Articles

Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer

*Collaborative Group on Hormonal Factors in Breast Cancer**

Summary

Background The Collaborative Group on Hormonal Factors in Breast Cancer has brought together and reanalysed about 90% of the worldwide epidemiological evidence on the relation between risk of breast cancer and use of hormone replacement therapy (HRT).

Methods Individual data on 52 705 women with breast cancer and 108 411 women without breast cancer from 51 studies in 21 countries were collected, checked, and analysed centrally. The main analyses are based on 53 865 postmenopausal women with a known age at menopause, of whom 17 830 (33%) had used HRT at some time. The median age at first use was 48 years, and 34% of ever-users had used HRT for 5 years or longer. Estimates of the relative risk of breast cancer associated with the use of HRT were obtained after stratification of all analyses by study, age at diagnosis, time since menopause, body-mass index, parity, and the age a woman was when her first child was born.

Findings Among current users of HRT or those who ceased use 1–4 years previously, the relative risk of having breast cancer diagnosed increased by a factor of 1·023 (95% CI 1·011–1·036; 2p=0·0002) for each year of use; the relative risk was 1·35 (1·21–1·49; 2p=0·00001) for women who had used HRT for 5 years or longer (average duration of use in this group 11 years). This increase is comparable with the effect on breast cancer of delaying menopause, since among never-users of HRT the relative risk of breast cancer increases by a factor of 1·028 (95% CI 1·021–1·034) for each year older at menopause. 5 or more years after cessation of HRT use, there was no significant excess of breast cancer overall or in relation to duration of use. These main findings did not vary between individual studies. Of the many factors examined that might affect the relation between breast cancer risk and use of HRT, only a woman's weight and body-mass index had a material effect: the increase in the relative risk of breast cancer associated with long durations of use in current and recent users was greater for women of lower than of higher weight or body-mass index. There was no marked variation in the results according to hormonal type or dose but little information was available about long durations of use of any specific preparation. Cancers diagnosed in women who had ever used HRT tended to be less advanced clinically than those diagnosed in never-users. In North America and Europe the cumulative incidence of breast cancer between the ages of 50 and 70 in never-users of HRT is about 45 per 1000 women. The cumulative excess numbers of breast cancers diagnosed between these ages per 1000 women who began use of HRT at age 50 and used it for 5, 10, and 15 years, respectively, are estimated to be 2 (95% CI 1–3), 6 (3–9), and 12 (5–20). Whether HRT affects mortality from breast cancer is not known.

Interpretation The risk of having breast cancer diagnosed is increased in women using HRT and increases with increasing duration of use. This effect is reduced after cessation of use of HRT and has largely, if not wholly, disappeared after about 5 years. These findings should be considered in the context of the benefits and other risks associated with the use of HRT.

Lancet 1997; **350:** 1047–59

See Commentaries pages 1042, 1043

Introduction

For almost half a century various oestrogens and progestagens have been prescribed to replace the cyclical production of ovarian hormones that normally ceases at the menopause. In the early years such hormone replacement therapy (HRT) was mostly in the form of oestrogenic compounds, but other hormones, mostly progestagens, have been increasingly used in combination with oestrogens. The relation between risk of breast cancer and use of HRT has been investigated in many epidemiological studies.[1-61] The Collaborative Group on Hormonal Factors in Breast Cancer has brought together and reanalysed the worldwide data on this topic.

Methods

Identification of studies and collection of data

Epidemiological studies were eligible for the collaboration if they included at least 100 women with breast cancer and had obtained information from each woman on the use of HRT and on factors related to reproduction and the menopause. Studies were identified from review articles, literature searches, and discussions with colleagues. Principal investigators of eligible studies were invited to take part in the collaboration. All collaborators were then sent a list of studies and key references and were asked if they knew of additional studies, published or unpublished, that were not listed. Few additional studies have come to light from these enquiries, and in view of the wide consultation it seems unlikely that any substantial studies were missed. Of the 63 eligible studies identified, original data were contributed by 51, 49 published[1-49] and two unpublished. Original data could not be retrieved for ten studies[50-59] and one research group declined to collaborate.[60,61]

Data on individual women were sought so that analyses could, as far as possible, use similar definitions across studies. For each

*Collaborators and analysis and writing committee listed at end of paper

Correspondence to: Prof Valerie Beral, Secretariat, ICRF Cancer Epidemiology Unit, Gibson Building, Radcliffe Infirmary, Oxford OX2 6HE, UK

case-control study, data were sought on the use of HRT, sociodemographic factors, family history of breast cancer, height, weight, age at menarche, reproductive history, use of hormonal contraceptives, gynaecological surgery, whether menstrual periods had ceased, and, if so, the age at which they ceased and the reason for cessation. Prospective studies were included by means of a nested case-control design in which four controls were randomly selected for each woman with breast cancer and similar data were sought for each case and control. The method of selecting controls has been described elsewhere.[62,63]

Consistency and comparability of data

Many consistency checks were made. Apparently inconsistent, implausible, or missing data were clarified and, where possible, rectified by correspondence. After the records had been checked and corrected, investigators were asked to check summary tables and listings of the variables that were to be used in the analysis. Additional corrections were made, if necessary, and the process was repeated until no further corrections were required.

Details of the study design, methods of data collection, and the participants in each study included in previous reports by the Collaborative Group have been summarised elsewhere.[63] Data from seven additional studies are included in this report.[3,19,36,40,42,46,48] Information on the use of HRT, reproductive factors, and the menopause had been collected in fairly similar ways in most studies, so generally similar definitions could be used across studies.

Current use of HRT was defined as use at the time of or within 12 months of the diagnosis of breast cancer (or of pseudodiagnosis for controls). Information on the specific hormonal constituents of the therapy used was available for 22 studies[1,2,4,5,8,11,13-15,19,22,29,31,33,37-39,41,45,46] (and two unpublished studies), and details of the specific type and dose of oestrogen, progestagen, or any other substance in each preparation were compiled centrally. Where possible, the preparation used most by each woman was ascertained and women were grouped according to whether they had predominantly used preparations containing oestrogens alone, preparations containing both oestrogen and progestagen or progestagens alone, or preparations containing oestrogen together with some other compound. Women who had predominantly used preparations containing oestrogens alone were also subclassified according to the type and dose of oestrogen used.

In all analyses cases were defined as women with invasive breast cancer, and controls were defined as women without breast cancer. Information on tumour spread was available for 21 studies[1,4,7,13,14,16,17,21,25,28,33-35,37-39,43,45,46] (and two unpublished studies), and for those, women with invasive breast cancer were further classified according to tumour localisation (localised to the breast or spread beyond the breast), by means of criteria described elsewhere.[62,63]

Conventions were adopted to ensure that menopausal status and age at menopause were defined as consistently as possible across studies. The aim was to classify each woman according to whether or not her ovaries were likely to be producing hormones cyclically at around the time that her breast cancer was diagnosed (or at pseudodiagnosis for controls) and, if not, her age when cyclical ovarian function was likely to have ceased. Women who were reported to be still menstruating at the date of diagnosis/pseudodiagnosis were classified as premenopausal; the small proportion of women (1·5% of the total) whose menstruation was reported to have ceased during the year of diagnosis/pseudodiagnosis were also classified as premenopausal because it was not always clear whether the cessation was a consequence of treatment. Women were classified as postmenopausal if a natural menopause or cessation of menstruation because of bilateral oophorectomy or irradiation of the ovaries was reported. Women reported to be perimenopausal and those who had undergone hysterectomy without bilateral oophorectomy before the natural menopause were classified in separate categories.

For postmenopausal women, age at menopause was generally defined as the age when menstruation ceased. However, women reported to have started HRT use before their stated age at natural menopause were classified as having an unknown age at menopause, since it was unclear when their cyclical ovarian function had ceased. Women reported to be perimenopausal and those who had undergone hysterectomy without bilateral oophorectomy before the natural menopause were also classified as having unknown age at menopause, again because it was unclear when their cyclical ovarian function had ceased, if at all.

Menopause category	Cases (n=52 705)	Controls (n=108 411)
Premenopausal	21 661 (41%)	43 443 (40%)
Perimenopausal	1567 (3%)	2249 (2%)
Postmenopausal		
Total	22 189 (42%)	45 181 (42%)
Natural menopause	18 755	37 623
Bilateral oophorectomy*	3434	7558
Hysterectomy before menopause	5539 (11%)	12 368 (11%)
Unknown	1749 (3%)	5170 (5%)

*Includes 94 cases and 115 controls with menopause due to irradiation of ovaries.

Table 1: **Distribution of cases and controls according to menopause category**

In prospective studies, additional conventions were necessary to define use of HRT, menopause category, and age at menopause at the time of diagnosis/pseudodiagnosis from information that was recorded at the time of last contact with the woman. If less than 2 years had elapsed between the date of last contact and the date of diagnosis/pseudodiagnosis, variables relating to menopause and use of HRT were taken to be those last recorded. Otherwise, details of use of HRT and of menopause (in previously premenopausal women) were classified as unknown, the only exception being for previously premenopausal women aged under 40 years at diagnosis/pseudodiagnosis, who were assumed to be premenopausal.

Statistical analysis

The statistical methods used were identical to those used in analyses of risk of breast cancer in relation to the use of hormonal contraceptives.[62-66] Data from different studies were combined by means of the Mantel-Haenszel stratification technique, the stratum-specific quantities calculated being the standard "observed minus expected" (O − E) numbers of women with breast cancer, together with their variances and covariances.[64,65] Use of these simple stratified O − E values in preference to more complex mathematical models sacrifices a little statistical power but has the advantage of avoiding assumptions about the precise forms of any relations in the data. The stratified O − E values, together with their variances and covariances, yield both statistical descriptions (odds ratios, subsequently referred to as relative risks) and statistical tests (p values). Relative-risk estimates were obtained from O − E values by the one-step method,[64] as were their standard errors (SE) and confidence intervals (CI) when only two groups were being compared. All relative risks are presented without further modification, but when more than two groups were compared, the variances were estimated by treatment of the relative risks as floating absolute risks.[66] This approach yields floated standard errors (FSE) and floated confidence intervals (FCI). The use of floating rather than conventional methods does not alter the relative risks but slightly reduces the variances attributed to the relative risks that are not defined as 1·0, and also reduces unwanted covariances between them. Presentation of the results in this way enables valid comparisons between any two exposure groups, even if neither is the baseline group. Any comparison between groups must take the variation in each estimate into account.

