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Menopausal Hormone Therapy and Breast Cancer Risk in the NIH-AARP Diet and Health Study Cohort

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Abstract

BACKGROUND—Results from the Women’s Health Initiative (WHI) trial raise new questions regarding the effects of estrogen therapy (ET) and estrogen plus progestin therapy (EPT) on breast cancer risk.

METHODS—We analyzed data from 126,638 females, 50–71 years of age at baseline, who completed two questionnaires (1995–1996, 1996–1997) as part of the NIH-AARP Diet and Health Cohort Study and in whom 3,657 incident breast cancers were identified through June 30, 2002. Hormone-associated relative risks (RR) and 95% confidence intervals (CI) of breast cancer were estimated via multivariable regression models.

RESULTS—Among thin women (body mass index $<25 \text{ kg/m}^2$), ET use was associated with a significant 60% excess risk after 10 years of use. EPT was associated with a significantly increased risk among women with intact uteri, with the highest risk among current, long-term (≥ 10 years) users (RR=2.44, 95% CI 2.13–2.79). These risks were slightly higher when progestins were prescribed continuously than sequentially (<15 days/month) (respective RRs of 2.76 vs. 2.01). EPT associations were strongest in thin women, but elevated risks persisted among heavy women. EPT use was strongly related to estrogen receptor positive (ER+) tumors, requiring consideration of this parameter when assessing relationships according to other clinical features. For instance, ER– ductal tumors were unaffected by EPT use, but all histologic subgroups of ER+ tumors were increased, especially low-grade and mixed ductal-lobular tumors.

CONCLUSIONS—Both ET and EPT were associated with breast cancer risks with the magnitude of increase varying according to body mass and clinical characteristics of the tumors.

Keywords

breast cancer; hormones; menopause; risk; tumor characteristics

Introduction

A significant elevation in breast cancer risk among users of menopausal estrogen plus progestin therapy (EPT) has been observed across multiple studies (1), including the recently conducted Women’s Health Initiative (WHI) clinical trial (2,3). When results from this trial were announced in 2002, clinical guidelines were re-formulated to recommend that women use hormones at low doses for short periods of time only for symptom management, leading

millions of women to discontinue usage (4). The strength of evidence between EPT use and increased breast cancer risk was reinforced when population data subsequently showed marked declines in breast cancer incidence (5,6).

Limited data exist on how risks change after cessation of use, but resolution of this is now more important than ever. Further, questions exist about the role of unopposed estrogen therapy (ET), which has been linked to elevated breast cancer risks in numerous observational studies (7), but not in WHI (2). WHI data surprisingly showed somewhat of an inverse relationship (2), although recent analyses suggest that this might reflect more extended intervals between menopause and age at first use of hormones among trial participants (8). With respect to EPT, results from WHI focused on continuous regimens of 0.625 mg. of conjugated equine estrogen plus 2.5 mg. of medroxyprogesterone acetate (MPA) per day, but data relating to other regimens are limited. In particular, it has not yet been possible to resolve whether usage of progestins sequentially (SEPT) affects risk differently than continuous usage (CEPT) (9–16).

Although many investigations support that hormones exert stronger relationships among thin women (13,17–23), it is unclear whether the increasing prevalence of obesity in the U.S. could explain some of the divergence of results between more recent studies and earlier investigations, which nearly all showed increased breast cancer risks related to ET (1,17). Whether there continues to be an increased risk associated with certain hormone usage patterns among heavier women is also unclear.

Increasing evidence suggests that hormone associations may be dependent on tumor characteristics, including stage or grade (24–26), histology (9–13,25,27–34) and hormone receptor status (12,19,24,26,27,33–35), although results have not been entirely consistent. While most studies show that hormone associations are generally stronger for tumors with favorable clinical characteristics, WHI showed the reverse (36). Some of the difficulty in resolving tumor subtype associations may reflect that most investigations have assessed relationships with clinical characteristics in isolation of each other, despite there being a high degree of inter-correlation. For instance, recent studies have suggested stronger hormone associations for lobular than ductal tumors (25,27,29,31,32), but most have not considered how relationships by histology are affected by estrogen receptor positivity, also linked to enhanced hormone associations.

To clarify these unresolved questions, we evaluated relationships within the large prospective NIH-AARP Diet and Health Study.

Methods

Study Population

The NIH-AARP Diet and Health Study Cohort was established in 1995–1996 when a questionnaire requesting information on demographic characteristics, dietary intake, and health-related behaviors was sent to 3.5 million AARP members (37). Recipients of the questionnaire included members aged 50–71 years who resided in one of six U.S. states (CA, FL, LA, NH, NC, and PA) or two metropolitan areas (Atlanta, GA, and Detroit, MI). A total of 617,119 persons (17.6%) returned the questionnaire, with 567,169 (16.2%) satisfactorily completing it. In 1996–1997, a second risk factor questionnaire was sent to collect additional information on diet, family history of cancer, anthropometry, physical activity, and use of menopausal hormones, with a 59.4% response rate (n=337,074). After excluding participants who died (n=1,619), moved out of the study area before their second questionnaires were received and scanned (n=547), had proxies complete their baseline (n=6,959) or second (3,424) questionnaires, or were male (n=188,117), 136,408 potentially eligible women remained. The

Special Studies Institutional Review Board of the National Cancer Institute approved this study.

Exposure Ascertainment

The second questionnaire, administered in 1996–1997, collected detailed data on ever-use, dates of first and last use, total duration of use, regimen, usual dose, and pill used for the longest period of time for both estrogens and progestins. Current usage was defined according to usage patterns at the time of administration of this questionnaire. Subjects were asked about individual years of usage up to 10 years, with longer term use collected only as 10 or more years. We used reported ages at first and last use to estimate longer term usage for selective analyses.

We considered women who reported taking both estrogen and progestin pills to have used estrogen plus progestin if the reported dates of first use were within 90 days of each other or if reported durations of use were identical. Such women were further subdivided according to whether their usual pattern of use of progestins was sequential (for fewer than 15 days per cycle) or continuous (every day of the cycle). The 408 and 2,058 women who reported taking progestins for 15–19 or 20–25 days per cycle were categorized as having used the continuous regimen.

Cohort Follow-up

Cohort members were followed annually for address changes and vital status. Address changes were identified through linkage to the U.S. Postal Service's (USPS) National Change of Address database, USPS updates received with undeliverable mail, use of other address change update services, and participants' notifications. Vital status was updated through linkage to the Social Security Administration Death Master File and verified by the National Death Index (NDI).

