6-1-2006

Estrogen-Progestin Postmenopausal Hormone Replacement Therapy and the Risk of Breast Cancer

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ESTROGEN-PROGESTIN POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY AND THE RISK OF BREAST CANCER: A META-ANALYSIS OF THE EVIDENCE PRIOR TO THE PUBLICATION OF THE WOMEN'S HEALTH INITIATIVE TRIAL RESULTS

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B.A., University of New Hampshire, 1991

A Thesis

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Public Health

at the

University of Connecticut

2006

APPROVAL PAGE

Master of Public Health Thesis

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Presented by
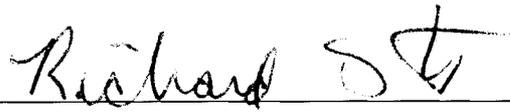
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The Women's Health Initiative (WHI) was the first randomized trial to assess the overall risk and benefit of estrogen (0.625 mg/day conjugated equine estrogen) plus progestin (2.5 mg/day medroxyprogesterone-acetate) (EP) in healthy postmenopausal women with an intact uterus (1). The WHI designated invasive breast cancer as a primary adverse outcome based on observational data (1) obtained from prior studies (2, 3). These studies included a meta-analysis of estrogen replacement therapy's effect on breast cancer risk that concluded by indicating a need to determine if breast cancer risk is affected by progestin use (2) and another meta-analysis of estrogen and EP therapy which concluded that the uncertainty of EP therapy's risk for breast cancer had not been studied adequately (3).

The hormone replacement therapy (HRT) component of the WHI clinical trial was designed to randomize 27,500 women for an average follow-up of approximately 9 years (4). Statistical stopping rules for the trial were determined by using hypothetical sets of interim trial results (scenarios) after an average follow-up of 6 years (5). Members of the Data and Safety Monitoring Committee (DSMC) reviewed the scenarios and made recommendations on whether or not to stop the trial (5).

The WHI trial was stopped early after an average follow-up of 5.2 years because while the adverse effects of cardiovascular diseases remained within the monitoring boundaries, the invasive breast cancer test statistic exceeded the adverse effect stopping boundary and the risk exceeding the benefits was supported by the global index statistic (defined as the earliest occurrence of coronary heart disease, stroke, pulmonary embolism, invasive breast cancer, endometrial cancer, colorectal cancer, hip fracture, or

death from other causes) (1). The trial found that among 10,000 women taking EP compared with placebo, eight more might experience invasive breast cancers over a 1-year period, representing a 26% increase in breast cancer risk (1).

The WHI trial design was based on data available in 1991-1992 (1). Thus, we performed a systematic review and meta-analysis of the available published studies on the use of EP therapy and the risk of breast cancer in postmenopausal women that were accepted for publication prior to the publication of the WHI's results (1) in July of 2002. Our analysis examines EP HRT and the risk of developing breast cancer associated with ever, recent, or past, and never use of EP HRT. International studies were not included in the analysis since conjugated estrogens and medroxyprogesterone-acetate are primarily used in the US, whereas in Europe, oestradiol combined with testosterone-like progestins are commonly used (6). Our analysis of the literature determines if more recent evidence in the literature could have had implications in guiding the stopping rules of the WHI trial.

Methods

Literature Search

We searched PubMed (National Library of Medicine and the National Institutes of Health, Bethesda, MD) using combinations of keywords and some MeSH terms for the keywords postmenopausal, estrogen, oestrogen, progestin, hormone replacement therapy, estrogen replacement therapy, oestrogen replacement therapy, breast cancer, and breast neoplasms. Evidence Based Medicine (EBM) Reviews from the Cochrane Central Register of Controlled Trials (CCTR) was searched using the keywords estrogen,

progestin, postmenopausal (variations of the word), breast cancer, and breast neoplasms. The American College of Physicians (ACP) Journal Club, Cochrane Database of Systematic Reviews (CDSR), and the Database of Abstracts of Reviews of Effects (DARE) from the EBM Reviews were searched using the keywords estrogen, progestin, variations of the word postmenopausal, breast cancer, and breast neoplasms. We searched the ACP Journal Club, CCTR, CDSR, DARE, and PubMed for meta-analyses or reviews from 2001 through 2005 in an effort to find publications prior to the WHI trial results published in 2002 that might be listed in the reference lists of these publications. We reviewed all titles and abstracts identified by our searches and the reference lists of relevant papers to broaden our search for additional articles.