To ensure that women in one study were compared directly with similar women in the same study, all analyses were routinely stratified by study, by centre within study, and by fine divisions of age at diagnosis (16–19, 20–24, 25–29, by single year from 30 to 79, 80–84, and 85–89). In addition, analyses were stratified by

a: By menopausal status and age at menopause

	Cases/Controls	RR (FSE)*
Premenopausal	20165/41561	1.00 (0.026)
Perimenopausal	1171/1728	0.77 (0.045)
Postmenopausal		
By age at natural menopause (years)		
<35	64/168	0.46 (0.108)
35-39	230/544	0.51 (0.062)
40-44	1125/2655	0.62 (0.032)
45-49	3597/7552	0.70 (0.020)
50-54	5363/9135	0.81 (0.021)
≥55	1094/1541	0.85 (0.044)
By age at bilateral oophorectomy (years)		
<35	88/268	0.48 (0.091)
35-39	122/295	0.65 (0.096)
40-44	225/464	0.65 (0.072)
45-49	303/570	0.72 (0.068)
≥50	256/376	0.90 (0.089)

b: By menopausal status and time since menopause

	Cases/Controls	RR (FSE)*
Premenopausal	20165/41561	1.00 (0.026)
Perimenopausal	1171/1728	0.77 (0.045)
Postmenopausal		
By time since natural menopause (years)		
1-4	2656/5600	0.70 (0.025)
5-9	2808/5512	0.66 (0.024)
10-14	2394/4339	0.59 (0.028)
≥15	3615/6144	0.50 (0.031)
By time since bilateral oophorectomy (years)		
1-4	190/386	0.86 (0.095)
5-9	206/383	0.70 (0.081)
10-14	188/370	0.52 (0.072)
≥15	410/834	0.48 (0.051)

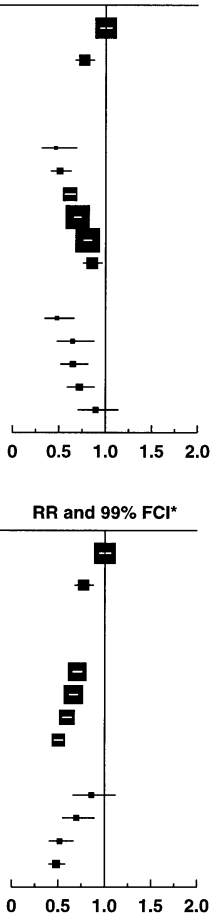


Figure 1: Relative risk (RR) of breast cancer in relation to menopause in women who had never used HRT

*Relative to premenopausal women, stratified by study, age at diagnosis, parity, and the age a woman was when her first child was born. Floated SE (FSE) and CI (FCI) calculated from floated variance for each exposure category (see methods).[66] Any comparison between groups must take variation in each estimate into account.

Each analysis based on aggregated data from all studies. Black squares indicate RR, area of which is proportional to amount of information contributed (ie, to inverse of variance of logarithm of RR). Lines indicate 99% FCI (lines are white when 99% FCI are so narrow as to be entirely within width of square).

parity and age at first birth with nulliparous women assigned to a separate stratum, parous women cross-classified according to their age when their first child was born (<20, 20–29, ⩾30) and their parity (one or two, three or more); women with unknown parity or age at first birth were assigned to a separate stratum. For many analyses, postmenopausal women were also stratified by time since menopause (1–4, 5–9, 10–14, ⩾15 years) and by body-mass index (<25 kg/m^2, ⩾25 kg/m^2).

For most analyses, results are presented as plots of squares and lines, representing the relative risks and CI/FCI, respectively. The position of the square indicates the value of the relative risk, and its area is inversely proportional to the variance of the logarithm of the relative risk, thereby providing an indication of the amount of statistical information available for that particular estimate. Owing to the large number of relative-risk estimates calculated, 99% CI/FCI are used in all plots and 95% CI are used to summarise the main findings only. The precise stratification and method used to calculate variances are specified for each plot.

Results

Most of the 51 studies in this collaborative reanalysis were carried out in North America or Europe, although 21 countries are represented. Together, the studies included 52 705 women with invasive breast cancer (cases) and 108 411 women without breast cancer (controls).

Relation of menopause to risk of breast cancer and use of HRT

The effect of menopause on risk of breast cancer and the pattern of HRT use is described here because these findings provide a background to the approach used in subsequent analyses. Most of the women were premenopausal (40%) or postmenopausal (42%); a small proportion were perimenopausal (2%), and 11% had undergone hysterectomy without bilateral oophorectomy before the natural menopause (table 1). Of postmenopausal women, 84% had had a natural menopause and 16% bilateral oophorectomy. The median age at natural menopause was 50 years; 77% of women reported that their age at menopause was between 45 and 54 years. The median age at bilateral oophorectomy was 44 years (between the ages of 35 and 49 years in 68%).

To examine the effect of the menopause on the risk of breast cancer independently of the effect of HRT, these analyses were restricted to women who had never used HRT. Postmenopausal women had a lower risk of breast cancer than premenopausal women of the same age and childbearing pattern, and the relative risk of breast cancer increased with increasing age at menopause (figure 1a). The relation between age at menopause and breast cancer risk was similar for women whose menopause was natural and for those whose menopause was the result of bilateral oophorectomy; the relative risk increased by 2·9% (SE 0·3) and 2·4% (1·0), respectively, for each year older at menopause (χ^2 for heterogeneity [1 df] 0·9; p=0·34). The overall increase was 2·8% (0·3) per year, and the younger women were when breast cancer was diagnosed, the greater the increase in breast cancer risk with age at menopause: the relative risk for each year older at menopause increased by 4·0% (SE 0·5), 2·5% (0·4), and 1·3% (0·7), respectively, for women aged 50–59, 60–69, and 70–79 at the time of diagnosis (χ^2 for heterogeneity [2 df] 9·9; p=0·007).

For women of a given age, age at menopause also defines their time since menopause, and so the relation of breast cancer risk with time since menopause is the inverse of its relation with age at menopause (figure 1b). Women whose menopause occurred 1–4 years before diagnosis had a substantially lower risk of breast cancer than premenopausal women of the same age and childbearing history. Thereafter, the relative risk of breast cancer among postmenopausal women declined progressively with time since menopause (decrease 2·7% [0·3]) for each year after menopause. This trend did not differ significantly between women with a natural menopause and women with bilateral oophorectomy

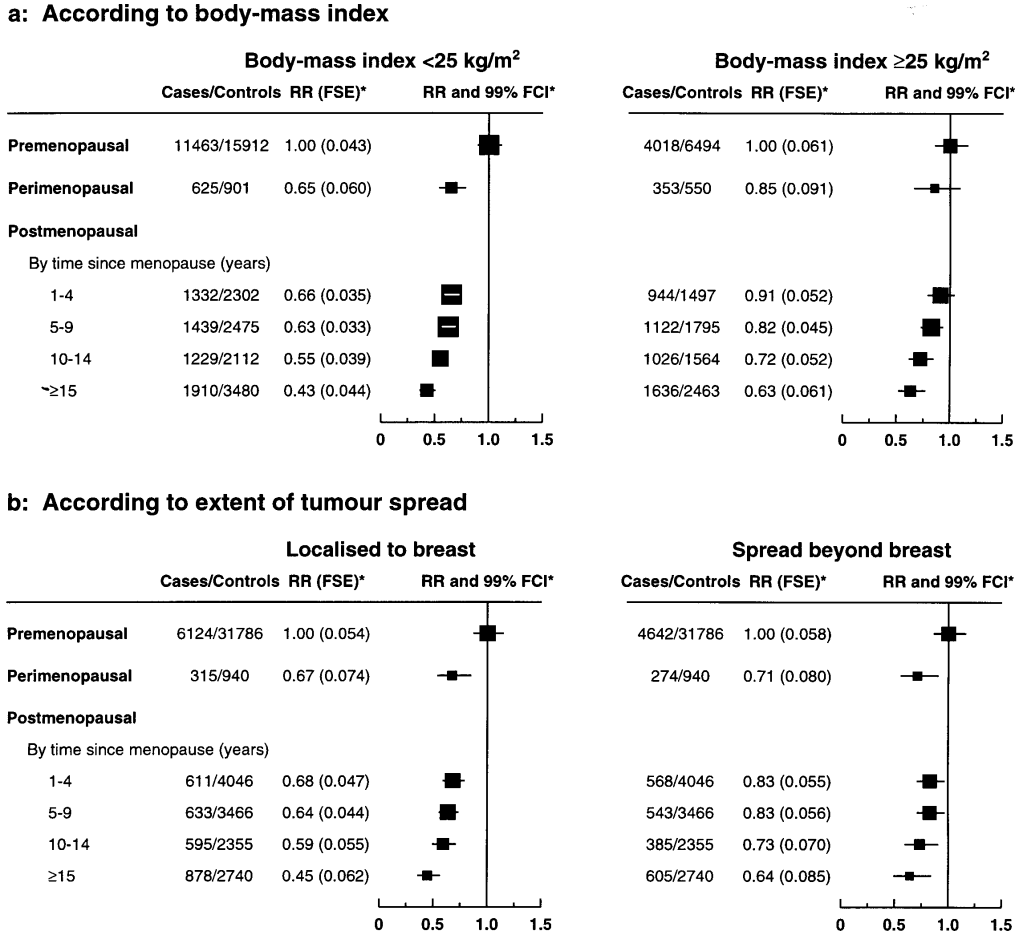


Figure 2: Relative risk (RR) of breast cancer in relation to menopause, body-mass index, and extent of tumour spread for women who had never used HRT

*Relative to premenopausal women, stratified by study, age at diagnosis, parity, the age a woman was when her first child was born, and (in b only) body-mass index. FSE, FCI, and format as in figure 1.

(2·8% [0·3] *vs* 2·3% [1·0], χ^2 for heterogeneity [1 df] 1·4; p=0·24). The risk of breast cancer in perimenopausal women relative to that of premenopausal women of the same age and childbearing history was 0·77, which is similar to the relative risk for women in the 1–4 years after menopause.