Incident Cancers

Based on annually updated residence information and using first and last name, address, sex, date of birth, and social security number obtained from the baseline questionnaire, incident cases of *in situ* and invasive breast cancers were identified by probabilistic linkage to the cancer registries in the eight states from which study subjects were derived. All suspected matches underwent review to reject the potential matches that were unlikely to be true (an estimated 4%), and uncertain matches underwent final manual review. An earlier validation study that compared registry findings with self-reports and medical records estimated that linkage validly identified approximately 90% of all incident cancers among study participants (38). The cancer registry ascertainment area was recently expanded to include three additional states (Texas, Arizona, and Nevada) to capture cancers occurring among participants who moved to those states during follow-up.

Dates of diagnosis and tumor characteristics were obtained from the cancer registries. Using histologic codes from the *International Classification of Diseases for Oncology, Third Edition* (ICD-O-3), we classified breast cancer into ductal (ICD-O-3 codes 8500 or 8523), lobular (ICD-O-3 codes 8520 or 8524), and mixed ductal/lobular tumors (ICD-O-3 code 8522).

Analytic Population

We excluded 9,022 women who reported a history of cancer other than non-melanoma skin cancer on either questionnaire (including 942 breast cancers), 745 women who were missing all information on menopausal hormone use, and 3 women with no follow-up. Analyses therefore focused on 126,638 women.

Study entry and follow-up began at the age at which the second questionnaire was scanned, and continued until June 30, 2002 or the earliest of the following: participant diagnosed with breast cancer, moved out of the registry catchment area, or died from any cause. The censoring or exit date was chosen to account for declines by approximately 50% in hormone use (39) subsequent to release in July, 2002 of findings from the WHI that linked EPT with increased breast cancer risks (40). During follow-up in our study, a total of 3,657 women developed breast cancer (607 *in situ* cancers, 3,035 invasive cancers, 15 with missing stage information).

Because the Florida, Pennsylvania, and Michigan state cancer registries did not collect hormone receptor information, estrogen and progesterone receptor data were available for only 1,451 (39.7%) and 1,403 (38.4%), respectively, of the breast cancer cases. Analyses regarding hormone receptor status excluded women from these three states. There were no substantial risk factor differences between women from states where hormone receptor information was available and states where it was unavailable.

Statistical Analysis

We used Cox proportional hazards regression (using SAS 8.2 software, SAS Institute, Inc., Cary, NC), with age as the time scale and ties handled by complete enumeration (41), to estimate the relative risk (RR) and 95% confidence intervals (CI) of developing breast cancer. Tests of the proportional hazards assumptions for exposures and other variables included in statistical models revealed no departures.

Although most women who use ET have had a hysterectomy, older women with intact uteri had opportunities to take ET before added progestins became routine. We therefore analyzed ET associations in the entire cohort as well as in the 51,237 women with hysterectomy at baseline. We limited the assessment of EPT to the 73,986 women with intact uteri at baseline. A total of 1,415 women were excluded from these analyses due to missing data.

We initially evaluated potential confounding by all identified risk factors but ultimately chose a parsimonious combination of variables that were associated with both exposure and outcome and changed the hormone therapy parameter estimates compared with estimates from models adjusted for only age at entry. Our statistical models adjusted for age at entry, race/ethnicity, age at first birth, menopausal status (including oophorectomy status), age at menopause, number of breast biopsies, family history of breast cancer in a first degree relative, and number of mammograms in the three years preceding the second questionnaire. Adjustment for additional risk factors, including years of education, parity, physical activity levels, alcohol consumption and usage of non-steroidal inflammatory drugs, had minimal effects on hormone risks. To assess possible biases associated with unknown types of or ages at menopause (including those with simple hysterectomies) (42,43), we conducted sensitivity analyses with different assumptions. Our results were unchanged by eliminating those women who were unable to report ages at menopause or by setting age at menopause among women with simple hysterectomies to the date of first usage of menopausal hormones.

Results

Characteristics of the Cohort

The 126,638 women contributed 671,546.2 person-years. The mean durations of follow-up (and ranges) were 2.76 years (0.003–5.62) for those who developed breast cancer and 5.38 (0.003–5.67) for those who did not. The mean ages at entry and exit were 62.6 and 67.9 years, respectively. The standardized incidence ratio for breast cancer among AARP members compared with the NCI's Surveillance, Epidemiology and End Results rate (ages 50–79 years) was 1.10 (95% confidence interval [CI] = 1.07–1.13).

Most women in the cohort were white, postmenopausal, and in their 60s when they completed the second questionnaire (Table 1). Whites were at a higher risk than non-whites. Breast cancer risk was positively associated with age at first birth, age at natural menopause, body mass index (BMI), number of breast biopsies, a family history of breast cancer, number of recent mammograms, and number of alcoholic drinks per day. Inverse relations of risk were observed with age at menarche, parity, and age at bilateral oophorectomy.

Hormone Usage Patterns

A total of 38.8% of the person-years were contributed by women who never used hormones, while 27.9% were contributed by ET-only users and 21.8% by EPT users (either EPT alone or EPT use preceded by ET, with both types of users having similar risks). The remaining women (11.5%) used other combinations of use of hormones (PT followed by EPT, ET followed by PT, PT followed by ET, EPT followed by PT, EPT followed by ET, EPT unknown, other combinations or unknown).

Compared with non-users of hormones, women who had used hormones were more likely to be white, married, oral contraceptive users, and thin ($BMI < 25 \text{ kg/m}^2$), and to have had multiple breast biopsies. ET users were more likely to have had a surgical menopause and given birth at younger ages. EPT users were more likely to be younger, be college graduates, have reported more frequent recent mammograms, and be in excellent or very good health at baseline.

Unopposed Estrogen Therapy (ET)

Among all women, ET-only use was associated with a RR of 1.15 (95% CI 1.04–1.27) (Table 2), with no further evidence of increase seen for longer durations of use. Current users were at a slightly higher risk ($RR=1.24$) than former users (0.99). There was no evidence that risk rose with increasing durations of use among current users. Among former users, no trend in risk was apparent according to time since last use, although recent quitters were at reduced risk (0.71, 0.51–0.98). Analyses restricted to women with a hysterectomy at baseline confirmed only weak associations with ET, although estimates were slightly lower than those observed among all women.