Inclusion Criteria

Limits used for some of the searches included United States (US), clinical trial, English, and human. Publications were eligible for inclusion in the analysis if they were accepted for publication prior to the publication of the WHI's results (1) in July of 2002, if the incidence of breast cancer was reported in postmenopausal women who used EP HRT, and if the study had a comparison group of never users (i.e., women who never used any combination of estrogen or progestin HRT (e.g., estrogen only or EP HRT)). Due to the limited availability of these published studies, we included studies into our analysis regardless of the type or dosage of estrogen or progestin used, or the number of days per month that progestin was used.

Studies limited to Canadian women were excluded from the analysis. However, we did include one study in our analysis (7) that presented data from six US and one

Canadian city. We included this study in our analysis since we had a limited number of US studies and because Canadian data is often considered a proxy for US data.

We found that many of the papers that were eligible for inclusion in the analysis covered the same cohort of women. For our analysis, we included the papers that reported longer follow-up of the study cohort, more person-years of observation, a larger study cohort, papers that placed more emphasis on EP HRT versus emphasis on other types of HRT, or papers that placed an emphasis on breast cancers associated with the usage of HRT rather than breast cancer associated with other risk factors (e.g., body mass index).

Data Abstraction

One author abstracted from each eligible study the first author's last name, year of publication, the relative risk (RR) estimate (i.e., adjusted odds ratio (OR), relative odds (RO), or relative risk), upper and lower 95% confidence intervals (CI), adjustments (adjusted or unadjusted RR estimates), study type (case-control or cohort), exposure (ever, recent, past), type of non-exposed subjects (never used any HRT, never used EP HRT), race (all, White, Black, Hispanic, non-Hispanic), cancer type (where invasive was defined as a minimum of 83% of cases included in the study were invasive, or the type of cancer was not specified), time period of first cases of diagnosed breast cancer (1960s-1970s, 1980s-1990s), and study location, included in the analysis since treatment practices in different parts of the US may affect the estimates. We considered analyzing breast cancer incidence versus mortality, but all eligible studies reported breast cancer incidence, not breast cancer mortality, therefore we were not able to compare incidence versus mortality. We defined recent use of EP therapy as use within the last 2 years

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immediately prior to the reference date and past use as use of EP >2 years ago. Ever use was defined as recent plus past use.

Four slight variations to our categorization of use included 1) the recent use data in the Schairer (8) study which provided an adjusted estimate for current users, not including use in the past 1-2 years, 2) the past use data in the Schairer (8) study which included data from 1-2 years, 3) the Newcomb (9) study in the past/never use analysis where past included use <5 years ago but separated out the current users, and 4) the Ross (10) study in the past/never use analysis which ascertained exposure histories up to one year before the reference date.

There were two ways of classifying study locale, one for the ever/never results and one for the recent/never results, because all of the studies in the ever/never and recent/never analyses could not be grouped into a single type of locale descriptor that was suitable for all study locations. In the ever/never studies, Eastern US was defined as studies done in Eastern or Central time zones, and Western US was defined as studies that had some sites in the Western part as well as across the US. The recent/never studies were categorized according to studies conducted in one or two time zones in the US, or studies representative of cities across the US and/or one city in Canada. We were not able to classify study local for the past/never studies into two distinct study local descriptors that were suitable for all study locations due to the limited number of studies in this analysis.

Statistical Analysis

Meta-analyses of three groupings of the published studies were performed: 1) ever/never EP HRT use, 2) recent/never EP HRT use, and 3) past/never EP HRT use. We categorized never use of EP HRT into two categories: 1) women who never used any combination of estrogen or progestin HRT (i.e., estrogen only or EP HRT) during their lifetime, and 2) women who never used EP HRT (i.e., combined estrogen and progestin HRT). Some of the studies were used in more than one analysis because results within the particular study were categorized according to more than one of the three types of use (i.e., ever, recent, past).

