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Systematic review about breast cancer incidence in relation to hormone replacement therapy use

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ABSTRACT

Background Several studies report a decrease in breast cancer incidence subsequent to the decrease in hormone replacement therapy (HRT) use. But its magnitude and the time-lag may vary between countries. This may reflect differences in populations, previous type and prevalence of HRT use and breast cancer screening.

Aim To review systematically studies assessing the relation between breast cancer incidence and change of HRT use.

Material and method Descriptive analysis of the methodology of the studies including design limitations and presence of confounding factors, data sources for breast cancer and HRT and regimens of HRT used.

Results and discussion Eighteen articles were selected. Most studies were ecological and confounding factors such as mammography screening and changes in reproductive and lifestyle habits could not be excluded. Sources of data on breast cancer and HRT were heterogeneous and only few data on HRT regimens used were available. Most studies concluded that the decrease in HRT use during the last decade was probably associated with a decrease in breast cancer incidence, especially for women aged 50 years or more.

Conclusions Data, mostly from epidemiological studies, suggest that the decrease in breast cancer incidence can be partly attributed to the drop in HRT use. Nevertheless, available studies are hampered by a number of limitations and it remains difficult to evaluate the exact impact of the drop in HRT use on the decrease in breast cancer incidence. Especially, the studies are seldom based on detailed individual data and do not provide information on regimens used, type of cancers and possible confounding factors.

INTRODUCTION

The first Women's Health Initiative (WHI) randomized study comparing women treated with conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) versus placebo concluded that an increased risk of breast cancer is associated with use of hormone replacement therapy (HRT)[1]. Since then, HRT consumption has decreased in many countries and several studies reported a subsequent decrease in breast cancer incidence[2–10]. The extent of this decrease and the time between the drop in HRT use and the decrease in breast cancer incidence varies between countries[2,3,9].

This may reflect differences in population-related incidences, but also differences in the type of HRT used. Indeed, in the latest WHI publication, the authors reported, paradoxically, not an increase, but a decrease in breast cancer incidence in the follow-up of estrogen users (CEE) versus placebo users[11], while there was increased breast cancer incidence in combined HRT users[1]. Several other studies observed differences in risk related to the HRT regimen: in the initial

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REVIEW

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report of the E3N study, a French observational study of teachers, no increase in breast cancer risk had been observed in estrogen-only users or in women using combined HRT of estrogens and micronized progesterone or dydrogesterone, while an increased risk was observed in women using estrogen combined with MPA or norethisterone acetate (NETA)[12]. In their last report, however, increased risks were also reported, although to a lesser extent, in estrogen-only users or users of estrogen combined with micronized progesterone or dydrogesterone[13]. Finally, a recent Fin Observation study reported that sequential progestin use resulted in a smaller increase for relative risk of breast cancer compared with continuous progestin use, but one should note that in this study most patients used NETA[14].

Prevalence of HRT use may also have an influence since the impact of less HRT prescription on breast cancer incidence is expected to be small in countries of low use.

Breast cancer screening varies widely between countries: in some countries there is no screening at all; in others, screening has been implemented but its uptake is still being developed and in yet others the screening uptake has been high for many years. The impact of screening on breast cancer incidence may, therefore, also vary between countries, since we know that breast cancer incidence increases at the beginning of screening implementation[15].

Publications concerning decrease in breast cancer incidence and lower HRT prescription are ecological data, for which no individual data are available, and for which certain biases exist.

In this article, we will present an overview of the studies evaluating, in various countries, the relation between breast cancer incidence and lower HRT use, within the last years.

MATERIAL AND METHOD

In order to identify all of the studies published after the WHI study reporting the evolution of breast cancer incidence in relation to the HRT use, we conducted a Medline search, up to November 2012, using the following key words: "hormone replacement therapy", "menopause hormone therapy", "breast cancer" and "incidence". We completed our search for references by checking the bibliographies of original articles and review articles.

We used the following inclusion criteria: articles should be written in English or French and should be original articles about the evolution of breast cancer incidence in relation to HRT use in a specific population, region or country.

Thirty-seven articles were found but some were excluded (Figure 1). Ten articles were excluded because they were duplicate publications (in such cases we selected the article with the most recent or more complete data)[4,5,9,16–22]. Five were excluded because they were publications concerning only a portion of a country since publications about the whole country were available[23–27] and three because they were subanalyses[28–30]. The excluded articles came to the same conclusions as the selected ones. One article was excluded because it included no data at all on HRT use in its region[31].

Finally, we selected 18 articles from which we extracted, when these data were available, information about the material and methods and about results and conclusions. Data about material and methods are presented in Table 1: the country, the region or the population of origin, the period of assessment, data sources on breast cancer incidence and HRT use, the size of the studied population, the methodology used by the authors, the adjustments made and the reported limitations of the study. Results and conclusions are presented in Table 2: the breast cancer screening, the type of HRT used, the changes in breast cancer incidence and in HRT consumption and the principal findings and conclusions of the authors.

In most studies, no details were provided about the type of HRT regimens. We therefore estimated the proportions of CEE, estradiol, low-potency estrogens and of micronized progesterone, progesterone derivates and testosterone derivates from Bakken and colleagues[32], for the countries for which these data were reported.

We made a descriptive analysis of this information for all the selected articles.