Estrogen Plus Progestin Therapy (EPT)

Among women with intact uteri, EPT use was associated with a significantly increased risk ($RR=1.82$, 95% CI 1.65–2.01) (Table 3). The increased risks were driven by high risks associated with current usage, with women having discontinued hormone use 5 or more years previously showing no evidence of any increased risk. Among current users, risks increased with extended durations of use, rising to 2.44 (2.13–2.79) among women exposed for ≥ 10 years. Women who had used progestins sequentially (< 15 days/month) were at a slightly lower risk (1.63, 1.42–1.86) than those who had used them continuously (1.98, 1.78–2.21). These differences became even more marked when attention focused on current long-term users (≥ 10 years), with the risks rising to 2.01 (1.65–2.45) for sequential users and 2.76 (2.35–3.25) for continuous users. Risk did not vary in any systematic way with dose of or actual days progestins were used, apart from there being somewhat higher risks for those who used progestins for ≥ 10 days vs. < 10 days.

Analyses restricted to the most common modes of therapy, namely sequential regimens containing 5.0 mg/day or 10.0 mg/day of medroxyprogesterone acetate (MPA) or continuous regimens containing 2.5 mg/day or 5.0 mg/day of MPA produced similar associations to those of all reported sequential or continuous regimens (data not shown).

Modifications of Relationships by Other Factors

The risks associated with ET (among all women) and EPT (among women with intact uteri) were evaluated further according to the presence or absence of breast cancer risk factors (Table 4). The risks associated with hormone use did not vary substantially by most risk factors. However, there were significant interactions between body mass and both years of ET and EPT (interaction p values for both of 0.01). In thin women, ET use of 10 or more years was associated with a RR of 1.60 (95% CI 1.31–1.96), while there was no increased risk among the heaviest women. Extended EPT use led to nearly a 3-fold increased risk among the thin women, but even among the heaviest women there was an approximate 2-fold increased risk.

Relationships with hormone use were also explored according to tumor characteristics (Table 5). ET relationships did not vary substantially or in any systematic manner by tumor stage (*in situ* vs. invasive) or estrogen receptor (ER) status (negative vs. positive). However, relationships with ever and current usage were slightly stronger for low-grade and mixed ductal/lobular tumors, albeit without evidence of a trend in risk with increasing durations of use.

Although EPT associations also did not vary substantially by tumor stage, there was some variation in risks by the other clinical characteristics. While there was no increased risk associated with long-term use for ER– tumors, over a 3-fold increased risk was seen for ER+ tumors. Further, higher hormone-associated risks were seen for low-grade and mixed histology tumors. While long-term EPT use related only to a 1.7-fold increased risk of grade 3 tumors, the elevation in risk for grade 1 tumors approached a 5-fold excess. A similar excess 5-fold increased risk associated with long-term use was seen for mixed ductal/lobular tumors, which contrasted with RRs of 2.54 for ductal and 1.37 for lobular tumors.

The majority of the tumors with available hormone receptor data were ER+, with somewhat higher rates of ER positivity seen for lobular and mixed ductal/lobular tumors (Table 6). The high correlation between the various tumor markers made it difficult to discern the independence of effects. However, among women with intact uteri, there appeared to be no relationship of EPT use to risk of ductal tumors that were ER– (RR=1.02), but over a doubling of risk for such tumors that were ER+ (RR= 2.61, 95% CI 2.10–3.24). A similar increase in risk associated with EPT use was seen for ER+ lobular tumors, but even higher risks were observed for ER+ tumors with mixed histologies (6.37, 3.45–11.79). Similarly elevated risks associated with EPT use were seen for low-grade, ER+ tumors. Somewhat less predictive of risk were combinations of tumors defined jointly by histology and grade.

Cumulative Incidence

The cumulative incidence of developing breast cancer in this population was 54.5 per 10,000 person-years. Among all women, ET users had a 9% higher cumulative incidence compared with non-HT users (48.8 versus 44.7 per 10,000 person-years). Among women with intact uteri, the cumulative incidences compared to non-users were 75%, 59% and 89% higher, respectively, for all EPT users, sequential users and continuous users (76.4, 69.5, and 82.6 per 10,000 person-years, respectively) compared with non-HT users (43.7 per 10,000 person-years).

Discussion

Results from this large prospective study confirmed elevations in breast cancer risk associated with current usage of menopausal hormones. The highest risks were seen among current, long-term EPT users, although ET use also led to elevated risks among thin women. Risks quickly

dissipated after discontinuation of hormone use, with no increases in risk seen five or more years after discontinuation.

These results are generally consistent with other recent prospective (18–20,22,27,33,44–46) and case-control (13,16,29,30,32,47) studies and the growing consensus that EPT use is a breast cancer risk factor. However, somewhat reduced risks seen for ET in WHI starkly contrasted with results from many observational studies. This included data from the large Collaborative Group on Hormonal Factors and Breast Cancer (17), which showed clear increases in breast cancer risk among current long-term ET users. Further confusion regarding the relationship has arisen since some recent U.S. observational studies failed to show increased risks of ET use related to breast cancer risk (7,9,10,12,15,16,48). These studies contrast with most studies in Europe which have shown fairly consistent risk increases associated with ET use (18,21, 27,44,46). This has raised questions as to whether such differences could reflect variations in the types of estrogens prescribed in the U.S. versus Europe (conjugated equine estrogens versus the more potent estrogen 17 β estradiol), although results from the recent Million Women Study (18) found no substantial differences in risk between the two estrogen types.

In the U.S., use of ET and its typical users have changed in the last 30 years. Although today ET use is generally limited to women with hysterectomy, this was not the case prior to the mid-1990s (4). Thus, much of the early literature on ET and breast cancer focused on women with intact uteri (17). These temporal changes occurred concurrently with a change from use for symptoms to use for potential disease prevention (49), and with trends of increasing obesity (50). Thus, compared with earlier studies, ET users in our study included more hysterectomized and heavy women, both factors that would tend to attenuate ET risks.

Our results and those from most other contemporary investigations (13,17–23) indicate that a complete assessment of hormone effects must assess modifying effects of body size. Weak associations between ET and breast cancer were in stark contrast to nearly a doubling in risk for EPT. However, among thin women, we found that long-term ET use was associated with a 60% significantly elevated risk, similar to findings of most European investigations (18,21, 44,46). EPT relationships were also stronger among thin women, but of note was that EPT continued to exert increases in breast cancer risk even among heavier women. Thus, even among the heaviest women in our study, we still observed a 2-fold increased risk associated with long-term use of EPT.