STATA Version 9.1 (Stata Corp., College Station, TX) was used to analyze the effect of EP HRT on the risk of breast cancer in postmenopausal women. The published studies reported ORs, RRs, or ROs for case-control studies and RRs for cohort studies, unless they reported only patient years of observation. We report all published ORs as RRs since the risk ratio and rate ratio are approximately equal over the follow-up period when the outcome is rare (11).

We always abstracted adjusted RR estimates wherever they were available and made sure that they were properly adjusted for potential confounders. When adjusted estimates were not available, we computed unadjusted estimates ourselves using either Episheet (12), or the "metan" command in Stata when risk ratios, rather than rates or hazards, were reported in the published paper.

We generated forest plots and used the "metabias" command in Stata as an indication of the potential for publication bias. We produced funnel plots and looked for evidence of funnel plot asymmetry visually and with the Begg and Mazumdar test (13),

the Egger et al. test (14), and the Duval and Tweedie trim and fill imputation method (15). We assessed overall heterogeneity of the literature by examining Cochrane Q P values from the "meta" analysis in Stata.

We examined studies for heterogeneity with regard to specific study characteristics by performing stratified and random effects meta-regression (16) analyses using the restricted maximum likelihood method to estimate the among study variance. Associations between RR estimates and characteristics of studies and patients were analyzed. We inferred the standard errors of the log RR estimates from their 95% confidence intervals (17).

Multi-variable meta-regression was not possible due to the small number of studies. All meta-regression results were transformed back to the original ratio scale. After transformation, each meta-regression coefficient estimated the ratio of the average RR in studies with one characteristic to the average RR in studies with another characteristic. These models quantified the degree of association between study characteristics and results.

Study characteristics analyzed included adjustments, type of study, time of diagnosis, type of cancer, and study location in the ever/never analysis; and study type, time of diagnosis, and study location in the recent/never analysis. Meta-regression analyses were conducted only when there were at least two studies in each category of a study characteristic.

Results

Of the ten eligible studies (7-10, 18-23) that met the inclusion criteria for the analysis (Table 1), six, five, and three studies were included in the ever/never, recent/never, and past/never analyses, respectively. One study (i.e., Li et al. (24)) was excluded from our analysis since it was the only study that presented results according to never use of the combined EP HRT regimen.

Adjusted RR estimates were used for all analyses with the exception of the Gambrell study (18) in the ever/never analysis, and the Newcomb (9), Ross (10), and Schairer (8) studies in the past/never analysis, where only unadjusted RR estimates were available by using our calculations. We estimated the 22-year risk ratio from the one cohort study by Nachtigall (20). The characteristics of the individual studies and the analysis that they were used in are presented in Table 1.

Ever/Never Use

Four of the six estimates are below the null value in the direction of a reduced rate of breast cancer among EP users. Nachtigall (20) is by far the least precise estimate (i.e., furthest away from the null) (Figure 1). Some of these estimates are much more (and less) imprecise than others. The three least precise estimates are below the null and the three very precise estimates are close to the null. The estimate we computed from Nachitgall's study (20) is an exceedingly imprecise estimate. Inconsistent study results indicate heterogeneity.

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Evidence of asymmetry was observed in the funnel plot, however some of the estimates were computed and are imprecise. The Begg and Egger tests (13, 14) both gave P=0.02, indicating evidence of funnel plot asymmetry, but the trim and fill analysis (15) imputed no hypothetically missing studies. The overall heterogeneity value of P=0.001 is indicative of a very heterogeneous literature.

Fixed and random summary effects estimates are likely to be different due to imprecise estimates. Fixed stratified results are reported for most study characteristics, however random stratified results are reported for the study type, time of diagnosis, and study location study characteristics. Study characteristic analyses (Table 2) that included studies that were adjusted, specified invasive breast cancer, and had sites in the Western US as study characteristics suggest an increased risk of breast cancer of 22%, 22%, and 10%, respectively among ever users of EP HRT. These study characteristics gave higher summary RRs on average than the study characteristics of study sites that gave unadjusted RR estimates, did not specify the type of breast cancer, and were conducted in the Eastern US. When the unadjusted RR estimates, non-specified types of breast cancer, and studies conducted in the Eastern US were removed from the analysis, the summary RR indicated increased risks of breast cancer among women who ever used EP HRT. All 95% CIs for summary RR estimates were wide. Our analysis suggests that the risk of developing breast cancer in women that ever used EP HRT was decreased in studies that reported unadjusted RR estimates, did not specify the type of breast cancer, or had sites only in the Eastern part of the US by 82%, 82%, and 53% respectively.