RESULTS

Results about material and methods are reported in Table 1. The reported period of evaluation of breast cancer incidence varied considerably between studies. Most studies had long periods of evaluation before and after the WHI publications with a follow-up of 8–31 years[3,7,8,10,33–36]. Some others reported a long follow-up from 13 to 28 years but stopped a few years after the WHI publications appeared (in 2003–2004)[37–39], some began just before the WHI publications in 2000–2001 with a follow-up of 4–7 years[6,40,41] or even after, in 2003–2004, with a follow-up of 4 years[42,43], and some were very short with a follow-up of only 3 years[2].

The breast cancer data were obtained from private health insurance plans[33], national health fund data[2,37], cancer registries data[3,6,7,10,34–36,38–41,43] or national statistics[8,42,44]. Data about HRT use were extracted from previous publications[2,34,37–39,44], national statistics[7], national health plans[8,41], corporations of pharmacies[10], national and private health insurance data[6,33,40,42], national prescription registries[3,35] and sales data[36,43].

The population size was mentioned in ten studies[2,7,10,33,34,37–41]. Six studies gave the coverage of their data source which varied between 9% and 62% of the country's total population[2,7,10,38,39,41]; five provided the number of breast cancer cases in their population ranging from 41 358 to 394 891[7,37,38–40] and six gave the size of the whole population ranging from 118 724 to 14.8 millions of persons or women[7,10,33,34,38,41].

Various models were used to assess a possible relation between breast cancer incidence and HRT use. Some studies evaluated the HRT use and the breast cancer incidence during well-defined periods and observed a relationship between

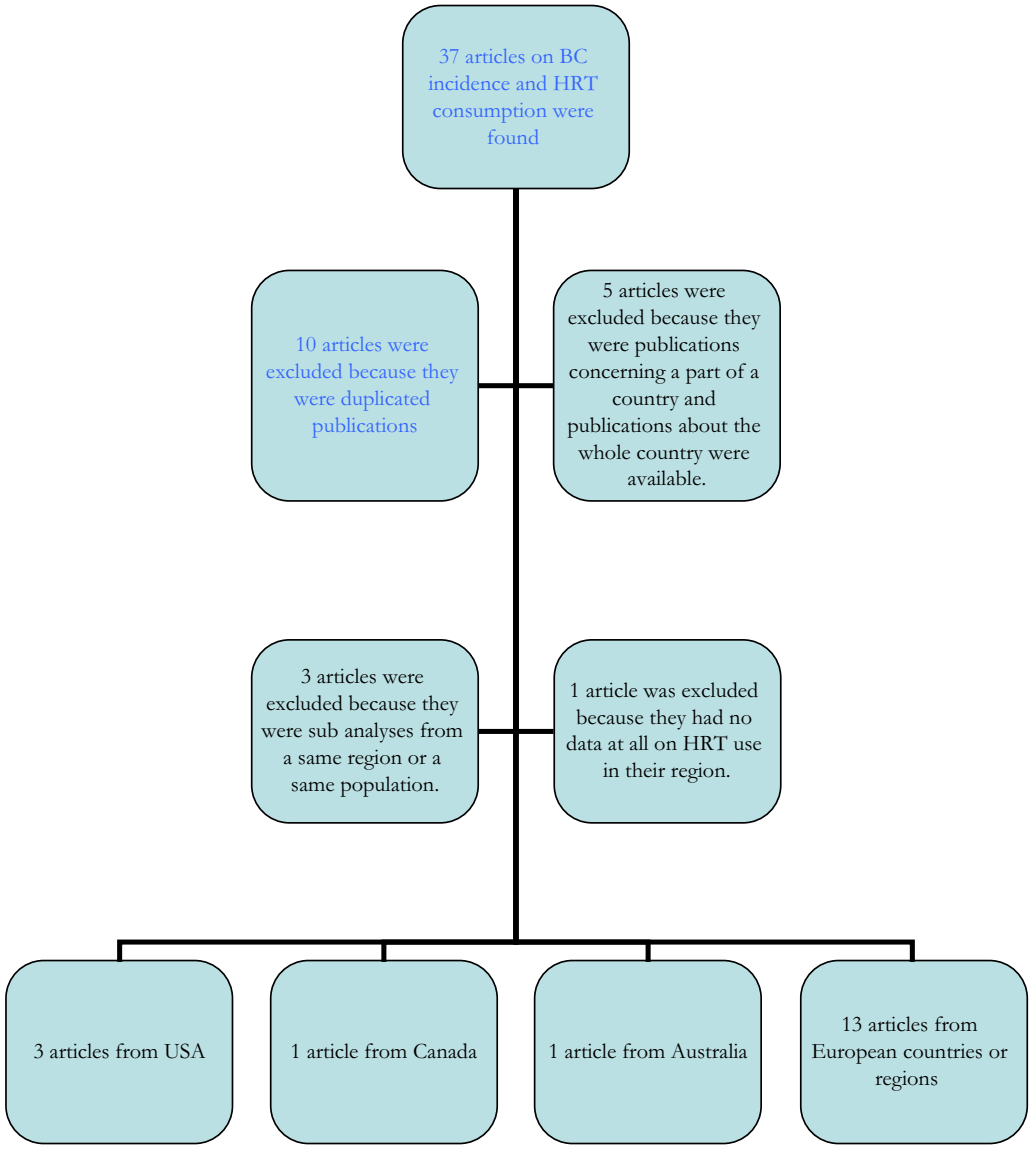

Figure 1 Selection of articles. BC, breast cancer; HRT, hormone replacement therapy

them[2,10,33,34,37–40,42]. Others analyzed whether a statistically significant relationship existed (e.g. thanks to the use of regression models like Generalized Estimating Equations) between HRT use and breast cancer incidence, eventually using some adjustments[3,6,7,35,36,41,43]. Finally, others considered that an 'a priori' increased risk of breast cancer was associated with HRT use. These authors used relative risks, drawn from other studies (such as the Million Women Study[45]), to test whether the change in HRT use could explain the evolution of breast cancer incidence[8,44].