In postmenopausal women, the relative risk of breast cancer was related to body-mass index, increasing by 3·1% (0·4) per kg/m^2. The magnitude of the reduction in the relative risk of breast cancer after the menopause was also related to body-mass index, the difference between postmenopausal and premenopausal women being substantially greater for women of low body-mass index than for those of higher body-mass index (figure 2a; χ^2 for heterogeneity [1 df] 12·7; p=0·0004). The reduction in relative risk of breast cancer associated with the menopause was greater for localised cancer than for cancer that had spread beyond the breast (figure 2b; χ^2 for heterogeneity [1 df] 4·3; p=0·04). The relations shown in figure 2 did not differ significantly between women with natural menopause and with bilateral oophorectomy or between women of different ages at diagnosis.

The use of HRT is closely linked to the menopause. Overall, 19% of controls reported use of HRT at some time, but the prevalence of ever-use varied widely across the categories of menopause. For example, ever-use was more common among controls who had undergone bilateral oophorectomy (63%) or hysterectomy without oophorectomy (46%) than among controls who had experienced a natural menopause (22%). The pattern of use was further affected by the time since the menopause: postmenopausal controls whose menopause was less than 10 years previously were more likely to be current users of HRT than were postmenopausal controls whose menopause was 10 or more years previously (17 *vs* 9%), but those with menopauses less than 10 years previously were less likely to have used HRT for a duration of 5 years or longer (4 *vs* 9%).

Among postmenopausal controls, ever-use of HRT was also related to body-mass index (38% among women of body-mass index <25 kg/m^2 *vs* 31% for those of body-mass index ≥25 kg/m^2). Women in the lower body-mass-index category were more likely to be current users (18 *vs* 13%) and to have used HRT for 5 years or longer (9 *vs* 6%).

Thus, these analyses show that for women of a given age and childbearing pattern who have never used HRT the relative risk of breast cancer is affected by menopausal status and by recency of menopause. Since use of HRT is also strongly related to these characteristics, there is substantial scope for confounding between the effects of the menopause and the effects of HRT on risk of breast cancer. Indeed, for women who begin using HRT at the time of their menopause and do so continuously, their

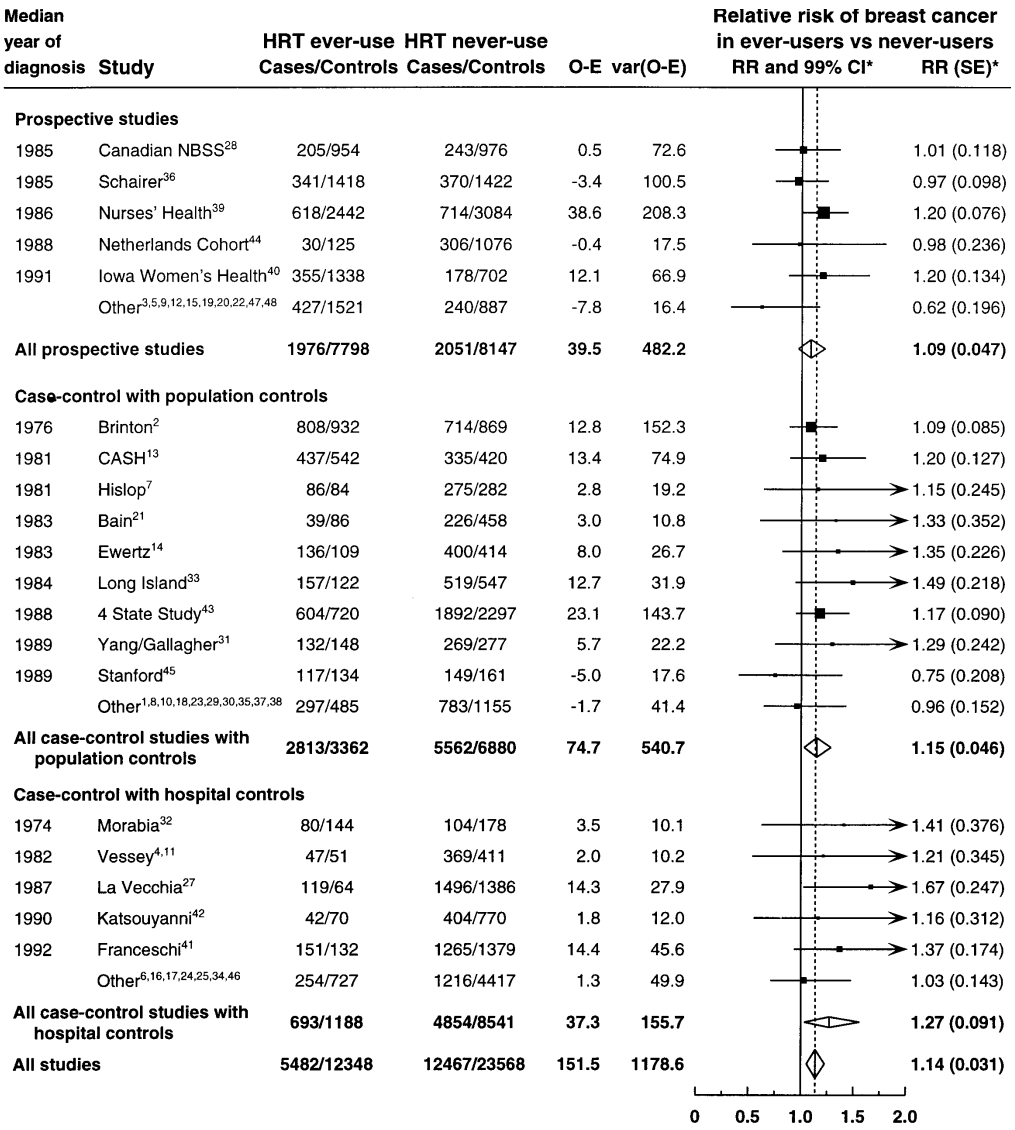


Figure 3: Relative risk (RR) of breast cancer in ever-users compared with never-users of HRT

*Relative to never-users, stratified by study, age at diagnosis, time since menopause, body-mass index, parity, and the age a woman was when her first child was born. SE and CI are not floated. Separate results given for studies with O−E≥10. Area of square is proportional to amount of statistical information contributed and length of line indicates 99% CI. Diamonds indicate 99% CI for totals. Broken line indicates relative risk for all studies combined.

Test for heterogeneity between study designs χ^2 (2 df) 3·2, p=0·20. Test for heterogeneity between studies χ^2 (21 df) 26·3, p=0·20.

total duration of use of HRT is equal to their time since menopause. Careful account must therefore be taken of time since menopause when looking at the relation between use of HRT and risk of breast cancer. A woman's relative weight can also confound such a relation, since body-mass index is related both to risk of breast cancer and to use of HRT in postmenopausal women. We therefore stratified all these analyses by time since menopause and by body-mass index, as well as by study, age, and reproductive history. Since the trends according to time since menopause are similar for natural menopause and bilateral oophorectomy, these are not treated separately in the stratification. The main analyses exclude all premenopausal and perimenopausal women and all postmenopausal women with an unknown age at menopause.

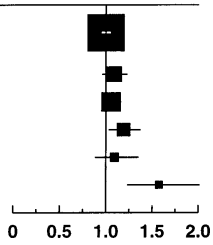
Ever-use of HRT and relation to breast cancer risk

The main analyses of the relation between risk of breast cancer and use of HRT include 53 865 postmenopausal women (17 949 cases and 35 916 controls) with known age at menopause and known use of HRT. The median year of birth of these women was 1925 and the median year of diagnosis/pseudodiagnosis was 1985. 85% were parous, with an average parity of 3·1. For the women with breast cancer, the median age at diagnosis was 60 years. 5482 (30%) of the cases and 12 348 (34%) controls had used HRT at some time. The overall median age at first use was 48 years, and 96% of users started use before age 60. The median age at last use was 53 years, and 92% of users stopped use before age 65. The median age at diagnosis or pseudodiagnosis for ever-users was 59 years. Only 2% of ever-users were aged 75 or older.

Figure 3 shows for individual studies the numbers of ever-users and of never-users of HRT and the relative risks associated with ever-use. The studies are grouped according to study design. Within the groups the results for individual studies are listed chronologically, according

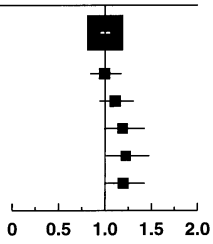
a: By duration of use (years)

	Cases/Controls	RR (FSE)*	RR and 99% FCI*
Never-user	12467/23568	1.00 (0.020)	
<1	1154/2546	1.09 (0.050)	
1-4	1660/3999	1.05 (0.039)	
5-9	813/1912	1.19 (0.061)	
10-14	386/867	1.09 (0.087)	
≥15	337/584	1.58 (0.121)	



b: By time since first use (years)

	Cases/Controls	RR (FSE)*	RR and 99% FCI*
Never-user	12467/23568	1.00 (0.021)	
<5	932/1646	0.99 (0.065)	
5-9	876/1439	1.11 (0.068)	
10-14	710/1188	1.19 (0.077)	
15-19	548/1026	1.22 (0.081)	
≥20	640/1297	1.20 (0.075)	



c: By time since last use (years)

	Cases/Controls	RR (FSE)*	RR and 99% FCI*
Never-user	12467/23568	1.00 (0.019)	
Current	1796/3814	1.21 (0.044)	
1-4	702/1660	1.10 (0.063)	
5-9	500/1239	1.01 (0.068)	
10-14	346/821	1.05 (0.084)	
≥15	416/729	1.12 (0.084)	

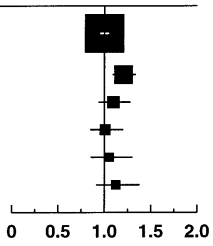


Figure 4: Relative risk (RR) of breast cancer according to timing of HRT use
*Relative to never-users, stratified by study, age at diagnosis, time since menopause, body-mass index, parity, and the age a woman was when her first child was born. FSE, FCI, and format as in figure 1.

to the median year of diagnosis of breast cancer. The results for unpublished studies and studies in which the information content, var(O−E), is less than 10·0 are included in the "other" category. For all studies combined there was a significant increase in the relative risk of breast cancer associated with ever-use of HRT (relative risk 1·14 [SE 0·03], 2p=0·00001). There was no significant variation in the results between the three types of study design, or between the individual studies.