The risk of developing breast cancer was negligible (1%) in case-control studies and in studies with cases first diagnosed in the 1980s and 1990s. The risk of developing

breast cancer was increased in studies with adjusted RRs, case control studies, first cases of breast cancer diagnosed during the 1980s and 1990s, invasive breast, and studies that included results from states in the Western part of the US. These study characteristics increase the risk of developing breast cancer by 6½, 2½, 2½, 6½, and >2 times, respectively. A modest increase in the risk of developing breast cancer was observed in studies with unadjusted RRs, cohort studies, first cases of breast cancer diagnosed during the 1960s and 1970s, unspecified types of cancer, and studies that included results from states in the Eastern part of the US. All 95% CIs for the ratio of RR estimates were wide.

The homogeneity P values for the unadjusted studies and the studies with unspecified types of cancer were >0.2. This suggests homogeneity amongst the studies and that the studies do not differ a lot due to chance. The low P values (P<0.2) for all other study characteristics tested suggest heterogeneity amongst the studies and inconsistency due to chance.

There is a lot of overall heterogeneity and several study characteristics have strong, but imprecise associations with study results. The funnel plot asymmetry may or may not be due to biased literature; or the asymmetry may be due to one or more characteristics of studies that produce less precise estimates compared to studies that give more precise estimates. The study characteristics analysis lends support to the latter reason since it is hard to calculate estimates (i.e., Nachtigall (20), Gambrell (18)) and these values were further away from the null. Since the results were further away from the null and not reported by the authors, this is opposite of what we would expect if there was evidence of publication bias. In addition, two of the three imprecise and inverse associations (i.e., Nachtigall (20), Gambrell (18)) were unadjusted and did not specify the

type of cancer, therefore this analysis relies on the three more precise studies and all three are near the null. As a result, a single point summary estimate of this literature is contraindicated. Essentially, any study characteristic that separates two or all three of Nachtigall (20), Moorman (19), and Gambrell (18) from the others is going to show an association with an increased risk of breast cancer.

Recent/Never Use

All five estimates are above the null value in the direction of an increased rate of breast cancer among EP users (Figure 1). Some of these estimates are much more or less imprecise than others, with Kaufman (7) as the least precise estimate. Estimates from the three largest studies were more precise. These results indicate some homogeneity amongst the three largest studies.

Evidence of asymmetry was observed in the funnel plot. There was also some evidence of funnel plot asymmetry with Begg (13) and Egger (14) P values of 0.2 and 0.02, respectively. In addition, the trim and fill analysis (15) did impute one small, hypothetically missing study. However, the overall heterogeneity P value of 1.0 is indicative of a more homogeneous body of literature.

Fixed and random summary effect estimates are likely to be similar due to a more homogeneous literature, thus fixed stratified results are reported for all study characteristics. Study characteristic analyses (Table 2) resulted in all examined study characteristics giving approximately the same summary RR. All 95% CIs for summary RR estimates were wide. All ratios of RR estimates were 1.0, indicating an approximately identical probability of disease in women who were recently exposed and not exposed to

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EP HRT. All study characteristic homogeneity P values were greater than 0.2, suggesting homogeneity amongst the studies and that the studies do not differ a lot due to chance. We did not perform a study characteristic analysis for the type of cancer study characteristic due to the lack of available studies for this study characteristic.

Our analysis showed that there was not nearly as much overall heterogeneity to begin with, and none of the study characteristics were associated with the results. Overall, there was evidence of a symmetrical funnel plot, homogeneity P values were high, and all RR were equal to 1.0, warranting a summary estimate. The summary RR estimate for the recent-never results was 1.42 (95% CI, 1.26-1.60) representing a 40% increase in the risk of breast cancer among women who recently used EP HRT. This estimate was similar to the trim and fill estimate of 1.41 (95% CI 1.25-1.59).

Past/Never Use

All three estimates are above the null value in the direction of an increased rate of breast cancer among EP users (Figure 1). All estimates were computed, and some of these estimates are much more (and less) imprecise than others, with the Newcomb (9) estimate being the least precise estimate. Inconsistent study results are indicative of a heterogeneous literature.