All of the studies, with the exception of two, which are based on individual data[36,41], were ecological studies (i.e. descriptive analyses of population-based rates, rather than individual data).

Confounding factors, such as changes in lifestyle, environmental factors, reproductive patterns, smoking status, physical activity, body mass index, alcohol, breast density and use of raloxifene, tamoxifen, aromatase inhibitors or other medication, were mentioned in only half of the studies[2,7,10,33–38,43]. Among them, Weedon-Fekjær and colleagues only adjusted their results for some of these factors. They used an age-period-cohort model and included variables across time for breast cancer screening, current use of HRT, age, and age at first childbirth[36]. Data about breast cancer screening are presented in Table 2.

Data regarding the results and conclusions of the studies are presented in Table 2. All the selected articles provided some information on breast cancer screening. In a few

Table 1 Epidemiological publications from different countries analyzing data on hormone replacement therapy (HRT) in relation to breast cancer (BC) incidence: material and methods

Author	*Publication country/period of assessment*	*Data sources on BC*	*Data sources on HRT*	*Size of the studied populations*	*Comments on method of analysis*	*Level of evidence*	*Adjustments*	*Limitations*
Ravdin[2]	USA (9 districts), 2001–2004	SEER program of NCI (9 cancer registries)	HRT data provided by previous studies	SEER program, 9% of US population		2c	Trends in incidence adjusted to standard population in 2000 and adjusted for reporting delays; age-standardization	Multiple imputation used to generate ER values for missing data; omitted years with rapid changes
Jemal[37]	USA, 1975–2003	SEER program of NCI (9 cancer registries); 1975–2003 stage of diagnosis; 1988–2003: tumor size; 1990–2003: ER+/PR+		394 891 invasive BC and 59 837 *in situ* BC	APC in BC incidence	2c	Age-standardization; analyses adjusted for delayed reporting	Analyses restricted to women aged ≥ 40; HRT data provided by previous studies but not presented in detail
Glass[33]	USA, 1980–2006	KPNW tumor registry	KPNW pharmacy database	KPNW female population: 255 171		2c	Age-standardization; adjusted for screening use and dispensed menopausal hormone therapy prescriptions	
De P[40]	Canada, 2001–2006	Canadian Cancer Registry	Data of Canadian retail pharmacies provided by health-care industry information company for prescription; HRT use reported from NPHS	196 159 BC diagnosed among Canadian women aged ≥ 40	APC	2c	Age-standardization	HRT use self-reported; overestimation of screening

(*Continued*)

Table 1 (*Continued*)

Author	*Publication country/period of assessment*	*Data sources on BC*	*Data sources on HRT*	*Size of the studied populations*	*Comments on method of analysis*	*Level of evidence*	*Adjustments*	*Limitations*
Canfell (update)[6]	Australia, 2001–2005	Australian Institute of Health and Welfare (data from state registries on cancers)	Medicare Safety Net scheme (subsidized HRT prescription, concession car holders)		Poisson regression	2c	Age standardization	Tibolone not included because not subsidized; trends in prescribing in this group were confirmed by comparison with other data sources (Australian statistics on medicines reports)
Soerjomataram[44]	Netherlands	Data from publications and comprehensive cancer centers	Data from publications			2c		
Hemminki[3]	Nordic countries, 1995–2005	Nationwide Cancer Registries	Finnish drug control authority, prescription registers in Finland, Norway and Sweden		Poisson regression	2c	Age-standardization	
Katalinic[7]	Germany, 1997–2005	BC registries, Federal Statistic Office (population data)	Health insurance data, DDD	163 100 BC in a population of 14.8 million women; 35% of German population was included	Pearson's correlation coefficients	2c	EASR of HRT use and BC incidence	Age-specific analyses for HRT were not possible; not all cancer registries could provide data for the whole study period
Lambe[10]	Sweden, 1997–2007	Data from three population-based Regional Clinical Registries on BC, women 50–69 years old	HRT sales from National Corporation of Pharmacies data, DDD	Registries on BC covering 62% of Swedish population (5 million inhabitants)		2c	Age-standardization	

Parkin[8]	Great Britain (England, Wales, Scotland), BC incidence 1975–2005, female sex hormone use 1992–2006	Statistical Information Service of Cancer Research UK, 1975–2005	GPRD (in women 15–85 years old), 1992–2006		'Excess relative risk' is estimated based on MWS	2c		Prevalence of use extrapolated; progesterone-only preparations assumed to be accompanied by estrogens
Pollán[38]	Spain, 1980–2004	16 population-based cancer registries (European Network of Cancer Registries)	HRT data provided by previous publications	26% of female population of Spain; 80 453 BC in female population of 5 298 119		2c	Age-standardization	Transposable to all Spanish women?; quality of registries variable; HRT use rare (previous studies)
Bouchardy[34]	Switzerland (Geneva), 1975–2006	Geneva cancer registry, 3 groups: 25–49 years, 50–60 years, > 70 years	Previous publications, APC	Canton of Geneva: ~ 450 000 inhabitants	'Deficit' in BC incidence estimated by difference between 2005–2006 and 2002–2003 in 50–69 age group	2c	Age-standardization	
Crocetti[39]	Italy, 1991–2004	Italian Network of Cancer Registries	Sparse publications	30% of Italian resident population (BC = 41 358)	APC	2c		Few data on HRT prescription (some publications)
Séradour (update)[42]	France, HRT use 2001–2007, BC incidence 2003–2007	Annual BC incidence rates, (National Institute for Statistics and Economics Studies)	HRT and mammography data from reimbursements databanks of the National Health fund			2c	Age-standardization	