Timing of exposure

Ever-use is a crude measure of exposure to HRT, and figure 4 shows analyses of the relative risk of breast cancer in relation to total duration of use, time since first use, and time since last use of HRT. These three indices are correlated, so if the risk is directly related to any one factor it may be indirectly related to the others. To find out which factors show an independent relation with risk of breast cancer, risk was examined initially with respect to each factor separately and, where appropriate, joint effects were then considered.

Total duration of use—Among women who had ever used HRT, the median duration of use was 2 years. The total duration of use was less than a year in 26% of ever-users, 5 years or longer in 34%, and 10 years or longer in 15%. Among ever-users of HRT, there was evidence of an increasing relative risk of breast cancer with increasing duration of use (χ^2 for trend across the five categories of duration [1 df] 8·7; p=0·003; figure 4a).

Time since first use—Among women who had used HRT, the median time since first use was 11 years. 19% of users began use 20 or more years before their cancer was diagnosed. The relative risk of breast cancer was greater than 1·0 for each of the categories of time since first use except use that began less than 5 years ago (figure 4b). There was some evidence of a trend of increasing risk with increasing time since first use (χ^2 for trend across the five categories of time since first use [1 df] 4·9; p=0·03).

Time since last use—Among ever-users of HRT, 47% were current users at the time of diagnosis/pseudodiagnosis (figure 4c). The relative risk of breast cancer was significantly increased among current users (1·21 [SE 0·05], 2p=0·00002), but not among past users (1·07 [SE 0·04]; p=0·10).

Duration of use and time since last use—Although each of the indices of use shown in figure 4 shows some statistically significant association with risk of breast cancer, these indices are highly correlated and, once recency and duration of use are accounted for, time since first use provides little additional information and hence has no residual relation with risk. Figure 5 shows the results by duration of use separately for current users together with women whose use ceased less than 5 years before diagnosis/pseudodiagnosis and for women whose use ceased 5 or more years before. For those whose last use was less than 5 years before diagnosis there was strong evidence of a trend of increasing relative risk of breast cancer with increasing duration of use; the risk increased by a factor of 1·023 (SE 0·060)—ie, by 2·3% (0·6%)—for each year of use (2p=0·0002). Most of the long-duration use in this group was among current users, but the trend with increasing duration of use did not differ significantly between current users and those whose use ceased 1-4 years before diagnosis (the respective relative risks increased by factors of 1·026 and 1·018 for each year of use: χ^2 for heterogeneity [1 df] 0·6; p=0·44). By contrast, for women who stopped use 5 or more years before diagnosis/pseudodiagnosis, there was no significant overall increase in the relative risk of breast cancer (1·07 [SE 0·05]). The non-significant decrease in the relative risk by a factor of 0·978 (0·014) for each year of use differed significantly from the trend in current or recent users (χ^2 for heterogeneity [1 df] 8·3; p=0·004).

After duration of use and time since last use had been taken into account, no residual effects remained for any other index of the timing of exposure to HRT, including age at first use and the related measure time between menopause and first use. The effects of time since last use

Duration of use and time since last use	Cases/Controls	RR (FSE)*
Never-user	12467/23568	1.00 (0.021)
Last use <5 years before diagnosis		
Duration <1 year	368/860	0.99 (0.085)
Duration 1-4 years	891/2037	1.08 (0.060)
Duration 5-9 years	588/1279	1.31 (0.079)
Duration 10-14 years	304/633	1.24 (0.108)
Duration ≥15 years	294/514	1.56 (0.128)
Last use ≥5 years before diagnosis		
Duration <1 year	437/890	1.12 (0.079)
Duration 1-4 years	566/1256	1.12 (0.068)
Duration 5-9 years	151/374	0.90 (0.115)
Duration ≥10 years	93/233	0.95 (0.145)

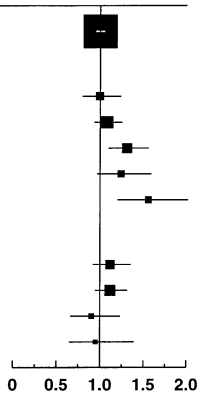


Figure 5: Relative risk (RR) of breast cancer for duration of use within categories of time since last use of HRT

*Relative to never-users, stratified by study, age at diagnosis, time since menopause, body-mass index, parity, and the age a woman was when her first child was born. FSE, FCI, and format as in figure 1.

"Last use within 5 years before diagnosis" includes current users.

and duration of use were also examined by means of a conditional logistic regression model in which additional adjustment for other factors, such as family history of breast cancer, ethnic group, and education, was made by entering each factor in turn into the model. None of these factors changed the pattern or the magnitude of the results shown in figure 5.

Consistency of main findings

The main findings are that for current or recent users of HRT the relative risk of breast cancer increases in relation to increasing duration of use, but that for past users there is no significant increase in the relative risk of breast cancer, either overall or in relation to duration of use. There was no marked variation in these main findings across different studies (data not shown). In figure 6 the consistency of these main findings is examined for various subgroups of women, even though analyses restricted to particular subgroups may, by chance alone, yield misleadingly irregular patterns. Similar patterns of risk are evident for most subgroups. Of the 42 comparisons shown in figure 6, only two closely related factors showed a significant result—namely, weight and body-mass index among current or recent users who had a duration of use of HRT of 5 years or longer (figure 6b; χ^2 for heterogeneity [1 df] 12·8, p=0·0004, for weight categories; 10·2, p=0·001, for body-mass index categories). Furthermore, the relative risk associated with long durations of current or recent use decreased progressively with increasing weight (1·65 [SE 0·12], 1·32 [0·13], and 1·05 [0·14] for weights of <60 kg, 60–69 kg, and ⩾70 kg, respectively; χ^2 for trend [1 df] 8·1; 2p=0·004) and with increasing body-mass index (1·73 [0·12], 1·29 [0·14], and 1·02 [0·11], for body-mass indices of <22·5, 22·5–24·9, and ⩾25·0, respectively; χ^2 for trend [1 df] 14·5; 2p=0·0001).

Tumour spread

Information on the extent of tumour spread was available for 9668 (54%) of the postmenopausal women with breast cancer. Compared with tumours in never-users, those in ever-users were less likely to have spread to axillary lymph nodes (2p=0·02) or to more distant sites (2p=0·01) than to be localised to the breast (χ^2 for heterogeneity [2 df] 10·4; p=0·005; figure 7). Among current or recent users of HRT the excess risk of breast cancer was confined to localised disease (figure 8). There was, however, a significant increase in the relative risk of spread disease with increasing duration of use (χ^2 for trend 7·3; 2p=0·007). The lack of an overall excess of cancer that had spread beyond the breast in women with short-duration use (figure 8b) is largely because women who began using HRT in the 5 years before their cancer was diagnosed had a low relative risk of spread disease (0·59 [SE 0·12], 2p=0·001). The information on the relative risk of breast cancer according to tumour spread in past users was limited, but there was no significant increase in risk among such users, either for localised or for spread disease.

Hormonal constituents

Information about the hormonal constituents of the preparations used most was available for 4640 (39%) of eligible women (table 2). Of these women, 80% had mostly used preparations containing oestrogens alone and 12% preparations containing combinations of oestrogen and progestagen. There was no significant variation in the relative risk of breast cancer according to the type or the dose of oestrogen used mostly and no evidence of marked differences between preparations containing oestrogen alone and preparations containing both oestrogen and progestagen. Although there was little information about current or recent use of specific preparations for long periods of time, there was weak evidence of variation in the relative risk of breast cancer among women with 5 or more years of use according to broad groupings of the type of preparation mostly used. This finding may be due to chance, especially since the category showing the highest relative risk (oestrogen and other, or other), is a heterogeneous group that includes users of various unrelated compounds, none of which is individually the cause of the raised relative risk.

Women with an unknown age at menopause

Failure to take time since menopause into account leads to substantial underestimation of the relative risk of breast cancer among current and recent users: for example the relative risk associated with ever-use would have been 1·07 (SE 0·03; 2p=0·003) instead of 1·14 (0·03; 2p=0·00001) and the percentage increase in relative risk for each year of use in current or recent users (figure 5) would have been 0·8% (0·5; 2p=0·10), instead of 2·3% (0·6; 2p=0·0002), without such stratification. About 18% of the study population were classified as having an unknown age at menopause; a large proportion of women had undergone hysterectomy before the onset of their natural menopause. Findings on the relation between use of HRT and risk of breast cancer in women with an unknown age at menopause can vary depending on what assumption is made about the age at which such women might have experienced natural menopause. Three different assumptions were made about their possible age at menopause: first, that it was the same as the median age at menopause for women who had a natural menopause (ie, age 50); second, that was equal to their age at hysterectomy; and third, that it was equal to their age when they began using HRT. Under each of these