Evidence of asymmetry was observed in the funnel plot. Begg (13) and Egger (14) P values were 0.3 and 0.6, respectively and suggest funnel plot symmetry. The trim and fill method (15) imputed no hypothetically missing studies. The overall heterogeneity P value of 0.1 is indicative of heterogeneous literature.

Due to the limited number of studies in this analysis, study characteristics analyses were not performed and a single summary estimate was contraindicated.

Discussion

This systematic review suggests that there was limited information about the risk of EP HRT and the risk of breast cancer in postmenopausal North American women prior to the publication of the WHI trial results. This analysis of the ten observational studies conducted prior to the publication of the WHI results suggest that there was consistent evidence of increased risk from using these preparations recently, as opposed to never, and inconsistent results for ever use, with the most precise estimates being very close to the null.

Limitations of our analysis include restricting our analysis to studies accepted for publication prior to the publication of the WHI's results (1) in July of 2002, including only studies conducted in the US, not considering dosages or types of EP HRT used in the studies, and the limited number of studies available for our analysis.

We decided early in our analysis not to summarize the data into a single point summary estimate due to the limited amount of data and the difficulty assessing it for evidence of publication bias. Overall heterogeneity P values for the ever/never and the past/never analysis are suggestive of a heterogeneous body of literature, whereas the P value for the recent/never analysis was suggestive of a more homogeneous body of literature. As a result we decided after our analysis of the literature that a summary estimate was warranted for the recent/never analysis

We could not pin down the heterogeneity of the ever/never results to a single study characteristic. Every one we looked at had some kind of association with the

studies' results and there is not much more that can be done with only six studies. For the recent/never analysis, there was not much evidence of heterogeneity to begin with and the associations with all the study characteristics were about as null as they could be expected to be in such a small number of studies.

The WHI trial (1) reported a 26% increase in invasive breast cancer and suggested that the increased risk was consistent with the nonsignificant 27% increase reported after 6.8 years of follow-up in the HERS study (25). The HERS study was not included in our meta-analysis. The WHI findings are consistent with other epidemiological data (26) that reported a 15% increase of breast cancer when EP was used <5 years and a 53% increase for use >5 years and our analysis that reports a 40% increase in the risk of breast cancer among recent users of EP HRT.

Lack of evidence (2) and inconsistencies in the data (3) prevented calculation of a summary estimate in prior meta-analyses conducted in the early 1990s. However, the literature published through mid-2002, combined with different methodological techniques used in our analysis, allowed for a single summary estimate of the literature for recent EP HRT use. Our findings indicate that the literature in the early 1990s looks very different from the literature in mid-2002.

Our ever/never and recent/never analysis results look different. Including past use in the ever use category may have diluted out the recent use. Past exposure is less relevant to risk and may result in misclassification of exposure. This may explain why there was no association amongst the three largest studies in the ever/never analysis and why there was a consistent, appreciable increase in risk in the recent/never analysis. Our

analysis of the literature resulted in a 40% relative increase in breast cancer in women that used EP HRT. This represents an absolute increase in risk of approximately 5% (27).

Our findings do not imply that the stopping rules of the WHI trial (1) should have been changed based on the literature available in mid-2002, especially since the stopping rule that our analysis suggests is less conservative than the stopping rules that were applied during the trial. In addition, our analysis had limitations, thus we conclude that the WHI trial (1) was a very important trial to conduct since it was the first randomized controlled trial designed to assess the risk and benefit of EP HRT as opposed to using observational data and because it represented a larger cohort of postmenopausal women. The findings from the WHI should continue to inform relevant postmenopausal hormone therapy treatment options for women.