The growing trends towards more American women becoming obese (50) thus raises questions as to whether hormone effects may have been underestimated in recent U.S. studies, including the WHI trial where over 80% of study subjects were classified as having heavier than ideal body masses. In the WHI trial, some attempts were made to address effect modification by body size; EPT relations were somewhat stronger among thin women (51), but this was not true for ET (52). These analyses, however, were limited by small numbers of thin women and short follow-up periods. Additionally, it has recently been shown that much of the lower breast cancer risk seen in the WHI unopposed estrogen trial was among women who had not previously used hormones (8), resulting in adjustment for the time from menopause to first use of ET raising risk estimates to those of the trial's observational subcohort data. This further complicates the assessment of the extent to which hormone effects may have been underestimated by an inability to adequately take weight into account. Thus, resolution of the impact of obesity on breast cancer hormone relationships (both ET and EPT) will require additional large observational studies.

An additional difficulty in resolving associations of ET on breast cancer risk in observational studies is that this mode of therapy is now recommended only for women who have undergone a hysterectomy, many of whom also keep their ovaries (53). It is impossible to determine a

“true” age at menopause for women who undergo a simple hysterectomy. The resulting potential bias to estimates of hormone associations has received extensive previous attention (42,43). However, there is no single ideal approach for addressing this problem, even though women with simple hysterectomy comprise a substantial proportion of all hormone users (especially ET users). We conducted different sensitivity analyses to assess the extent of this bias, and were not convinced that our risk estimates were confounded by imprecise information. Because of the older age of our respondents, we also had a unique opportunity to compare ET results between those who received it in conjunction with a hysterectomy and those who never had any surgical intervention, who comprised a sizeable number of all of our ET users. The lack of difference in results between these two groups was reassuring. Nonetheless, it is possible that our results for ET were somewhat biased because of the inability to precisely identify age at menopause among women with a simple hysterectomy, although this would, if anything, have tended to underestimate the risks presented.

Previous studies have provided discrepant results regarding how the administration of progestins in EPT affects breast cancer risk, with some showing higher risks associated with continuous therapy (10,14,16,21,34,45,46,54–56), another showed a higher risk associated with sequential therapy (15), and still others showing no major differences in the two regimens (9,12,13,18,29,47). We found somewhat stronger associations for continuous than sequential EPT use, particularly for current and long-term use. Our finding emphasizes the importance of future investigations being able to evaluate high-risk use patterns to clarify differences according to hormone regimens.

As in previous investigations (12,19,24,26,27,33–35), we found that combined therapy was strongly related to ER+ tumors, but unrelated to ER– tumors. Our findings are consistent with recent U.S. preferential declines in the incidence of ER+ tumors (5,6) following the 2002 WHI report and subsequent cessation of this regimen. We also found a somewhat stronger relationship with low grade tumors, in line with several previous investigations (24–26).

Numerous studies have reported stronger hormone associations for invasive lobular than ductal tumors (9–13,25,27,29–34). Few epidemiological studies, however, have been able to assess associations according to newer diagnostic criteria which incorporate classification of mixed ductal-lobular carcinomas as well as the more conventional categories of ductal and lobular tumors. Two studies that have assessed hormone risks for mixed tumors found EPT risks intermediate between those for pure ductal and lobular tumors (30,31), but we, like one other study (27) found the highest hormone risks for mixed tumors, with little difference in hormone associations for ductal versus lobular tumors.

In comparing our results with those of others, the generally older age of our study subjects must be considered, resulting in the majority of tumors being ER+. This may explain some of the discrepancy in our results versus those of others. As noted elsewhere (25), the high degree of inter-correlation between clinical features complicates the interpretation of epidemiologic associations. For instance, our mixed histology tumors tended to be ER+, the group in whom hormone risks were highest. EPT use was unrelated to ER– ductal tumors, but led to a 2.6-fold increased risk of ER+ ductal tumors. Our findings stress the complexity of breast cancer as a heterogeneous disease and support the need for additional development of statistical approaches for assessing effects of correlated tumor characteristics.

Some study limitations may have affected our findings. Updated hormone therapy data were not available after the second questionnaire. However, the short follow-up period should have minimized potential exposure misclassification, particularly since hormone use increased in the U.S. during this time, leading many participants to continue usage through 2002. Nonetheless, we could not evaluate whether cessation of or changes in use after baseline

differed by exposure or breast cancer status. Further, reported duration of use at baseline would have systematically underestimated the true total duration of hormone therapy use in the population during the study period.

Additionally, although the baseline questionnaire was sent to a large and representative group of women over age 50, it generated a relatively low response rate. A greater proportion (nearly 60%) of its respondents completed the second questionnaire, which was the basis for deriving most of the hormone exposures considered. Nonetheless, compared with nonrespondents, respondents to the second questionnaire were more likely to be older, Caucasian, educated, in good health, thin, and current or longer-term hormone users, which may have limited the generalizability of our results. Finally, we lacked hormone receptor data for a substantial proportion of the cancers. Although this hindered our ability to assess relationships according to hormone receptor status, we do not believe that this biased our results, given that the absence of data was systematic rather than unsystematic (relating to whether cancer registries recorded such data). It was further reassuring that other risk factors did not differ substantially between state registries that recorded hormone receptor data and those that did not record such data.

In summary, our study provides unique data relevant to recent patterns of hormone usage in the U.S. Of particular concern were our EPT results, which were consistent with an increase of approximately 33 cases of breast cancer for every 10,000 users (as compared with 4 additional cases for every 10,000 ET users). However, certain subgroups of users, notably thin women, may experience even higher risks, particularly for certain tumor subgroups. Thus, a true appreciation of hormone effects on breast cancer risk is dependent on considering modifying effects of body size and variation in risks according to combined breast cancer clinical features.