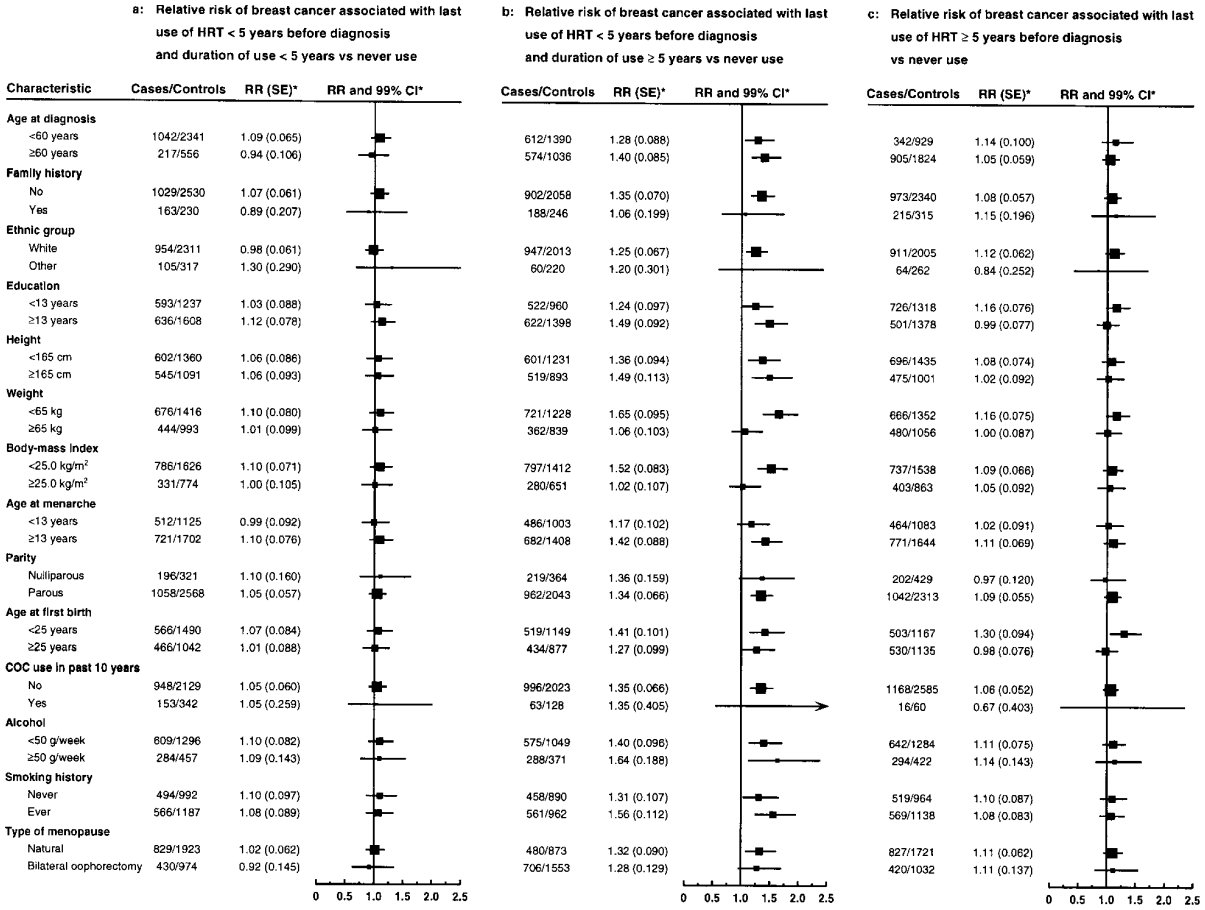


Figure 6:Relative risk (RR) of breast cancer according to use of HRT among women with differing characteristics
*Relative to never-users, stratified by study, age at diagnosis, time since menopause, body-mass index, parity, and the age a woman was when her first child was born. SE and CI are not floated. Family history=mother or sister with breast cancer; COC=combined oral contraceptives.

assumptions the estimated increase in the relative risk of breast cancer associated with each year of use of HRT was 0·4% (0·8), 0·6% (0·8), and 1·6% (1·1), respectively, for current or recent users who had a hysterectomy before their natural menopause; among past users there was no evidence of an increasing relative risk with increasing duration of use under either assumption. Since none of the assumptions is satisfactory and since time since menopause is such an important confounding factor, inclusion of women with unknown values in the main analysis would be inappropriate.

Discussion

The main findings are that the risk of breast cancer is increased in women using HRT and increases with increasing duration of use, but that this excess risk is reduced after use ceases and has largely, if not completely, disappeared after about 5 years. The increase in the relative risk of breast cancer among current or recent users was greater for women of low than for those of high relative weight. Furthermore, the breast cancers diagnosed in women who had used HRT were less advanced clinically than those diagnosed in never-users.

Menopause and breast cancer risk

Although the menopause is known to affect risk of breast cancer, the large amount of information assembled for this collaboration allowed detailed analysis of the relation between this risk and the timing of menopause. Though breast cancer incidence increases with age, post-menopausal women have a lower risk of breast cancer than do premenopausal women of the same age. We found that compared with premenopausal women of similar age and childbearing history, there was a substantial reduction in the relative risk of breast cancer in the first 5 years after the menopause and that thereafter the relative risk declined by 2·7% (95% CI 2·1–3·2) for every year since menopause (figures 1 and 2). These relations did not differ significantly between women with a natural menopause and women with a bilateral oophorectomy. The reduction in the relative risk of breast cancer in postmenopausal compared with premenopausal women is, however, more pronounced for women of low rather than high relative weight and is more pronounced for localised breast cancers than for more advanced disease.

The changes in the relative risk of breast cancer associated with the menopause are believed to be due to the cessation of cyclical ovarian hormone production at the menopause. Although circulating oestradiol concentrations are an order of magnitude lower in postmenopausal than in premenopausal women, the concentration in postmenopausal women increases with body-mass index,[49] largely because adipose tissue becomes the main site of oestrogen production after the menopause. The reduction in circulating hormone concentrations at the menopause therefore seems to lead within 5 years to a reduction in the relative risk of breast cancer, and the magnitude of this reduction is greatest for women of low body-mass index, who also

Extent of tumour spread	HRT ever-users/never-users	RR (FSE)*	RR and 99% FCI*
Localised to breast	1387/4104	1.00 (0.056)	
Spread to axillary lymph nodes only	940/2827	0.82 (0.060)	
Metastatic beyond breast and lymph nodes	98/312	0.54 (0.173)	

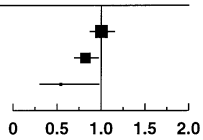


Figure 7: **Analysis relating extent of tumour spread among women with breast cancer to ever-use of HRT**

*Relative probability that a woman with breast cancer is an ever-user rather than a never-user. Relative to women with localised disease, stratified by study, age at diagnosis, time since menopause, body-mass index, parity, and the age a woman was when her first child was born. FSE, FCI, and format as in figure 1.

have low oestradiol concentrations after the menopause. Furthermore, the fall in circulating hormone concentrations at the menopause is apparently associated with a greater reduction in the relative risk of localised than of more advanced cancer.

Confounding and bias

The fine stratification used in these analyses ensures that no direct comparisons are made between women in different studies, and that a woman's use of HRT is compared only with that of a woman in the same study, of the same age, and with a similar time since menopause, body-mass index, and childbearing history.

There is strong potential for confounding between the timing of menopause and use of HRT. Failure to take time since menopause into account leads to substantial underestimation of the risk of breast cancer associated with the use of HRT; only a weak and non-significant increase in the relative risk of breast cancer associated with duration of use in current or recent use would have been found without such stratification. Women who had a hysterectomy without bilateral oophorectomy or who began using HRT before their natural menopause were excluded from the main analyses because their time since menopause cannot be reliably estimated. They constitute about 18% of the study population and their inclusion would have seriously biased the results.

There is also potential for confounding between body-mass index and use of HRT, since lighter postmenopausal women are more likely than heavier women to use HRT and are at an otherwise lower risk of breast cancer than heavier women of the same age and childbearing history. Failure to stratify by body-mass index could also lead to an underestimation of breast cancer risk associated with use of HRT. To assess whether other factors confounded the relations observed, the main results were re-examined by means of conditional logistic regression; neither family history of breast cancer, ethnic group, nor the other factors listed in figure 6 confounded the relations observed.

Users of HRT may have different opportunities for breast cancer to be diagnosed than never-users, and this difference could bias the results. For example, there was some evidence that women are more likely to be examined for breast cancer before first being prescribed HRT: in the first 5 years after the start of HRT use there was a large deficit of advanced breast cancer. Another possibility is that women might have more frequent mammographic or other examinations for breast cancer while they are taking HRT, possibly leading to an earlier diagnosis of breast cancer. Although information on the frequency of mammographic or other examinations was not collected systematically from these studies, the excess of localised disease compared with spread disease in current or recent users is consistent with this possibility. There might be differential reporting of use of HRT in case-control studies, but the results were similar in prospective studies, where no such bias could have occurred. It is not clear what overall effect such potential biases might have, or whether they could lead to the trend of increasing breast cancer risk with increasing duration of use in current and recent users but not in past users.

Combination of results from many studies

The increase in the relative risk of breast cancer associated with each year of use in current and recent users is small, so inevitably some studies would, by chance alone, show significant associations and others would not. Combination of the results across many studies has the obvious advantage of reducing such random fluctuations. There was no significant variation in the results across the 51 studies included in this analysis, and no single study was so large as to dominate the overall results.

The data included represent about 90% of the available epidemiological evidence on the topic. For the 12 eligible studies not included, the overall relative risk of breast cancer associated with ever-use of HRT was 1·0 (95% CI

Duration of use and time since last use	a: Cancers localised to breast Cases/Controls	RR (FSE)*	RR and 99% FCI*	b: Cancers spread beyond breast Cases/Controls	RR (FSE)*	RR and 99% FCI*
Never-user	2717/23568	1.00 (0.033)		2101/23568	1.00 (0.039)	
Last use <5 years before diagnosis						
Duration <1 year	99/860	1.09 (0.159)		58/860	0.68 (0.146)	
Duration 1-4 years	288/2037	1.32 (0.110)		184/2037	0.90 (0.108)	
Duration 5-9 years	192/1279	1.67 (0.155)		119/1279	1.04 (0.141)	
Duration ≥10 years	196/1147	1.42 (0.146)		130/1147	1.25 (0.164)	
Last use ≥5 years before diagnosis						
Duration <1 year	109/890	1.12 (0.151)		68/890	1.01 (0.171)	
Duration 1-4 years	174/1256	1.13 (0.117)		108/1256	1.08 (0.143)	
Duration ≥5 years	97/607	1.23 (0.173)		47/607	0.88 (0.189)	

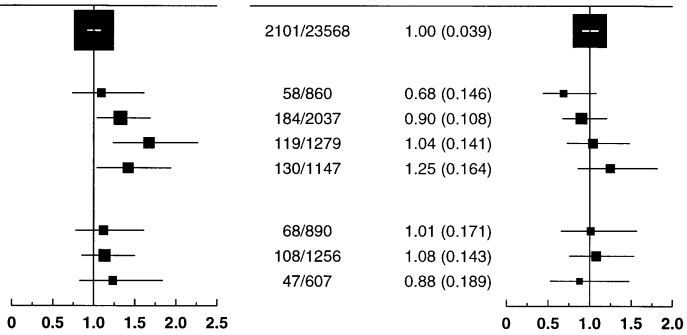


Figure 8:Relative risk (RR) of breast cancer by duration and time since last use of HRT according to extent of tumour spread

*Relative to never-users, stratified by study, age at diagnosis, time since menopause, body-mass index, parity, and the age a woman was when her first child was born. FSE, FCI, and format as in figure 1. "Last use within 5 years before diagnosis" includes current users.