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Table 1: Characteristics of Studies Containing Estimates of Breast Cancer Relative Risks According to the Use of Estrogen and Progestin Postmenopausal Hormone Replacement Therapy

Analysis	First Author	Publication Year	Study Design	Adjustment	RR	95% CI	Cancer Type	Time of Diagnosis	Location
Ever/Never	Gambrell (18)	1986	Cohort	No	0.19	0.09-0.40	Not specified	1960s & 1970s	Eastern US[b]
	Moorman (19)	2000	Case-control	Yes	0.70	0.40-1.1	Invasive[a]	1980s & 1990s	Eastern US[b]
	Nachtigall (20)	1992	Cohort	No	0.04	0-0.68	Not specified	1960s & 1970s	Eastern US[b]
	Newcomb (9)	2002	Case-control	Yes	1.4	1.2-1.7	Invasive	1980s & 1990s	Eastern US[b]
	Schairer (8)	2000	Cohort	Yes	1.3	1.0-1.6	Invasive	1960s & 1970s	Western US[c]
	Stanford (21)	1995	Case-control	Yes	0.90	0.70-1.3	Invasive	1980s & 1990s	Western US[c]
Recent/Never	Chen (22)	2002	Case-control	Yes	1.5	1.0-2.1	Invasive	1980s & 1990s	1-2 US time zones
	Colditz (23)	1995	Cohort	Yes	1.4	1.2-1.7	Invasive	1960s & 1970s	Across US
	Kaufman (7)	1991	Case-control	Yes	1.7	0.90-3.6	Not specified	1980s & 1990s	Across US[d]
	Newcomb (9)	2002	Case-control	Yes	1.4	1.1-1.7	Invasive	1980s & 1990s	1-2 US time zones
	Schairer (8)	2000	Cohort	Yes	1.4	1.1-1.9	Invasive	1960s & 1970s	Across US
Past/Never	Newcomb (9)	2002	Case-control	No	1.9	1.2-3.2	Invasive	1980s & 1990s	NA
	Ross (10)	2000	Case-control	No	1.2	0.99-1.4	Invasive	1980s & 1990s	NA
	Schairer (8)	2000	Cohort	No	1.1	0.73-1.7	Invasive	1960s & 1970s	NA

[a] Where at least 83-89% of the cases were invasive.
[b] Studies done in Eastern and Central time zones
[c] Studies that have some sites in the Western part of the US.
[d] Included the Canadian city of London, Ontario.
Abbreviations: NA, not applicable; US, United States

Figure 1: Forest Plots of Ever/Never, Recent/Never, and Past/Never Meta-Analyses

EVER-NEVER USE
Gambrell (1986)
Nachtigall (1992)
Stanford (1995)
Moorman (2000)
Schairer (2000)
Newcomb (2002)

RECENT-NEVER USE
Kaufman (1991)
Colditz (1995)
Schairer (2000)
Chen (2002)
Newcomb (2002)
SUMMARY

PAST-NEVER USE
Ross (2000)
Schairer (2000)
Newcomb (2002)