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Reference List

1. Colditz GA. Estrogen, estrogen plus progestin therapy, and risk of breast cancer. *Clin Cancer Res* 2005 Jan 15;11(2 Pt 2):909s–917s. [PubMed: 15701886]
2. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004 Apr 14;291(14):1701–1712. [PubMed: 15082697]
3. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002 Jul 17;288(3):321–333. [PubMed: 12117397]
4. Stefanick ML. Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. *Am J Med* 2005 Dec 19;118:64–73. [PubMed: 16414329]

5. Glass AG, Lacey JV Jr, Carreon JD, Hoover RN. Breast Cancer Incidence, 1980 2006: Combined Roles of Menopausal Hormone Therapy, Screening Mammography, and Estrogen Receptor Status. *J Natl Cancer Inst* 2007;99:1152–1161. [PubMed: 17652280]
6. Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med* 2007 Apr 19;356(16):1670–1674. [PubMed: 17442911]
7. Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995 Jun 15;332(24):1589–1593. [PubMed: 7753136]
8. Prentice RL, Chlebowski RT, Stefanick ML, Manson JE, Langer RD, Pettinger M, et al. Conjugated Equine Estrogens and Breast Cancer Risk in the Women's Health Initiative Clinical Trial and Observational Study. *Am J Epidemiol* 2008;167:1407–1415. [PubMed: 18448442]
9. Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. *JAMA* 2002 Feb 13;287(6):734–741. [PubMed: 11851540]
10. Daling JR, Malone KE, Doody DR, Voigt LF, Bernstein L, Coates RJ, et al. Relation of regimens of combined hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma. *Cancer* 2002 Dec 15;95(12):2455–2464. [PubMed: 12467057]
11. Li CI, Weiss NS, Stanford JL, Daling JR. Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. *Cancer* 2000 Jun 1;88(11):2570–2577. [PubMed: 10861435]
12. Li CI, Malone KE, Porter PL, Weiss NS, Tang MT, Cushing-Haugen KL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. *JAMA* 2003 Jun 25;289(24):3254–3263. [PubMed: 12824206]
13. Newcomb PA, Titus-Ernstoff L, Egan KM, Trentham-Dietz A, Baron JA, Storer BE, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2002 Jul;11(7):593–600. [PubMed: 12101105]
14. Porch JV, Lee IM, Cook NR, Rexrode KM, Burin JE. Estrogen-progestin replacement therapy and breast cancer risk: the Women's Health Study (United States). *Cancer Causes Control* 2002 Nov;13(9):847–854. [PubMed: 12462550]
15. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000 Feb 16;92(4):328–332. [PubMed: 10675382]
16. Weiss LK, Burkman RT, Cushing-Haugen KL, Voigt LF, Simon MS, Daling JR, et al. Hormone replacement therapy regimens and breast cancer risk. *Obstet Gynecol* 2002 Dec;100(6):1148–1158. [PubMed: 12468157]
17. Collaborative Group on Hormonal Factors in Breast Cancer. 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. *Lancet* 1997 Oct 11;350(9084):1047–1059. [PubMed: 10213546]
18. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003 Aug 9;362(9382):419–427. [PubMed: 12927427]
19. Chen WY, Manson JE, Hankinson SE, Rosner B, Holmes MD, Willett WC, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med* 2006 May 8;166(9):1027–1032. [PubMed: 16682578]
20. Lee S, Kolonel L, Wilkens L, Wan P, Henderson B, Pike M. Postmenopausal hormone therapy and breast cancer risk: the Multiethnic Cohort. *Int J Cancer* 2006 Mar 1;118(5):1285–1291. [PubMed: 16170777]
21. Magnusson C, Baron JA, Correia N, Bergstrom R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. *Int J Cancer* 1999 May 5;81(3):339–344. [PubMed: 10209946]
22. Rosenberg L, Palmer JR, Wise LA, Adams-Campbell LL. A prospective study of female hormone use and breast cancer among black women. *Arch Intern Med* 2006 Apr 10;166(7):760–765. [PubMed: 16606813]

23. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000 Jan 26;283(4):485–491. [PubMed: 10659874]
24. Daling JR, Malone KE, Doody DR, Voigt LF, Bernstein L, Marchbanks PA, et al. Association of regimens of hormone replacement therapy to prognostic factors among women diagnosed with breast cancer aged 50–64 years. *Cancer Epidemiol Biomarkers Prev* 2003 Nov;12(11 Pt 1):1175–1181. [PubMed: 14652277]
25. Garcia-Closas M, Brinton LA, Lissowska J, Chatterjee N, Peplonska B, Anderson WF, et al. Established breast cancer risk factors by clinically important tumour characteristics. *Br J Cancer* 2006 Jul 3;95(1):123–129. [PubMed: 16755295]
26. Stahlberg C, Pedersen AT, Andersen ZJ, Keiding N, Hundrup YA, Obel EB, et al. Breast cancer with different prognostic characteristics developing in Danish women using hormone replacement therapy. *Br J Cancer* 2004 Aug 16;91(4):644–650. [PubMed: 15238982]
27. Fournier A, Fabre A, Mesrine S, Boutron-Ruault MC, Berrino F, Clavel-Chapelon F. Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. *J Clin Oncol* 2008 Mar 10;26(8):1260–1268. [PubMed: 18323549]
28. Gapstur SM, Morrow M, Sellers TA. Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. *JAMA* 1999 Jun 9;281(22):2091–2097. [PubMed: 10367819]
29. Li CI, Malone KE, Porter PL, Lawton TJ, Voigt LF, Cushing-Haugen KL, et al. Relationship between menopausal hormone therapy and risk of ductal, lobular, and ductal-lobular breast carcinomas. *Cancer Epidemiol Biomarkers Prev* 2008 Jan;17(1):43–50. [PubMed: 18199710]
30. Newcomer LM, Newcomb PA, Potter JD, Yasui Y, Trentham-Dietz A, Storer BE, et al. Postmenopausal hormone therapy and risk of breast cancer by histologic type (United States). *Cancer Causes Control* 2003 Apr;14(3):225–233. [PubMed: 12814201]
31. Reeves GK, Beral V, Green J, Gathani T, Bull D. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol* 2006 Nov;7(11):910–918. [PubMed: 17081916]
32. Rosenberg LU, Magnusson C, Lindstrom E, Wedren S, Hall P, Dickman PW. Menopausal hormone therapy and other breast cancer risk factors in relation to the risk of different histological subtypes of breast cancer: a case-control study. *Breast Cancer Res* 2006;8(1):R11. [PubMed: 16507159]
33. Tjonneland A, Christensen J, Thomsen BL, Olsen A, Overvad K, Ewertz M, et al. Hormone replacement therapy in relation to breast carcinoma incidence rate ratios: a prospective Danish cohort study. *Cancer* 2004 Jun 1;100(11):2328–2337. [PubMed: 15160335]
34. Ursin G, Tseng CC, Paganini-Hill A, Enger S, Wan PC, Formenti S, et al. Does menopausal hormone replacement therapy interact with known factors to increase risk of breast cancer? *J Clin Oncol* 2002 Feb 1;20(3):699–706. [PubMed: 11821451]
35. Chen WY, Hankinson SE, Schnitt SJ, Rosner BA, Holmes MD, Colditz GA. Association of hormone replacement therapy to estrogen and progesterone receptor status in invasive breast carcinoma. *Cancer* 2004 Oct 1;101(7):1490–1500. [PubMed: 15378477]
36. Antoine C, Liebens F, Carly B, Pastijn A, Rozenberg S. Influence of HRT on prognostic factors for breast cancer: a systematic review after the Women's Health Initiative trial. *Hum Reprod* 2004 Mar; 19(3):741–756. [PubMed: 14998980]
37. Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, Hollenbeck AR, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol* 2001 Dec 15;154(12):1119–1125. [PubMed: 11744517]
38. Michaud DS, Midthune D, Hermansen S, Leitzmann M, Harlan LC, Kipnis V, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. *J Regist Manag* 2005;32:70–75.
39. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA* 2004 Jan 7;291(1):47–53. [PubMed: 14709575]
40. NHLBI Stops Trial of Estrogen Plus Progestin Due to Increased Breast Cancer Risk, Lack of Overall Benefit. 2002 Jul 9. <http://www.nhlbi.nih.gov/new/press/02-07-09.htm>