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Table 1 (*Continued*)

Author	*Publication country/period of assessment*	*Data sources on BC*	*Data sources on HRT*	*Size of the studied populations*	*Comments on method of analysis*	*Level of evidence*	*Adjustments*	*Limitations*
Sharpe[35]	Scotland, 1997–2005	Scottish Cancer Registry (ISD)	Prescribing Information System (ISD) of NHS Scotland (E, E+P and others)		Poisson regression model	2c	Age-standardization	
Silverman[41]	Israel, 2000–2007	Israel National Cancer Registry and National Israeli Breast Cancer Detection Program	Maccabi Healthcare Services	25% of Israeli population; $n = 118\,724$ in 2000 to 154 447 in 2007	LOWESS and ARIMA models	3b	Cancer incidence modelled controlling for age, use of HRT in preceding year and screening mammography during preceding year	
Antoine (update)[43]	Belgium, 1999–2008 for Flanders and 2004–2008 for Brussels and Wallonia	Belgian Cancer Registry	IMS Health for sales data		Generalized estimating equations	2c	Adjustment for the number of women in each region; age-standardization	
Weedon-Fekjær[36]	Norway, 1987–2008	Norway's Cancer Registry	Wholesales drug statistics database (Norwegian Institute of Public Health)		Population study using aggregated data analyzed by extended age-period-cohort model	3b	Age standardization; age, age at first birth and number of children were also tested	

SEER, Surveillance, Epidemiology, and End Results registries; NCI, National Cancer Institute; ER, estrogen receptor; PR, progesterone receptor; APC, annual percent changes; KPNW, Kaiser Permanente Northwest health plan; NPHS, National Population Health Survey; EASR, European age-standardized rates; DDD, defined daily dose; GPRD, General Practice Research/Database; MWS, Million Women Study; ISD, Information Services Division; NHS, National Health Services; E, estrogens; P, progestogens

Table 2 Epidemiological publications from different countries analyzing data on hormone replacement therapy (HRT) in relation to incidence of breast cancer (BC): results and conclusions

Author	*Data on BC screening*	*Used estrogens and progestins*	*Change in HRT use*	*Change in BC incidence*	*Conclusions*
Ravdin[2]	Decrease of 3.2% in screening mammography rate for women aged 50–65 in 2003	Mainly CEE + MPA	−38% at end of 2002	Age < 50: + 1.3%; age 50–69: −11.8% (even more so in ER+: −14.7%); age ≥ 70: −11.1%	Probable relationship for ER+ tumors
Jemal[37]	Percentage of women who had a mammogram within past 2 years: 1999, 70.3%; 2000, 70.4%; 2003, 69.5%	Not specified	Not presented	2002–2003: age 55–59, −11.3%; age 60–64, −10.6%; age 65–69, −14.3%	2 patterns of decreases in BC: 1st in all ages due to screening saturation, 2nd from 2002 to 2003 in women 50–69 mainly in localized and ER+/PR+ tumors reflecting reduced HRT use
Glass[33]	For each year between 1993–2006, 75–79% of women > 45 years had a mammogram within past 2 years	Mainly CEE + MPA	1999–2006: CEE alone -69%; CEE + MPA −79%	APC incidence rates fell by 4.3% per year from 2001 to 2006, especially for 45–59 and ≥ 60 years	BC incidence rates, particularly for ER+ and localized tumors, parallel to changes in mammography screening and HRT use
De P[40]	Annual rates of mammography abstracted from NPHS; mammography rates rose sharply from late 1990s to 2000 among women aged 50–69 years; since 2000, rates stable at 72%	Mainly combined HRT	Age 50–69: −9.9%/year between 2002 and 2006; decline begins in 2001 but largest in 2002	Age 50–69: −8.0%/year between 2001 and 2004; decline in BC already before 2002, increase in BC in 2006	Link between HRT drop and BC decrease in absence of change of mammography habits
Canfell (update)[6]	Largely stable mammography rates in women aged 50–69 years: 2000–2001, 56.9%; 2002–2005, 56.2%	Not specified	2001–2005: −55%	2001–2005: -8.8% in women ≥ 50; no change < 50 years	Probable relationship

(*Continued*)

Table 2 (*Continued*)