0.02   0.05   0.1   0.4   1.0   2.7   7.4
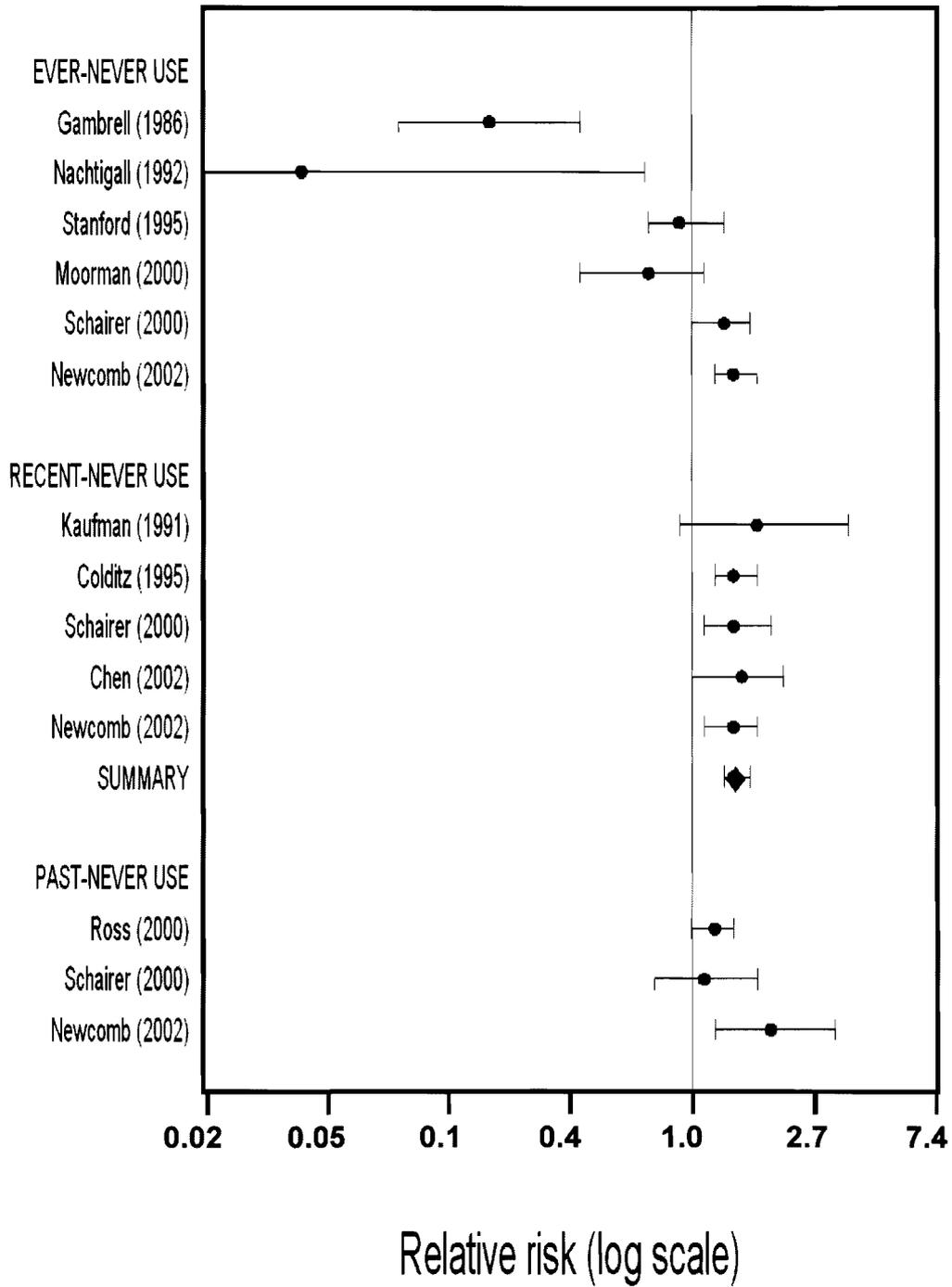
Relative risk (log scale)

Table 2. Analysis of Study Characteristics

Analysis	Study characteristic	Design	Number of studies	Homogeneity P-value	Summary RR (95% CI)	Ratio of RRs (95% CI)
Ever/Never	Adjustment	Unadjusted	2	0.28	0.18 (0.09 – 0.36)	1.0
		Adjusted	4	0.01	1.22 (1.07 – 1.39)	6.5 (2.6-15.9)
	Study design	Cohort	3	0.00	0.31 (0.05-1.79)	1.0
		Case control	3	0.01	1.01 (0.66-1.54)	2.5 (0.6-10.9)
	Time of diagnosis	1960s-1970s	3	0.00	0.31 (0.05-1.79)	1.0
		1980s-1990s	3	0.01	1.01 (0.66-1.54)	2.5 (0.6-10.9)
	Cancer type	Not specified	2	0.28	0.18 (0.09-0.36)	1.0
		>83% of cases were invasive	4	0.01	1.22 (1.07-1.39)	6.5 (2.6-15.9)
	Location	Eastern US	4	0.00	0.47 (0.16-1.33)	1.0
		Western US[a]	2	0.06	1.10 (0.77-1.57)	2.2 (0.5-10.0)
Recent/Never	Study design	Cohort	2	0.97	1.41 (1.19-1.66)	1.0
		Case control	3	0.84	1.43 (1.20-1.71)	1.0 (0.8-1.3)
	Time of diagnosis	1960s-1970s	2	0.97	1.41 (1.19-1.66)	1.0
		1980s-1990s	3	0.84	1.43 (1.20-1.71)	1.0 (0.8-1.3)
	Location	1-2 times zones in US	2	0.74	1.41 (1.18-1.70)	1.0
		Across US[b]	3	0.87	1.42 (1.21-1.67)	1.0 (0.8-1.3)

[a] Includes some studies conducted throughout the United States involving some Western states.
[b] One study included the Canadian city of London, Ontario.
Abbreviations: CI, confidence limits; RR, relative risk; NA, not applicable; US, United States.