41. Gail MH, Lubin JH, Rubinstein LV. Likelihood calculations for matched case-control studies and survival studies with tied death times. *Biometrika* 1981;68:703–707.
42. Pike MC, Ross RK, Spicer DV. Problems involved in including women with simple hysterectomy in epidemiologic studies measuring the effects of hormone replacement therapy on breast cancer risk. *Am J Epidemiol* 1998 Apr 15;147(8):718–721. [PubMed: 9554412]
43. Rockhill B, Colditz GA, Rosner B. Bias in breast cancer analyses due to error in age at menopause. *Am J Epidemiol* 2000 Feb 15;151(4):404–408. [PubMed: 10695599]
44. Ewertz M, Mellekjær L, Poulsen AH, Friis S, Sørensen HT, Pedersen L, et al. Hormone use for menopausal symptoms and risk of breast cancer. A Danish cohort study. *Br J Cancer* 2005 Apr 11;92(7):1293–1297. [PubMed: 15785751]
45. Jernstrom H, Bendahl PO, Lidfeldt J, Nerbrand C, Agardh CD, Samsioe G. A prospective study of different types of hormone replacement therapy use and the risk of subsequent breast cancer: the women's health in the Lund area (WHILA) study (Sweden). *Cancer Causes Control* 2003 Sep;14(7):673–680. [PubMed: 14575365]
46. Stahlberg C, Pedersen AT, Lynge E, Andersen ZJ, Keiding N, Hundrup YA, et al. Increased risk of breast cancer following different regimens of hormone replacement therapy frequently used in Europe. *Int J Cancer* 2004 May 1;109(5):721–727. [PubMed: 14999781]
47. Norman SA, Berlin JA, Weber AL, Strom BL, Daling JR, Weiss LK, et al. Combined effect of oral contraceptive use and hormone replacement therapy on breast cancer risk in postmenopausal women. *Cancer Causes Control* 2003 Dec;14(10):933–943. [PubMed: 14750532]
48. Zhang SM, Manson JE, Rexrode KM, Cook NR, Buring JE, Lee IM. Use of oral conjugated estrogen alone and risk of breast cancer. *Am J Epidemiol* 2007 Mar 1;165(5):524–529. [PubMed: 17132697]
49. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992 Dec 15;117(12):1016–1037. [PubMed: 1443971]
50. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002 Oct 9;288(14):1723–1727. [PubMed: 12365955]
51. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health initiative Randomized Trial. *JAMA* 2003 Jun 25;289(24):3243–3253. [PubMed: 12824205]
52. Stefanick ML, Anderson GL, Margolis KL, Hendrix SL, Rodabough RJ, Paskett ED, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 2006 Apr 12;295(14):1647–1657. [PubMed: 16609086]
53. Whiteman MK, Hillis SD, Jamieson DJ, Morrow B, Podgornik MN, Brett KM, et al. Inpatient hysterectomy surveillance in the United States, 2000–2004. *Am J Obstet Gynecol* 2008 Jan;198(1):34–37. [PubMed: 17981254]
54. Bakken K, Alsaker E, Eggen AE, Lund E. Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. *Int J Cancer* 2004 Oct 20;112(1):130–134. [PubMed: 15305384]
55. Kirsh V, Kreiger N. Estrogen and estrogen-progestin replacement therapy and risk of postmenopausal breast cancer in Canada. *Cancer Causes Control* 2002 Aug;13(6):583–590. [PubMed: 12195648]
56. Olsson HL, Ingvar C, Bladstrom A. Hormone replacement therapy containing progestins and given continuously increases breast carcinoma risk in Sweden. *Cancer* 2003 Mar 15;97(6):1387–1392. [PubMed: 12627501]

Table 1
Risk Factors for Breast Cancer Among 126,638 Women, NIH-AARP Diet and Health Study Cohort