Author	*Data on BC screening*	*Used estrogens and progestins*	*Change in HRT use*	*Change in BC incidence*	*Conclusions*
Soerjomataram[44]	Biannual mass screening with attendance rate >80% since early 1990s	Combined estrogen–progesterone and natural and semi-organic estrogen: *E2 61.2%; CEE 27.6%; NETA + MPA 64.6%; P derivatives 30.2%	13% of women aged 49–70 years used HRT between 1993 and 1997; HRT use decreased by 42% between 2001 and 2005	Incidence rate of BC has not changed until 2005	No change in BC incidence following HRT use drop but low level of use
Hemminki[3]	BC screening stable or expanding in Nordic countries in 2000s	Not specified	Sweden −60.6%; Norway −51.3%; Finland −24.8%; Iceland −42.8%	Decrease in Sweden 1998–2005: 50–54, −7.9%; 55–59, -10.8%; 60–64, +12.7%. Finland 2001–2005: 50–54, +9.3%; 55–59, +3.4%; 60–64, −3.7%. Iceland 1999–2005: 50–54, −40.3%; 55–59, −21.8%; 60–64, −23.4%. No decrease in Norway (1999–2005)	Correlation between HRT and BC is less clear than in the studies from US; time lag of 3–4 years; results more variable for 1-year lag
Katalinic[7]	Systematic mammography screening started between 2003 and 2005 and uptake still ongoing	80% HRT prescribed in age group 50–69 years; *CEE 54.9%; E2 37.5%; MPA + NETA 80%; P derivatives 19.5%	Decline in HRT (2001–2006): −59% in 6 years; decline started in 1999; decline E only 58% <E+ P 68%	Decrease in BC incidence of 12.8% in age class 50–69 between 2002 and 2005; 6.8% for all age groups; 40–49 and >70-year-old groups: no change	Correlation HRT–BC (the year after) ranging 0.83 ($p<0.01$) to −0.92 ($p<0.01$) in age group 50–69 years
Lambe[10]	Organized mammography screening began in 1974 and full national coverage achieved in 1997	Mainly E2 and NETA (MPA)	50–69 years: 1999, 27%; 2002, 23%; 2007, 9% (−70% between 1999 and 2007)	50–59 years old, 2003–2007: −4.5% per year ($p<0.05$); ER+ similar to all IC; no significant change for LCI or DCIS/LCIS	Time lag of 4–5 years between start of fall of HRT use and decline in BC incidence
Parkin[8]	National BC screening program introduced around 1990 for women aged 50–64 years; two-view mammography introduced since 1999; extended to women of 65–70 years in 2002	CEE 48%; E2 44%; MPA + NETA 65%	25% HRT use in age class 45–69 in 2000–2001; decrease by half in 2006; E + P –64%; E –49%	Since 1999: 50–59, −0.8% per year; 60–69, +4.1%	Excess risk due to HRT estimated around 27–31% in age class 50–60. Reduction by 14% due to HRT reduction

Pollan[38]	BC screening from 45–64 years or 50–64 years depending on region; full coverage year close to the change point of BC incidence	*E2 50.3%; other/ unknown 42.4%; P derivatives 78.9%	45–64 years: 1998, 5.9%; 2006, 4.2%	Decrease of 3.0% (95% CI 1.8–4.1%) per year from 2001, especially in the age group 45–64 years	Change in BC incidence best explained by screening saturation
Bouchardy[34]	Mammography screening program still expanding during period 2000–2003 and continues to expand	Not specified	2000–2002, 46% of women were HRT users; 2003, 31%	All ages: APC +1.7% ($p = 0.0001$); >70, APC −0.03% ($p = 0.8846$); 25–49, APC + 0.9% ($p = 0.0012$); 50–69, 1975–1986, APC −0.2% ($p = 0.7643$); 1986–2002, APC + 4.4% ($p = 0.0001$); 2002–2006, APC −6.0% ($p = 0.0264$)	Incidence of BC decreased with HRT use
Crocetti[39]	BC screening activation varied from 1991 (about 20% of municipalities) and 2000; >50% of municipalities activated 1997–1999	Not specified; *E2 71%; low-potency E 20.5%; P derivatives 83.9%; NETA + MPA 13.9%	HRT use may be estimated at about 10% with a decreasing trend in recent years	Since the 1990s: overall trend: −1.4%; 50–69, −2.2%	BC incidence seems to have changed several years before 2002 at the end of 1990s. BC incidence reduction seems to have resulted from introduction of screening
Séradour (update)[42]	Mammography use increased continuously in France between 1990 and 2005, and was stable in 2006 and 2007; participation rate: 2004, 40.2%; 2007, 50.8%	Not specified; *E2 61.4%; low-potency E 33.5%; micronized P 24.4%; P derivatives 68.6%	−64%, especially for women 50–64 years old	55–59 years, −14.7%; 60–64 years, −12.6%	Probable relationship in women older than 55 years
Sharpe[35]	BC screening introduced in 1988 for 50–64 and in 2003 for 65–70-year-olds; uptake: 1994, 71%; 2007, 76.5%	Not specified	All HRT categories 2000–2007: -61.8%; E + P −68.1%	ER+ BC, 2000–2005, −11.2%; ER− BC,1997–2005, −44.3%	Decline of BC incidence (especially for ER+) in age group 50–64 reflects fall in HRT use

(*Continued*)

Table 2 (*Continued*)