Type and dose of HRT	Current use or last use 1–4 years before diagnosis				Last use ⩾5 years before diagnosis	
	Duration <5 years		Duration ⩾5 years			
	RR (SE)*	Cases/controls	RR (SE)*	Cases/controls	RR (SE)*	Cases/controls
Oestrogen alone						
Total	0·99 (0·08)	498/993	1·34 (0·09)	558/951	1·12 (0·11)	310/451
Conjugated						
⩽0·625 mg	0·77 (0·13)	108/270	1·64 (0·25)	97/159	1·45 (0·22)	119/159
⩾1·85 mg	0·94 (0·17)	100/173	1·42 (0·16)	163/320	0·90 (0·24)	35/70
Unknown dose	1·18 (0·18)	130/254	1·18 (0·14)	191/315	0·82 (0·19)	61/101
Other oestrogen	1·15 (0·17)	160/296	1·26 (0·21)	107/157	1·22 (0·21)	95/121
Oestrogen and progestagen, or progestagen alone	1·15 (0·19)	136/212	1·53 (0·33)	58/86	1·30 (0·46)	21/24
Oestrogen and other, or other	0·88 (0·26)	34/74	2·57 (0·38)	71/91	0·99 (0·32)	30/42

*Relative to never-users, stratified by study, age at diagnosis, time since menopause, body-mass index, parity, and the age a woman was when her first child was born. SE not floated. Tests for heterogeneity: Current use or last use 1–4 years before diagnosis, Duration <5 years, Duration ⩾5 years, and Last use ⩾5 years previously, respectively: between oestrogen groups χ^2 (3 df) 4·7, p=0·19; χ^2 (3 df) 2·5, p=0·48; χ^2 (3 df) 5·2, p=0·16; between hormone types: χ^2 (2 df) 0·9, p=0·64; χ^2 (2 df) 7·4, p=0·03; χ^2 (2 df) 0·3, p=0·86.

Table 2: **Relative risk (RR) of breast cancer by time since last use, duration of use, and type and dose of preparation mainly used**

0·9–1·1). However, the analyses for these studies apparently included women with an unknown age at menopause, and adjustment for time since menopause or its equivalent was made in only four studies. Furthermore, none of the 12 studies presented data for duration of use separately for current or recent users and for past users. Since only about 10% of the data available worldwide are omitted from our analysis, their inclusion would be unlikely to have had a material effect on the results.

Increased relative risk in current or recent users

The increase in the relative risk of breast cancer for each year of use of HRT among current users or those who ceased use 1–4 years before diagnosis was highly statistically significant (1·023 [95% CI 1·011–1·036]; 2p=0·0002). This increase was seen consistently in different studies and in most subgroups, including the natural menopause and bilateral oophorectomy subgroups.

For current or recent users with a duration of use of 5 or more years, the relative risk of having breast cancer diagnosed was 1·35 (1·21–1·49; 2p=0·00001). Their average duration of use was 11 years and the relative risk of breast cancer did not vary significantly across most subgroups (figure 6). The only factors that seemed to modify the effect of HRT in current or recent users were a woman's weight and the related measure, her body-mass index. The effects of long durations of current or recent use were more pronounced for women of low body-mass index than for those of high body-mass index, and the trend of increasing relative risk with decreasing weight or body-mass index was highly significant (2p=0·004 and 2p=0·0001, respectively). Since so many subgroup analyses were done, this result might be due partly to chance. However, given the degree of statistical significance, the smooth gradation in the relation, and the fact that the effect of the menopause on breast cancer risk is influenced by body-mass index, this effect is likely to be real.

Information on the hormonal constituents of the therapy mainly used was available for 39% of the study population and 80% had used mostly preparations containing oestrogen alone. There was no marked variation in breast cancer risk according to a broad classification of the type or dose of preparation used, but there was little information about long durations of use of any specific type or dose of hormonal constituent of HRT. The data are therefore insufficient to permit reliable conclusions about the effects of different hormonal preparations on breast cancer risk.

The results for tumour spread in relation to current or recent use of HRT are difficult to interpret. The overall excess appears to be due to localised disease. This finding is, however, heavily influenced by the large deficit of advanced disease in the first 5 years after women start use of HRT. Without further information, is is impossible to know whether the pattern of risk observed is due to the biological effects of HRT, the exclusion of women with previously undiagnosed breast cancer before they began HRT, the earlier diagnosis of breast cancer in current or recent users than in never-users, or a combination of factors.

There was little information about current or recent use of HRT beginning long after the menopause or about use at older ages; 87% of the current or recent users had begun use within 5 years of the menopause and 97% were aged under 70 at the time of breast cancer diagnosis.

Absence of an increase in relative risk in past users

Although there is insufficient information to specify exactly how long the excess risk of breast cancer persists after women stop using HRT, 5 or more years after cessation of use there was no significant excess of breast cancer overall (relative risk 1·07 [95% CI 0·97–1·18]) or among women who had used HRT for 5 years or longer (relative risk 0·92 [0·72–1·12]; figure 5). This finding was consistent across studies and across various subgroups of women (figure 6). Virtually all the past users (96%) were aged under 75 at the time of breast cancer diagnosis; 79% of them had used HRT for less than 5 years and 87% had mainly used preparations containing oestrogens alone. Thus the available information on past use of HRT pertains mostly to short durations of use of preparations containing oestrogens alone.

Possible explanations of findings

Since HRT is usually prescribed to "replace" the falling levels of circulating ovarian hormones at the menopause, it might be expected that while women are using such therapy the effects of the menopause on breast cancer risk will be delayed. In certain ways this expectation seems to be so. Current or recent use of HRT was estimated to increase the relative risk of breast cancer by 2·3% for each year of use, which could perhaps be seen as comparable to the 2·8% increase in the relative risk of breast cancer that normally occurs for each year that menopause is delayed. Furthermore, the increase in the relative risk associated

Up to age (years)	Cumulative incidence per 1000 women						
	Never-users*	Use beginning at age 50†			Use beginning at age 55†		
		Use for 5 years	Use for 10 years	Use for 15 years	Use for 5 years	Use for 10 years	Use for 15 years
50	18	18	18	18	. .	. .	. .
55	27	28	28	28	27	27	27
60	38	40	41	41	39	39	39
65	50	52	56	57	52	53	53
70	63	65	69	75	65	69	70
75	77	79	83	89	79	83	90

*Based on incidence rates per 1000 for breast cancer intermediate between UK and USA incidence rates in mid-1980s.[63]

†With assumption that relative risk within current users and those who ceased use 1–4 years before increases by 2·3% for each year of use, and that all women are same age at menopause.

Table 3: **Estimated cumulative incidence of breast cancer in 1000 women in North America or Europe associated with postmenopausal use of HRT for various durations, beginning at various ages**

with use of HRT is more pronounced for women of low than of high bodyweight and for localised breast cancer than for cancer that had spread beyond the breast, as are the effects of the menopause on breast cancer risk. Because of these similarities, the associations seen may be, at least partly, due to the biological effects of hormonal therapy. Other explanations cannot be ruled out, however. For example, the excess relative risk of localised breast cancer seen among current and recent users of HRT may be due to the earlier diagnosis of breast cancer among such women.

Number of breast cancers diagnosed in ever-users and never-users

The cumulative numbers of breast cancers diagnosed in never-users and in women who used HRT for various durations beginning at various ages can be calculated by combining the estimates of relative risk by duration of use and time since last use (figure 5) with data on the incidence rates of breast cancer typical for women in North America or Europe.[63] The results of such calculations are shown in table 3. They give an approximate indication of the effect of use of HRT on the overall risk of having breast cancer diagnosed for the general population of women in North America or Europe and may not apply for women with substantially different background risks of breast cancer.

The longer the duration of use and, to a lesser extent, the older women are when they use HRT, the larger the cumulative excess number of cancers diagnosed (table 3). Figure 9 shows estimated cumulative numbers of cancers diagnosed by age 70 for 1000 never-users, 1000 women who used HRT for 5 years, and 1000 women who used HRT for 10 years. Between the ages of 50 and 70, the cumulative incidence in every 1000 never-users is 45 (ie, the cumulative incidence increases from 18 to 63 per 1000). Use of HRT for 5 years is associated with an estimated cumulative excess of 2 (95% CI 1–3) breast cancers for every 1000 users, and use for 10 years with a cumulative excess of 6 (3–9) for every 1000 users; use for 15 years is associated with a cumulative excess of 12 (5–20) breast cancers for every 1000 users. Use of HRT for about 4 years would therefore result in one extra breast cancer being diagnosed in every 1000 users, and use for about 13 years would result in one extra cancer being diagnosed in every 100 users.

Limitations of results and need for further research

Although this collaborative analysis has shown clearly that the relative risk of breast cancer increases with increasing duration of use while women are using HRT and soon after cessation of use, some questions about the effects of HRT remain unanswered. The women included in the main analyses had their breast cancers diagnosed on average in 1985, when the type of HRT used was predominantly oestrogen alone, only 12% having mainly used oestrogen and progestagen combinations. Furthermore, most women had begun use of such therapy at around the time of onset of their menopause, and there is virtually no information about the effects of such therapy on breast cancer risk beyond the age of 75. Since combination therapy is being increasingly used, and since use of HRT is being extended to older ages, additional information is needed about the relation of breast cancer risk to such patterns of use.

The results on tumour spread need further investigation. The increased risk of breast cancer associated with current or recent use seems to be due to an excess of localised cancer, and it is important to establish how far these findings are due to the biological effect of the hormones, the exclusion of women with previously undiagnosed breast cancer before they began

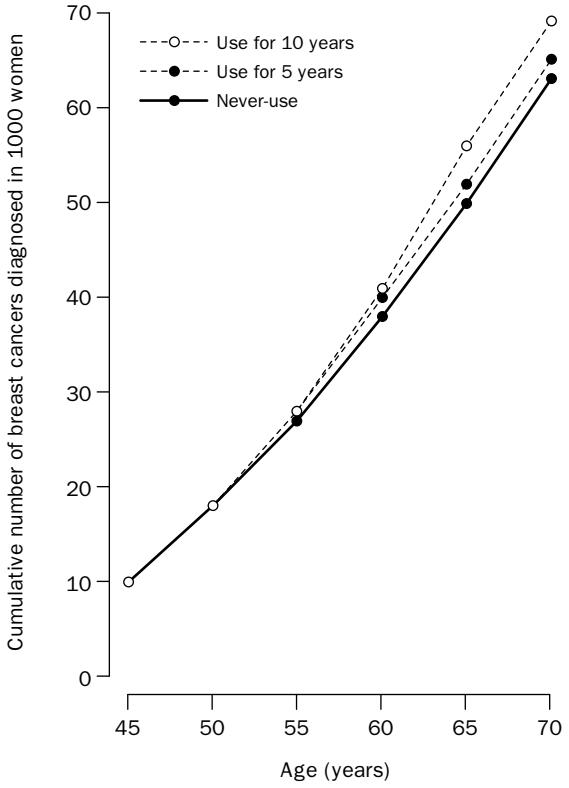


Figure 9: Estimated cumulative number of breast cancers diagnosed in 1000 never-users of HRT, 1000 users of HRT for 5 years, and 1000 users of HRT for 10 years

Estimated numbers for 1000 women in Europe or North America, with assumption that HRT use began at age 50.