	No. cancers	Person-years	RR [*]	95% CI
Age at study entry				
<57	581	128,537.4	1.00	Ref.
57–60	683	129,840.9	1.30	1.09–1.56
61–64	839	153,393.2	1.24	0.99–1.56
65–68	1,031	172,204.6	1.22	0.94–1.59
≥69	523	87,570.2	1.17	0.87–1.57
Race/ethnicity				
Caucasian	3,372	610,345.3	1.00	Ref.
Other/unknown	285	61,201.0	0.87	0.77–0.99
Age at menarche				
<13	1,833	326,606.8	1.00	Ref.
13–14	1,480	278,978.2	0.92	0.86–0.99
≥15	313	60,337.3	0.91	0.81–1.03
Parity				
Nulliparous	645	97,513.3	1.00	Ref.
1	380	68,161.8	0.86	0.75–0.97
2	917	173,999.8	0.79	0.71–0.87
≥3	1,643	320,333.7	0.76	0.70–0.84
Age at first birth				
Nulliparous	645	97,513.3	1.00	Ref.
<20	517	110,683.2	0.74	0.66–0.83
20–24	1,455	291,956.7	0.74	0.68–0.81
25–29	710	121,634.8	0.85	0.76–0.94
≥30	272	39,810.2	0.99	0.86–1.15
Menopausal status at baseline				
Pre-menopausal	155	25,326.4	1.18	0.99–1.40
Natural menopause, <45 years	211	43,752.9	0.82	0.71–0.95
Natural menopause, 45–49 years	542	103,254.7	0.90	0.81–1.00
Natural menopause, 50–54 years	1,088	185,007.9	1.00	Ref.
Natural menopause, ≥55 years	310	41,389.8	1.26	1.11–1.43
Surgical menopause, <40 years	460	101,560.0	0.80	0.72–0.89
Surgical menopause, 40–44 years	324	66,160.0	0.83	0.73–0.94
Surgical menopause, 45–49 years	285	54,466.8	0.89	0.78–1.01
Surgical menopause, ≥50 years	177	29,959.1	0.98	0.84–1.15
Unknown type or menopausal age	28	5,716.0	0.79	0.47–1.35

	No. cancers	Person-years	RR [*]	95% CI
Body mass index (BMI) at baseline				
<25	1,579	298,134.3	1.00	Ref.
25–29	1,168	210,824.9	1.07	0.99–1.16
≥30	812	144,254.7	1.13	1.04–1.23
Number of breast biopsies				
None	2,462	506,112.4	1.00	Ref.
1	740	105,286.0	1.41	1.30–1.53
2	230	29,313.4	1.56	1.36–1.78
≥3	193	24,436.1	1.58	1.36–1.83
Family history of breast cancer				
No	2,304	460,680.6	1.00	Ref.
Yes	698	89,974.4	1.48	1.36–1.61
Number of mammograms				
≤1	968	203,334.6	1.00	Ref.
≥2	2,668	463,668.0	1.13	1.05–1.22
Alcoholic Drinks Per Day				
Never	954	190,062.9	1.00	Ref.
0–1 per day	2,103	390,924.6	1.05	0.97–1.13
1–2 per day	476	72,081.8	1.25	1.12–1.40
≥3 per day	124	18,476.9	1.30	1.08–1.57

* RRs adjusted for age (continuous) and for race, age at first birth, menopausal status, number of breast biopsies, family history of breast cancer, and number of mammograms (per above categorizations). Numbers of cancers and person-years shown are variable given that individuals with unknowns are not presented (31 cases for age at menarche, 72 for parity, 58 for age at first birth, 77 for menopausal status, 98 for BMI, 32 for breast biopsies, 655 for family history, and 21 for number of mammograms).

[†] Hysterectomy, bilateral oophorectomy, or both.

Table 2
Associations Between Estrogen Therapy (ET)-Only Use and Breast Cancer Risk, NIH-AARP Diet and Health Study Cohort

Hormone therapy	All women (N=126,638)				Women with a hysterectomy (N=51,237)			
	No. cancers	Person-years	RR*	95% CI	No. cancers	Person-years	RR*	95% CI
No HT use	1165	260,789.1	1.00	Ref.	260	54,970.5	1.00	Ref.
ET-only use	914	187,159.2	1.15	1.04–1.27	774	157,479.6	1.07	0.93–1.24
Recency of use								
Former	222	51,705.2	0.99	0.85–1.15	140	33,238.3	0.91	0.74–1.12
Current	683	133,324.4	1.24	1.11–1.39	629	122,842.2	1.13	0.97–1.31
Duration of use (y)								
<5	305	62,033.8	1.16	1.02–1.33	201	40,437.8	1.09	0.90–1.31
5–9	137	30,773.1	1.09	0.90–1.31	121	27,621.0	0.97	0.78–1.21
≥10	457	91,340.8	1.16	1.02–1.31	440	87,056.6	1.09	0.93–1.28
Duration of use, extended to ≥20 (y) [†]								
<5	305	62,033.8	1.16	1.02–1.33	201	40,437.8	1.09	0.90–1.31
5–9	137	30,773.1	1.09	0.90–1.31	121	27,621.0	0.97	0.78–1.22
10–14	139	28,723.6	1.16	0.96–1.39	135	26,755.6	1.11	0.90–1.38
15–19	102	18,721.6	1.25	1.01–1.55	98	17,961.1	1.17	0.92–1.48
≥20	193	37,803.8	1.16	0.98–1.37	184	36,670.3	1.08	0.89–1.31
Duration of use among current users (y)								
<5	142	26,683.9	1.34	1.11–1.60	106	20,557.4	1.15	0.92–1.45
5–9	107	23,082.8	1.18	0.96–1.45	100	21,811.9	1.04	0.82–1.32
≥10	424	82,355.5	1.21	1.06–1.38	413	79,357.0	1.13	0.96–1.33
Time since last use among former users (y)								
<5	37	12,736.8	0.71	0.51–0.98	20	8,750.1	0.51	0.32–0.80
5–9	36	6,801.9	1.26	0.90–1.76	22	4,223.2	1.15	0.75–1.78
≥10	102	19,143.3	1.17	0.95–1.44	65	12,234.6	1.11	0.84–1.46

* RRs adjusted for age (continuous) and for race, age at first birth, menopausal status, number of breast biopsies, family history of breast cancer, and number of mammograms (per categorizations shown in Table 1). Models also include terms for other HT formulations (EPT only, ET then EPT, PT then EPT, PT then ET, EPT then PT, EPT then ET, EPT unknown, other combinations, unknown regimens).

Women with other forms of HT are not shown (1578 cases). Individuals with unknown information are also not shown (for all women, 9 cases for recency of use, 15 for duration of use, 38 for extended duration of use, 10 for duration of use among current users, 47 for time since last use).

[†]RR among all women for users of ET-only for ≥ 10 years without more specific information on duration of usage = 0.86 (0.56–1.30), for current users = 0.97 (0.61–1.53), RR among hysterectomized women for users of ET-only for ≥ 10 years without more specific information on duration of usage = 0.87 (0.57–1.34), for current users = 0.95 (0.60–1.52).