Author	*Data on BC screening*	*Used estrogens and progestins*	*Change in HRT use*	*Change in BC incidence*	*Conclusions*
Silverman[41]	Screening mammography: 2000, 18.0%; 2005, 34.1%	Mostly E + P	2000, 13.2%; 2007, 4.0%	BC incidence rose from 3.9 per 1000 in 2000 to 4.3 per 1000 in 2005	BC incidence increased in parallel with decreasing HRT use as a result of intensive mammography screening from 2004. Annual Cox proportional hazards modeling and ARIMA modeling demonstrated positive association between BC incidence and mammography or HRT thanks to individual data
Antoine (update)[43]	BC screening program began in 2000 and uptake still ongoing	Mainly E + androgenic progestins and E-alone or prescribed with a separate progestin	In the 3 regions HRT decreased about 57.5–59%	Flanders 2003–2006: overall population, −6.4%; 50–69, −12.2%; Brussels 2004–2006: overall population, stable; 50–69, −6.0%; Wallonia 2004–2006: overall population, −6.4%; 50–69: −9.9%	Significant association between invasive BC incidence rate and estimated rate of HRT users in previous year ($p < 0.001$)
Weedon-Fekjær[36]	BC screening program initiated in 1995. National coverage reached in 2004–2005 (78%)	Not specified; *E2 89.3%; NETA + MPA 99.3%		Especially in age group 50–69 years	Changes in BC incidence since 1990s may be attributed to screening and HRT (similar contribution)

CEE, conjugated estrogens; MPA, medroxyprogesterone acetate; ER, estrogen receptor; PR, progesterone receptor; APC, annual percent changes; NPHS, National Population Health Survey; NETA, norethisterone acetate; E2, estradiol; E, estrogens; P, progestogens; IC, invasive cancer, LIC: lobular invasive carcinoma; DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*.

*, From Bakken *et al.*[32]

countries, full coverage had been reached before the period of assessment[6,10,33,40,44] but, in the majority of the studied populations, screening uptake is still ongoing. Nevertheless, while many authors recognize that breast cancer screening may have an effect on breast cancer incidence, very few were able to adjust their analyses for this important confounding factor[36,41].

The type of HRT used was mentioned in only five studies[2,8,10,33,43] and could be found for six more studies from Bakken and colleagues[7,36,38,39,42,44]. Estradiol was prescribed more often in Europe except in Germany and the UK where CEE and estradiol were used. As it is well known, CEE was more often used in the USA[2,33]. Progestins that are testosterone derivatives such as NETA and levonorgestrel were much more common in Europe whereas the progesterone derivative MPA was the predominant progestogen in the USA. Progesterone derivatives represented 68.6–83.9% of prescribed progestins only in France, Italy and Spain[32].

Two studies did not present the changes in HRT use[37,38]. In Norway, these data were integrated in an age-period-cohort model and were not provided[36] and, in Italy, estimations of HRT use were very rough since only sparse data were available based on a few publications[39].

Fourteen out of 18 studies reported a decrease in HRT prescription (ranging between 25% and 80%) during the studied period[2,3,6–8,10,33–35,40–44].

Fourteen studies out of 18 reported a decrease in breast cancer incidence since the early 2000s[2,3,6–8,10,33–35,37,38,40,42,43]. Among them, 13 studies observed that this was especially the case in women 50 years old or more[2,6–8,10,33–35,37,38,40,42,43].

Fourteen studies also analyzed the evolution of breast cancer incidence in other age groups[2,3,6–8,10,34–40,43]. One study provided this information in the first publication only but not in the updated version[9,42]. Eleven of these studies observed no change in women younger than 50 years old[2,3,6–8,10,35,37,38,40,43], while four observed a moderate increase in breast cancer incidence[34,36,39,42].

The reported relative decrease in breast cancer incidence ranged from 5.6% to 40.3% but most were between 8 and 15%[2,3,6,7,35,37,38,40,42,43]. In Norway, Hemminki and colleagues reported no decrease in breast cancer incidence[3] while Weedon-Fekjaer and colleagues reported a modest decline[36]. There was no change in breast cancer incidence in the Netherlands[44]. During the study period, breast cancer incidence increased in Israel and Finland[3,41] and decreased very slowly in Italy[39]. In Canada, De P and colleagues showed, first a decrease in breast cancer incidence but then an increase in 2006[40].

The beginning of the decrease in breast cancer incidence may vary from 1999 (and even 1997 in Scotland for estrogen receptor-negative tumors[35]) to 2003[8,10]. Belgian data are not taken into account in this analysis because data on breast cancer incidence are only available from 2004 and for only a part of the country[43].

Five studies provided information on estrogen receptor (ER) status[2,10,33,35,37]. The data of the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program were analyzed by Ravdin and colleagues[2] and Jemal and colleagues[37] who showed that ER-positive tumor incidence dropped sharply in conjunction with HRT use while the decrease of ER-negative tumors occurred more progressively and to a lesser extent. The decreases were respectively of 14.7% and 9.1% for ER-positive tumors and 1.7% and 1.1% for ER-negative tumors. It should be noted that few data on ER-negative tumors are available. Sharpe and colleagues[35] in Scotland reported a decrease in ER-positive and -negative tumors but the decline in ER-positive tumors was concomitant with the drop in HRT use (increase from 1997 to 2000 by 31.5% then decrease by 11.2% by 2005), while the ER-negative tumor decline pre-existed and was unaffected by the decline in HRT use (decrease of 44.3% from 1997 to 2005). Lambe and colleagues[10] reported, in the Swedish population, a decreased incidence for ER-positive tumors only but not for ER-negative tumors. Finally, in the Kaiser Permanente Northwest health plan (KPNW) data, the incidence profile of ER-positive tumors was similar to the profile of global breast cancer incidence (increase until 2001 then decrease of 2.7% from 2001 to 2006) while ER-negative tumors did not increase before 2000 but also dropped rapidly after 2000 (decrease of 9.8% from 1999 to 2006)[33].

Breast cancer histological subtypes were analyzed by Lambe and colleagues[10]. These authors observed a decrease of invasive ductal carcinoma (IDC) but invasive lobular carcinoma (ILC) and *in situ* breast cancer remained stable.