HRT, the earlier diagnosis of breast cancer when women use HRT, and other possible reasons. Furthermore, without follow-up information it is not possible to know whether or not long-term use of HRT affects mortality from breast cancer. It is therefore desirable to ascertain the survival of women with breast cancer in relation to their previous pattern of use of HRT.

The estimates of the excess number of breast cancers diagnosed in women who use HRT should be considered in the context of HRT's other effects on health. Use of HRT has effects on organs other than the breast, and may well decrease the incidence of coronary heart disease and osteoporotic fractures, but increase the incidence of venous thromboembolism and endometrial cancer (particularly for preparations containing oestrogens alone). Information about the effects of HRT on these other conditions tends to be based on small numbers, and little is known about the precise nature of the effects of different patterns of use and, in particular, how long they persist after cessation of use. Reliable estimates of the overall balance of risks and benefits associated with the use of HRT can be derived only with more detailed information than exists at present about its effects on conditions other than breast cancer.

Collaborative Group on Hormonal Factors in Breast Cancer

Analysis and writing committee: V Beral, D Bull, R Doll, T Key, R Peto, G Reeves

Collaborators: American Cancer Society (EE Calle, CW Heath Jr); Atlanta, Emory University (RJ Coates, JM Liff); Aviano Cancer Center, Pordenone (S Franceschi, R Talamini); Bangkok, Mahidol University (N Chantarakul, S Koetsawang, D Rachawat); Breast Tumor Collaborative Study, Johns Hopkins University (A Morabia, L Schuman, W Stewart, M Szklo); Brisbane, University of Queensland (C Bain, F Schofield, V Siskind); British Columbia Cancer Agency (P Band, AJ Coldman, RP Gallagher, TG Hislop, P Yang); Cambridge, MRC Biostatistics Unit (SW Duffy); Cancer Research Center, University of Hawaii (LM Kolonel, AMY Nomura); Centers for Disease Control and Prevention (MW Oberle, HW Ory, HB Peterson, HG Wilson, PA Wingo); Central Institute of Cancer Research, German Democratic Republic (K Ebeling, D Kunde, P Nishan); Channing Laboratory, Brigham and Women's Hospital, Harvard Medical School (G Colditz for Nurses' Health Study Research Group); Chiang Mai University (N Martin, T Pardthaisong, S Silpisornkosol, C Theetranont); Chulalongkorn University (B Boosiri, S Chutivongse, P Jimakorn, P Virutamasen, C Wongsrichanalai); CSIRO Division of Human Nutrition, Adelaide (AJ McMichael, T Rohan); Danish Cancer Society (M Ewertz); Department of Medical Epidemiology, Karolinska Institute, Stockholm (HO Adami, R Bergkvist, I Persson); Dunedin, University of Otago (C Paul, DCG Skegg, GFS Spears); European Institute of Oncology (P Boyle, T Evstifeeva); Fred Hutchinson Cancer Research Center (JR Daling, WB Hutchinson, K Malone, EA Noonan, JL Stanford, DB Thomas, NS Weiss, E White); French Multicentre Breast Study, INSERM (N Andrieu, A Brâmond, F Clavel, B Gairard, J Lansac, L Piana, R Renaud); Holly Lodge (SRP Fine); Hospital General de Mexico (HR Cuevas, P Ontiveros, A Palet, SB Salazar); Hospital Universitario (N Aristizabal, A Cuadros); INSERM, Institut Gustave-Roussey, Villejuif (A Bachelot, MG Lê); Institute of Cancer Research, Sutton (J Deacon, J Peto, CN Taylor); Israel Chaim Sheba Medical Centre (B Modan, E Ron); Kaiser Permanente, California (GD Friedman, RA Hiatt); Lausanne, Institut universitaire de medecine sociale et preventive (F Levi); Leeds, ICRF Genetic Epidemiology Laboratory (T Bishop); Ljubljana, Institute of Oncology (K Kosmelj, M Primic-Zakelj, B Ravnihar, J Stare); Loma Linda University (WL Beeson, G Fraser); London, Imperial Cancer Research Fund (RD Bulbrook, J Cuzick, IS Fentiman, JL Hayward, DY Wang); London School of Hygiene and Tropical Medicine (K McPherson); Long Island Breast Cancer Study (RL Hanson, MC Leske, MC Mahoney, PC Nasca, AO Varma, AL Weinstein); Lund, University Hospital (TR Moller, H Olsson, J Ranstam); Maastricht University (RA Goldbohm, PA van den Brandt); Manila, University of Philippines (RA Apelo, J Baens, JR de la Cruz, B Javier, LB Lacaya, CA Ngelangel); Milan, Istituto "Mario Negri" (C La Vecchia, E Negri); Milan, Istituto Nazionale Tumori, Divisione di Statistica Medica e Biometria (E Marubini); Milan, Istituto di Statistica Medica e Biometria (M Ferraroni); Montpellier Cancer Centre and INSERM (M Gerber, S Richardson, C Segala); Nairobi Centre for Research in Reproduction (D Gatei, P Kenya, A Kungu, JG Mati); National Cancer Institute, Bethesda (LA Brinton, R Hoover, C Schairer); National Institute of Child Health and Human Development, Bethesda (R Spirtas); National University of Singapore (HP Lee); Netherlands Cancer Institute (MA Rookus, FE van Leeuwen for the Netherlands Oral Contraceptives and Breast Cancer Study Group); New Jersey State Department of Health (JA Schoenberg); New York, Columbia University School of Public Health (MD Gammon); Ontario Cancer Treatment and Research Foundation (EA Clarke); Oxford, Department of Public Health and Primary Care (L Jones, A Neil, M Vessey, D Yeates); Oxford, ICRF Cancer Epidemiology Unit, Secretariat (V Beral, D Bull, B Crossley, C Hermon, S Jones, T Key, C Lewis, G Reeves); Oxford, ICRF/MRC/BHF Clinical Trial Service Unit and Epidemiological Studies Unit (R Collins, R Doll, R Peto); Radiation Effects Research Foundation, Hiroshima (K Mabuchi, D Preston); Royal College of General Practitioners Oral Contraception Study (P Hannaford, C Kay); San Jose, University of Costa Rica (L Rosero-Bixby); Shanghai Cancer Institute (J-M Yuan); Shanghai Institute of Planned Parenthood Research (HY Wei, T Yun, C Zhiheng); Sydney, Department of Public Health (G Berry, J Cooper Booth, T Jelihovsky, R MacLennan, R Shearman); Tianjin Cancer Institute (Q-S Wang); Toronto, Department of Public Health Sciences (CJ Baines, AB Miller, C Wall); Tromso University (E Lund, H Stalsberg); University of Athens Medical School (K Katsouyanni, A Trichopoulou, D Trichopoulos); University of Chile (A Dabancens, L Martinez, R Molina, O Salas); University of Edinburgh (FE Alexander); University of Minnesota School of Public Health (AR Folsom on behalf of the Iowa Women's Health Study); University of North Carolina at Chapel Hill, School of Public Health (BS Hulka); University of Nottingham (CED Chilvers); University of Southern California (L Bernstein, RW Haile, A Paganini-Hill, MC Pike, RK Ross, G Ursin, MC Yu); University of Wisconsin Comprehensive Cancer Center (MP Longnecker, P Newcomb for the 4 State Study); Vasteras, Sweden (L Bergkvist); World Health Organization, UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (TMN Farley, S Holck, O Meirik).

Acknowledgments

Tens of thousands of women with and without breast cancer throughout the world have contributed to this research. This review would not have been possible without their help or without the careful collection and checking of data at each of the collaborating institutions. Central pooling and analysis was supported by the Imperial Cancer Research Fund.

References

1 Ross RK, Paganini-Hill A, Gerkins VR, et al. A case-control study of menopausal estrogen therapy and breast cancer. *JAMA* 1980; **243:**1635-39.

2 Brinton LA, Hoover RM, Szklo M, Fraumeni JF. Menopausal estrogen use and risk of breast cancer. *Cancer* 1981; **47:** 2517-22.

3 Thomas DB, Persing JP, Hutchinson WB. Exogenous oestrogens and other risk factors for breast cancer in women with benign breast diseases. *J Natl Cancer Inst* 1982; **69:** 1017-25.

4 Vessey M, Baron J, Doll R, McPherson K, Yeates D. Oral contraceptives and breast cancer: final report of an epidemiologic study. *Br J Cancer*1983; **47:** 455-62.

5 Hiatt RA, Bawol R, Friedman GD, Hoover R. Exogenous estrogen and breast cancer after bilateral oophorectomy. *Cancer*1984; **54:** 139-44.

6 Talamini R, La Vecchia C, Franceschi S, et al. Reproductive and hormonal factors and breast cancer in a Northern Italian population. *Int J Epidemiol* 1985; **14:** 70-74.

7 Hislop TG, Coldman AJ, Elwood JM, Brauer G, Kan L. Childhood and recent eating patterns and risk of breast cancer. *Cancer Detect Prevent* 1986; **9:** 47-58.

8 Nomura AMY, Kolonel LN, Hirohata T, Lee J. The association of replacement estrogens with breast cancer. *Int J Cancer* 1986; **37:** 49-53.

9 Alexander FE, Roberts MM, Huggins A. Risk factors for breast cancer with applications to selection for the prevalence screen. *J Epidemiol Commun Health* 1987; **41:** 101-06.

10 Lee NC, Rosero-Bixby L, Oberle MW, Grimaldo C, Whatley AS, Rovira EZ. A case-control study of breast cancer and hormonal contraception in Costa Rica. *J Natl Cancer Inst* 1987; **79:** 1247-54.

