6.1	1 043 480*3	p < 0.05
	All	Localized	2002–2003	–6.9		p < 0.05
	All	Regional metastases	2002–2003	–4.7		p < 0.05
	All	Distant metastases	2002–2003	–1.8		NA
	0–39	Total incidence	2002–2003	+0.8		NA
	40–49	Total incidence	2002–2003	–0.3		NA
	50–59	Total incidence	2002–2003	–7.4		p < 0.05
	60–69	Total incidence	2002–2003	–9.1		p < 0.05
	70–79	Total incidence	2002–2003	–7.9		p < 0.05
	80+	Total incidence	2002–2003	–7.6		p < 0.05
	All	In situ cancers	2002–2003	–2.7		p < 0.05
	All	White (Caucasian)	2002–2003	–6.4		NA
	All	Black	2002–2003	–2.7		NA
	All	Hispanic	2002–2003	–5.8		NA
	All	Asian/Pacific islanders	2002–2003	–6.1		NA
San Francisco region (7)	All	Total incidence	1988–2004	–2.2	NA	–2.6; –1.8
	All	Total incidence	1988–2004	+0.1		–0.6; 0.8
	40–69	Total incidence	1988–1999	+1.6		0.8; 2.4
	40–69	Total incidence	1999–2004	–4.3		–6.8; –1.7
	≥ 70	Total incidence	1988–2002	+0.5		0.0; 1.0
	≥ 70	Total incidence	2002–2004	–9.2		–18.4; 1.0

NA: 95% confidence interval and p value not reported; if p values were reported but not confidence intervals, the p value was used; relative changes: minus sign indicates a fall, plus sign a rise; *1 in 1975 to 2003, altogether 394 891 invasive cancers and 59 837 in situ cancers were registered; *2 different time intervals of constant trends resulted from the breakpoint regressions used; *3 in 1980 to 2006, 7386 invasive breast cancers were registered; *4 in 1999 to 2003, altogether 1 043 480 invasive and in situ cancers were registered.

been most pronounced, according to CDC analyses (7), whereas SEER data show a comparable fall in incidence in all three stages (1).

Arguments against

Jemal et al. did not find a decline in the incidence of in situ cancers when they analyzed the SEER data. The small drop in mammography rates in the US therefore did not affect in situ cancers, which are typically detected by mammography screening (2). A decline in the incidence of ER⁺ breast cancers by 14.7% in women aged 50 to 69 between 2002 and 2003 is not sufficiently explained by the gradual and very small decline in mammography rates, with only 3% in 2000 to 2005 (1).

The study by Kerlikowse et al. (22) is instructive. Women who participated in this study underwent mammography screening at regular intervals. Kerlikowse et al. studied the incidence trends of breast cancer in four US mammography screening programs in 1997 to 2004, based on 3238 cases of breast cancer.

Similar to Ravdin et al., they observed a 13% fall in the incidence of ER⁺ cancers in women aged 50 to 69 between 2002 and 2003. This means that this enormous drop in incidence is apparent even without a drop in the number of participants in mammography screening (22).

Decrease in incidence owing to completion of prevalence screening

Introducing efficient screening methods will yield increased incidence rates in tumors in the first round because the screening method will detect tumors that were clinically not apparent up to then. The effect is known as prevalence screening. It usually takes years to introduce population wide screening. Once the majority of the population has gone through the first screening round, the incidence of tumors will fall. Figure 3 shows the effect of introducing mammography screening on breast cancer incidence in Norway (10).

Arguments in favor

The incidence of breast cancer in Connecticut rose notably more in the years after mammography screening had been introduced. Especially the incidence of in situ cancers rose between the periods 1973–1977 and 1998–2002 by 1024% (from 3.7/100 000 to 14.6/100 000). In the same time period, the incidence of localized cancers rose by 86%, that of regionally metastasized cancers by 15%, and that of cancers with distant metastases by 20% (23). Anderson et al. concede that the incidence trend is due to an overlap of birth cohort effects and screening effects. However, they believe that the stage specific trend and the bigger increase in incidence since the introduction of screening mean that mammography screening will result in higher breast cancer incidence rates in the long term, compared with the rates before screening was introduced (23).

FIGURE 3

Prescriptions of HRT and breast cancer incidence in women aged 50 to 69 in four regions of Norway that include 40% of the total population. Mammography screening was introduced in 1996 to 1997; from: Zahl PH, Maehlen J: Letter to the editor. *N Engl J Med* 2007; 357: 509–10, With permission from the Massachusetts Medical Society

Jemal et al. conclude that the start of the drop in incidence in the US in 1999 marked a period effect due to the fact that mammography screening had plateaued (2). This assumption is favored by the fact that the drop in incidence was observed in almost all age groups and especially for smaller tumors (≤ 2 cm). In the US, the proportion of women aged 40 or older who had had a mammogram in the preceding two years rose by 29% from 1987 to 1999 and has remained constant at about 70% ever since (2, 6).

Arguments against

The explanation proffered by Jemal et al. for the decrease in the incidence of breast cancer in 1999 – mammography rates having plateaued – makes a gradual decline in breast cancer incidence since 1999 plausible at first glance. The drop might be due to the end of the prevalence round of screening. But it does not seem conclusive that the end of the prevalence round between 2002 and 2003 had effected such a dramatic drop in incidence in women aged 50 to 69 as was observed in the US (2).

Methodological reasons for the drop in incidence

Drop in the completeness of cancer registration

A sudden fall in completeness of registrations might explain a sudden drop in incidence. However, the absence of any signs and the particularities of the

decrease argue against this assumption. The sudden drop in registrations would have to have affected especially patients aged 50 or older and particularly those with ER⁺ cancers.

Changes to the classification of breast cancers over time

No relevant changes occurred to the ICD-10 and ICD-O classifications for the years of diagnosis 1999 to 2004 that might explain the fall in incidence. As regards tumor staging, a small change occurred to the SEER program, but this would have influenced stage specific incidence trends only.

Conclusions and outlook

In sum, a close temporal correlation exists in the US between a drop in prescriptions of HRT and the incidence of especially ER⁺ breast cancers in women aged 50 or older. In the case of coinciding events, no causal correlation can be logically inferred (24). The close temporal correlation between the drop in incidence and the decrease in EG-HRT consumption suggest a causal association. The alternative explanations for the sudden drop in incidence proffered so far can either be refuted or revealed as implausible. Analyses of incidence trends of the following years of diagnosis and monitoring of the prescriptions rates of EG-HRT might offer further insights. If EG-HRT is carcinogenic the extent to which this effect occurs remains unclear. Does withdrawal of HRT result in slower tumor growth or does it result in a proportion of sub-clinical tumors never becoming clinically apparent? If withdrawal results merely in slower tumor growth then the incidence of breast cancer in women aged 50 or older can be expected to increase again in the coming years, in spite of sustained low prescription rates of EG-HRT. If the incidence remains low, however, this might mean that EG-HRT with its carcinogenesis promoting effects makes the detection of those tumors more probable that without EG-HRT would have neither become clinically apparent nor be detected by mammography screening.

Conflict of interest statement

The author declares that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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