In the United States, Ravdin and colleagues reported a similar decrease for localized and more advanced disease[2]. They found a significant change only for primary breast cancer and not contralateral breast cancer. Jemal and colleagues described a significant decrease for small tumors (−4.1%) and localized tumors only (−3.1%)[37]. Data from the KPNW health plan showed that the localized tumor rate fell in the 2000s while the metastasis rate declined steadily since 1980[33].

Ten studies out of 18 concluded that there is a probable relationship between the decrease in HRT use and the decrease in breast cancer incidence[2,6–8,34,35,40–43] especially for women aged 50 years or more or for ER-positive tumors[2,6–8,34,35,40,42,43]. Three studies concluded that the decrease in HRT use and mammography screening saturation are both implicated in the lesser breast cancer incidence[33,36,37]. Two Scandinavian studies concluded that the time between the lower HRT use and the decrease in breast cancer incidence is longer than in other countries and that correlation between these observations is less clear than in other countries[3,10]. In the Netherlands, there was no correlation between the decrease in HRT use and the decrease in breast cancer incidence, but the level of HRT use has always remained very low there[44]. In Spain, screening saturation better explains than HRT use the drop in breast cancer incidence[38]. In Italy, the decrease in breast cancer incidence had started before the WHI publication and there was no sharp decline thereafter. The evolution of breast cancer incidence after the WHI publication seems to be more correlated to activation of breast cancer screening than to the decline in HRT use[39].

DISCUSSION

Most of the studies came to similar conclusions, i.e. that the decrease in breast cancer incidence during the last decade was probably associated with the decrease in HRT use, even if the time between these two parameters may vary between countries. Indeed, this was especially the case for women aged 50 years or more but not for those younger than 50 years (who generally do not use HRT)[2,3,6–8,10,34,35,40–43].

It remains difficult, however, to evaluate the exact impact of the drop in HRT use on the decrease in breast cancer incidence. Half of the studies were simply descriptive and all, with the exception of two, which are based on individual data, were ecological studies (Table 1). These studies used aggregate data to explore correlations and time trends, but no information on individual data was available[46]. Ecological studies have a level of evidence 2c and individual case–control studies a level of evidence 3b (Evidence based medicine centre, Oxford University). Their recommendation grade is B.

Breast cancer incidence and HRT prevalence were extrapolated from many sources and approximations were often needed when analyzing them.

Five studies out of 18 analyzed the ER status and four of them described a more pronounced decrease for ER-positive tumors. These are more influenced by HRT[47]. Some studies, not included in the review because their first aim was not the evolution of breast cancer incidence in relation to the evolution of HRT use, reported declining rates of ILC that were more substantial than those of IDC[48,49]. This may be consistent with the influence of HRT use rather than breast cancer screening, since ILC may be more influenced by HRT use and is not detected primarily through mammography. Nevertheless, Lambe and colleagues[10] and other investigators were unable to report such findings[50,51]. The results remain therefore conflicting.

The reported breast cancer incidence is also strongly influenced by available screening programs. Some studies concluded that the breast cancer incidence was related to HRT use and breast cancer screening or even to screening alone[33,36–39]. In some countries, population-based screening programs do not exist yet, in others they have been implemented recently, in some others the rollout has been completed but the uptake is still increasing and in others the uptake is already high (Table 2). This may have considerable impact on the reported breast cancer incidence, since the introduction of a screening program generally increases initially, but only for a few years, the number of cancer cases. Then this period is followed by a period of decreased cancer incidence, before reaching stabilization[52,53].

Confounding factors such as reproductive factors and environmental factors (i.e. obesity, alcohol intake, smoking status, physical activity, medication use) may also have a more profound impact in some countries than in others and may change with time[52]. For instance, fertility rates have decreased in most countries, but not in all (Eurostat report). Furthermore, breast cancer incidence varies considerably between countries (for instance from about 60/100 000 in Romania and Greece to more than 140/100 000 in Belgium in 2008) (Eurostat report, http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/)[54]. These reported incidences may be influenced, for instance, by ethnic variability and genetic predisposition. Recent studies reported interference between genetic predisposition and HRT[55].

Finally, the reported breast cancer incidence also depends on the quality of the reporting of cancer cases in cancer registries, which may also vary between countries and with time.

Most authors of these studies acknowledged the various sources of potential biases such as mammography screening bias or changes in reproductive and lifestyle habits[2,7,10,33–38,41,43], but only two tried to adjust their results for some of these confounding factors[36,41]. Various arguments have been highlighted to explain why the HRT decrease and not breast cancer screening is at the origin of the observed decrease in breast cancer incidence:

(1) In some countries, the uptake of breast cancer screening is still increasing and an increase in breast cancer incidence would be expected rather than a decrease[3,7,8,42,43].
(2) A decline in HRT use was the only substantially modified breast cancer risk factor during the studied period, suggesting a causal link[2,7,10].
(3) In countries with similar levels of breast cancer screening or in countries where breast cancer screening was stable, a decrease in breast cancer incidence was observed only in those associated with an important drop in HRT use[6,34,40].
(4) In some countries, a decrease in breast cancer incidence was observed even before the publication of the WHI trial. Some authors linked this to a first drop in HRT use, following the publication of the HERS study[33,40].
(5) Ductal carcinoma *in situ* (DCIS) is more often detected by mammography. Several authors consider that DCIS incidence can be used as a surrogate marker for measuring mammography saturation and utilization[56,57]. In Sweden, where the incidence rates of DCIS remained stable, indicating no major changes in the use of mammography, HRT and breast cancer decreased nevertheless[10].