11 McPherson K, Vessey MP, Neil A, Doll R, Jones L, Roberts M. Early oral contraceptive use and breast cancer: results of another case-control study. *Br J Cancer* 1987; **56:** 653-60.

12 Wang DY, De Stavola BL, Bulbrook RD, et al. The relationship between blood prolactin levels and risk of breast cancer in premenopausal women. *Eur J Clin Oncol*1987; **23:** 1541-48.

13 Wingo PA, Layde PM, Lee NC, Rubin G, Ory HW. The risk of breast cancer in postmenopausal women who have used estrogen replacement therapy. *JAMA*1987; **257:** 209-15.

14 Ewertz M. Influence of non-contraceptive exogenous and endogenous sex hormones on breast cancer risk in Denmark. *Int J Cancer* 1988;4**2:** 832-38.

15 Kay CR, Hannaford PC. Breast cancer and the pill - a further report

from the Royal College of General Practitioners' Oral Contraception Study. *Br J Cancer* 1988; **58:** 675-80.

16 Marubini E, Decarli A, Costa A,et al. The relationship of dietary intake and serum levels of retinol and beta-carotene with breast cancer: results of a case-control study. *Cancer* 1988; **61:** 173-80.

17 Ravnihar B, Primic Zakelj M, Kosmelj K, Stare J. A case-control study of breast cancer in relation to oral contraceptive use in Slovenia. *Neoplasma* 1988: **35:** 109-21.

18 Rohan TE, McMichael AJ. Non-contraceptive exogenous oestrogen therapy and breast cancer. *Med J Aust* 1988; **148:** 217-21.

19 Bergkvist L, Adami HO, Persson I, Hoover R, Schairer C. The risk of breast cancer after estrogen and estrogen-progestin replacement. *N Engl J Med* 1989; **321:** 293-97.

20 Mills PK, Beeson WL, Phillips RL, Fraser GE. Prospective study of exogenous hormone use and breast cancer in seventh-day adventists. *Cancer* 1989; **64:** 591-97.

21 Siskind V, Schofield F, Rice D, Bain C. Breast cancer and breast feeding: results from an Australian case-control study. *Am J Epidemiol* 1989; **130:** 229-36.

22 Vessey MP, McPherson K, Villard-Mackintosh L, Yeates D. Oral contraceptives and breast cancer: latest findings in a large cohort study. *Br J Cancer* 1989; **59:** 613-17.

23 Paul C, Skegg DCG, Spears GFS. Oral contraceptives and risk of breast cancer. *Int J Cancer* 1990; **46:** 366-73.

24 Hulka BS, Chambless LE, Deubner DC, Wilkinson WE. Breast cancer and estrogen replacement therapy. *Am J Obstet Gynecol* 1992; **143:** 638–44.

25 WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Breast cancer and combined oral contraceptives: results from a multinational study. *Br J Cancer* 1990; **61:** 110-19.

26 Segala C, Gerber M, Richardson S. The pattern of risk factors for breast cancer in a Southern France population: interest for a stratified analysis by age at diagnosis. *Br J Cancer* 1991; **64:** 919-25.

27 La Vecchia C, Negri E, Franceschi S, Parazzini F. Non contraceptive oestrogens and breast cancer. *Int J Cancer* 1992; **50:** 161-62.

28 Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study I: breast cancer detection and death rates among women aged 40-49 years. *Can Med Assoc J* 1992: **147:** 1459-76.

29 Palmer JR, Rosenberg L, Clarke EA, Miller DR, Shapiro S. Breast cancer risk after estrogen replacement therapy: results from the Toronto Breast Cancer Study. *Am J Epidemiol* 1991; **134:** 1386-95.

30 Ursin G, Aragaki CC, Paganini-Hill A, Siemiatycki J, Thompson WD, Haile RW. Oral contraceptives and premenopausal bilateral breast cancer: a case-control study. *Epidemiology* 1992; **3:** 414-19.

31 Yang CP, Daling JR, Band PR,Gallagher RP, White E, Weiss NS. Non contraceptive hormone use and risk of breast cancer. *Cancer Causes Control* 1992; **3:** 475-79.

32 Morabia A, Szklo M, Stewart W, Schuman L, Thomas DB. Consistent lack of association between breast cancer and oral contraceptives using either hospital or neighbourhood controls. *Prevent Med* 1993; **22:** 178–86.

33 Weinstein AL, Mahoney MC, Nasca PC, Hanson RL, Leske MC, Varma AO. Oestrogen replacement therapy and breast cancer risk: a case-control study. *Int J Epidemiol* 1993; **22:** 781-89.

34 Ngelangel CA, Lacaya LB, Cordero C, Laudico AV. Risk factors for breast cancer among Filipino women. *Phil J Intern Med* 1994; **32:** 231–36.

35 Rookus MA, van Leeuwen FE, for the Netherlands Oral Contraceptives and Breast Cancer Study Group. Oral contraceptives and risk of breast cancer in women aged 20-54 years. *Lancet* 1994; **344:** 844-51.

36 Schairer C, Byrne C, Keyl PM, Brinton LA, Sturgeon SR, Hoover RN. Menopausal estrogen and estrogen-progestin replacement therapy and risk of breast cancer (United States). *Cancer Causes Control* 1994; **5:** 491-500.

37 White E, Malone KE, Weiss NS, Daling JR. Breast cancer among young US women in relation to oral contraceptive use. *J Natl Cancer Inst* 1994; **86:** 505-14.

38 Brinton LA, Daling JR, Liff JM, et al. Oral contraceptives and breast cancer risk among younger women. *J Natl Cancer Inst* 1995; **87:** 827–35.

39 Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995; **332:** 1589-93.

40 Folsom AR, Mink PJ, Sellers TA, Hong C-P, Zheng W, Potter JD. Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. *Am J Public Health* 1995; **85:** 1128-32.

41 La Vecchia C, Negri E, Franceschi S, et al. Hormone replacement treatment and breast cancer risk: a cooperative Italian study. *Br J Cancer* 1995: **72:** 244-48.

42 Lipworth L, Katsouyanni K, Stuver S, Samoli E, Hankinson SE, Trichopoulos D. Oral contraceptives, menopausal estrogens, and the risk of breast cancer: a case-control study in Greece. *Int J Cancer* 1995; **62:** 548-51.

43 Newcomb PA, Longnecker MP, Storer BE, et al. Long-term hormone replacement therapy and risk of breast cancer in postmenopausal women. *Am J Epidemiol* 1995; **142:** 788-95.

44 Schuurman AG, van den Brandt PA, Goldbohm RA. Exogenous hormones and the risk of postmenopausal breast cancer: results from the Netherlands cohort study. *Cancer Causes Control* 1995; **6:** 416-24.

45 Stanford JL, Weiss NS, Voigt LF, Daling JR, Habel LA, Rossing MA. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. *JAMA* 1995; **274:** 137-42.

46 Levi F, Lucchini F, Pasche C, La Vecchia C. Oral contraceptives, menopausal hormone replacement therapy and breast cancer risk. *Eur J Cancer Prevent* 1996; **5:** 259-66.

47 Willis DB, Calle EE, Miracle-McMahill HL, Heath CW. Estrogen replacement therapy and risk of fatal breast cancer in a prospective cohort of postmenopausal women in the United States. *Cancer Causes Control* 1996; **7:** 449-57.

48 Goodman MT, Cologne J, Moriwaki H, Vaeth M, Mabuchi K. Risk factors for primary breast cancer in Japan: 8-year follow-up of atomic-bomb survivors. *Prevent Med* 1997; **26:** 144-53.

49 Thomas HV, Key TJ, Allen DS, et al. Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. *J Natl Cancer Inst* 1997; **89:** 396-97.

50 Sartwell PE, Arthes FG, Tonascia JA. Exogenous hormones, reproductive history and breast cancer. *J Natl Cancer Inst* 1977; **59:** 1589-92.

51 Wynder EL, MacCornack FA, Stellman SD. The epidemiology of breast cancer in 785 United States caucasian women. *Cancer* 1978; **41:** 2341-54.

52 Ravnihar B, Seigel DG, Lindtner J. An epidemiologic study of breast cancer and benign breast neoplasias in relation to the oral contraceptive and estrogen use. *Eur J Cancer* 1979; **15:** 395-405.

53 Hoover R, Glass A, Finkle WD, Azevedo D, Milne K. Conjugated estrogens and breast cancer risk in women. *J Natl Cancer Inst* 1981; **67:** 815-20.

54 Kelsey JL, Holford TR, White C, Mayer ES, Kilty SE, Acheson RM. Exogenous oestrogens and other factors in the epidemiology of breast cancer. *J Natl Cancer Inst* 1981; **67:** 327-33.

55 Sherman B, Wallace R, Bean J. Estrogen use and breast cancer: interaction with body mass. *Cancer* 1983; **51:** 1527-31.

56 Horwitz RI, Stewart KR. Effect of clinical features on the association of estrogens and breast cancer. *Am J Med* 1984; **76:** 192-98.

57 McDonald JA, Weiss NS, Daling JR, Francis AM, Polissar L. Menopausal estrogen use and the risk of breast cancer. *Breast Cancer Res Treat* 1986; **7:** 193-99.

58 Brownson RC, Blackwell CW, Pearson DK, Reynolds RD, Richens JW, Papermaster BW. Risk of breast cancer in relation to cigarette smoking. *Arch Intern Med* 1988; **148:** 140-44.

59 Harris RE, Namboodiri KK, Wynder EL. Breast cancer risk: effects of estrogen replacement therapy and body mass. *J Natl Cancer Inst* 1992; **84:** 1575-82.

60 Kaufman DW, Miller DR, Rosenberg L, et al. Noncontraceptive estrogen use and the risk of breast cancer. *JAMA* 1984; **252:** 63-67.

61 Kaufman DW, Palmer JR, de Mouzon J, et al. Estrogen replacement therapy and the risk of breast cancer: results from the case-control surveillance study. *Am J Epidemiol* 1991; **134:** 1375-85.

62 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996; **347:** 1713-27.

63 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: further results. *Contraception* 1996; **54 (suppl):** S1-106.

64 Peto R, Pike MC, Armitage P, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient- I: introduction and design. *Br J Cancer* 1976; **34:** 585-612.

65 Peto R, Pike MC, Armitage P, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient- II: analysis and examples. *Br J Cancer* 1977; **35:** 1-39.

66 Easton DF, Peto J, Babiker AGAG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med* 1991; **10:** 1025-35.