Recent publications enhance that screening conducts to a substantial overdiagnosis of breast cancer and has a relatively low effect on breast cancer mortality[58,59]. Moreover, HRT drop also seems associated with a drop in mammography rates[60]. This makes the analysis of the relationship between HRT and breast cancer even more complicated.

Still, some other potential biases have not been studied, such as the change in prescription habits. HRT consumption and the type of HRT regimens varied greatly between countries even before the WHI[61]. Following the WHI reports, physicians more often prescribed, for osteoporosis, bisphosphonates and raloxifene (which may actually reduce breast cancer risk), for cardiovascular prevention, statins (which may also reduce breast cancer risk)[62] and so-called 'safer HRT regimens'[63]. These include estrogen-only therapy, combined HRT regimens using low- or ultra-low-dose estrogens, progesterone

or didrogesterone instead of NETA or MPA, and tibolone[64,65]. Indeed, while the WHI trial, using combined HRT (CEE + MPA) reported an increased breast cancer risk, a reduction of breast cancer risk was reported using estrogen-only therapy and tibolone[11,66,67].

In the last report of the E3N study, an increased breast cancer risk was also reported, although to a lesser extent, in estrogen-only users or users of estrogen combined with micronized progesterone or dydrogesterone[13]. Finally, a recent Fin Observation study reported that sequential progestin use resulted in a trend toward a smaller increase in relative risk for breast cancer compared to continuous progestin use, but one should note that in this study most patients used NETA[14].

The type of HRT used was available for half of the studies and most of them evaluated the use of combined regimens of estrogens with either CEE + MPA or estradiol + NETA[68,69].

The mechanism by which HRT may promote breast cancer is still an open question. Many have hypothesized that HRT leads to an increase in the diagnosis of occult and previously undiagnosed breast cancer[10,70,71]. The disappearance of an increased risk after cessation of HRT, with similar mammographic frequency of screening, as observed in the WHI trial, is in favor of this hypothesis[72]. In this review, two studies out of three showed a more pronounced decrease for localized tumors[33,37]. Prevention trials of breast cancer with selective estrogen receptor modulators (SERMs) and aromatase inhibitors also reported a protective effect after short periods of treatment in unaffected women[73–75]. Furthermore, the impact of HRT on breast cancer risk and other diseases seems to be influenced by the elapsed time since menopause. A Danish randomized trial was recently published and showed a reduced risk of mortality, heart failure or myocardial infarction, without any increased risk of cancer, venous thromboembolism or stroke in women receiving HRT soon after menopause[76].

Some studies suggest that HRT-induced breast cancer has a better prognosis than non-induced breast cancer and would be diagnosed at an earlier stage since HRT users are screened more often, but these data are, again, conflicting[77–81].

Still, if the elevated risk after initiation of HRT and its rapid decrease after stopping medication are due in part to the promotion of pre-existing tumors, then this may also explain a rapid drop in breast cancer immediately following the decrease of HRT use in 2002, but this decrease should not have lasted for long and should have leveled out after the initial years. Most studies had long periods of evaluation but data on breast cancer incidence were rarely available after 2006–2007. In some studies, follow-up stopped soon after the WHI trial publication (Table 1). Only De P and colleagues, in Canada, observed a decrease in breast cancer incidence after the publication of the WHI study and then an increase of this incidence in 2006[40].

On the other hand, some recent fundamental research data suggest that at least some progestins are involved in breast cancer tumorogenesis. Indeed, synthetic progestins can promote mammary tumor formation in mouse models, by inducing the osteoclast differentiation factor RANKL, which acts on mammary epithelial cells through the RANKL receptor RANK[82]. Inhibition of RANKL, on the other hand, reduces tumorigenesis in hormone-induced mammary epithelium as well as in other mouse mammary gland tumor models[83].

Finally, one should be cautious when drawing conclusions from retrospective ecological studies. Such studies are subject to publication bias, as authors and journals may be more prone to publish results that show a significant association. Reduction of incidences of other diseases or mortality-related diseases have also been described during the last decades for cardiovascular disease, stroke, and osteoporosis[84,85]. Often, the authors of these publications have also tried to associate these decreases in incidence rates to either improved care, use of new medication or to a reduction in the prevalence of some risk factors but these are yet to be proven. Indeed, there are data suggesting that the relationship between a risk factor (for example obesity), and a disease (cardiovascular disease) may not be stable through time[86].

In conclusion, many data support the idea that the drop in breast cancer incidence can be partly attributed to the decrease in HRT use. Still, ecological studies are hampered by a number of limitations and it remains difficult to evaluate the exact impact of a HRT drop on the decrease in breast cancer incidence.

In clinical everyday practice, medical relief of menopausal symptoms remains necessary for many women and HRT is the most effective treatment. Many recent studies tend to rehabilitate HRT at least for younger women, where benefits may be important and risks very limited[76,87]. In this context, it is crucial to assess the extent of the risks that women take when using HRT[88].

It is necessary, therefore, to obtain detailed individual data on regimens used, type of cancers and possible confounding factors, in order to better analyze the relationship between breast cancer incidence and HRT use, in various populations. Indeed, it is likely that these risks may be population- and even regimen-dependent. This article advocates for the constitution of a prospective European database allowing assessment of the breast cancer–HRT relationship.

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