Table 3

Associations Between Estrogen Plus Progestin (EPT) Use Among Women with Intact Uteri and Breast Cancer Risk, NIH-AARP Diet and Health Study Cohort

Hormone therapy	Women with intact uteri (N=73,986)			
	No. cancers	Person-years	RR [*]	95% CI
No HT use	885	202,370.5	1.00	Ref.
EPT use	1001	128,175.7	1.82	1.65–2.01
Recency of use				
Former	101	22,726.4	1.03	0.84–1.27
Current	889	104,549.2	2.02	1.82–2.23
Duration of use				
<5 years	325	55,984.8	1.38	1.21–1.58
5–9 years	327	39,841.8	1.92	1.68–2.20
≥10 years	339	31,388.4	2.40	2.10–2.74
Duration of use, extended to ≥20 (y)				
<5	329	56,370.3	1.39	1.22–1.59
5–9	325	39,673.4	1.91	1.67–2.19
10–14	233	23,289.9	2.25	1.94–2.62
15–19	70	5,088.3	2.95	2.30–3.77
≥20	29	2,451.7	2.48	1.71–3.59
Duration of use among current users (y)				
<5	259	39,136.8	1.62	1.40–1.88
5–9	307	35,666.8	2.04	1.78–2.34
≥10	318	29,162.0	2.44	2.13–2.79
Time since last use among former users (y)				
<5	63	13,449.0	1.09	0.85–1.42
5–9	13	3,423.3	0.87	0.50–1.51
≥10	6	1,418.9	0.91	0.41–2.02
Regimen of use				
Sequential (<15 days)	329	46,556.1	1.63	1.42–1.86
Continuous	608	72,064.1	1.98	1.78–2.21
Regimen and recency				
Sequential, former	25	7,731.0	0.75	0.50–1.11
Sequential, current	303	38,556.2	1.84	1.60–2.12
Continuous, former	58	10,597.0	1.27	0.98–1.66
Continuous, current	541	61,049.7	2.10	1.88–2.35
Regimen and duration among current users (y)				
Sequential, <5	64	11,019.1	1.44	1.11–1.88
Sequential, 5–9	116	14,425.4	1.92	1.57–2.35
Sequential, ≥10	121	12,923.7	2.06	1.69–2.50
Continuous, <5	182	26,269.8	1.68	1.43–1.99
Continuous, 5–9	176	19,608.0	2.11	1.79–2.50
Continuous, ≥10	181	14,792.9	2.77	2.35–3.26

Hormone therapy	Women with intact uteri (N=73,986)			
	No. cancers	Person-years	RR [*]	95% CI
Progestin dose				
<1 mg.	35	4,600.0	1.80	1.28–2.53
2.5 mg.	538	62,220.0	2.02	1.81–2.27
5.0 mg.	161	18,950.0	1.98	1.67–2.36
10.0 mg.	124	16,444.5	1.75	1.44–2.13
Days progestin				
<10	81	13,915.2	1.33	1.06–1.68
10–14	248	32,640.8	1.76	1.52–2.05
15–19	25	2,544.1	2.29	1.54–3.41
20–25	110	12,937.5	1.95	1.59–2.38
Daily	498	59,126.6	2.00	1.78–2.24

* RRs adjusted for age (continuous) and for race, age at first birth, menopausal status, number of breast biopsies, family history of cancer, and number of mammograms (per categorizations shown in Table 1). Models also include terms for other HT formulations. Women with other forms of HT are not shown (358 cases). Individuals with unknown information are also not shown (11 cases for recency of use, 10 for duration of use, 15 for extended duration of use, 5 for duration of use among current users, 19 for time since last use, 64 for regimen of use, 74 for regimen and recency of use, 49 for regimen and duration among current users, 143 for progestin dose, and 39 for days progestin).

Associations Between Years of Estrogen Therapy (ET)-Only Use Among all Women and Estrogen Plus Progestin (EPT) Use Among Women with Intact Uteri and Breast Cancer Risk by Other Breast Cancer Risk Factors, NIH-AARP Diet and Health Study Cohort

Table 4

	All Women (N=126,638), Estrogen Therapy (ET)-Only Use						Women with intact uteri (N=73,986), Estrogen Plus Progestin (EPT) Use					
	Non-users			5–9 y use			Non-users			<5 y use		
	No. of cases	RR [*]	No. of cases	RR [*]	No. of cases	p for trend	No. of cases	RR [*]	No. of cases	RR [*]	No. of cases	p for trend
Age												
<57	145	1.00	59	1.33	39	1.42	119	1.00	121	1.51	70	2.05
57–60	173	1.00	51	1.13	27	0.79	126	1.00	82	1.44	110	1.79
61–64	259	1.00	66	1.33	31	1.32	200	1.00	38	1.04	79	2.14
65–68	380	1.00	82	1.11	26	1.04	287	1.00	60	1.67	48	2.57
≥69	208	1.00	47	1.06	14	0.92	153	1.00	24	1.11	20	2.22
Body mass index [‡]												
<25	370	1.00	119	1.49	50	1.19	296	1.00	173	1.70	170	2.75
25–29	391	1.00	97	1.07	45	1.06	304	1.00	89	1.31	105	1.97
≥30	366	1.00	81	1.06	38	1.24	263	1.00	57	1.18	48	1.99
Family history of breast cancer												
No	710	1.00	195	1.23	90	1.16	540	1.00	218	1.39	217	2.21
Yes	241	1.00	61	1.17	24	0.98	181	1.00	56	1.30	55	2.12
Parity												
Nulliparous	213	1.00	38	1.09	21	1.33	179	1.00	77	1.66	74	2.45
1	110	1.00	39	1.65	8	0.69	93	1.00	39	1.33	34	2.54
2	268	1.00	74	1.15	40	1.18	202	1.00	81	1.23	96	1.66
3+	548	1.00	152	1.16	62	1.03	399	1.00	124	1.39	120	2.44

^{*} RRs adjusted for age (continuous) and for race, age at first birth, menopausal status and age, number of breast biopsies, family history of cancer, and number of mammograms (per categorizations shown in Table 1). Models also include terms for other HT formulations.

Individuals with unknown information are also not shown (for all women, 61 cases for BMI, 369 for family history, 42 for parity; for women with intact uteri, 43 cases for BMI, 330 for family history, 26 for parity).

[‡] p value for interaction: ET x BMI - p=0.01; EPT x BMI - p=0.01

Associations Between Estrogen Therapy (ET)-Only Use Among All Women and Estrogen Plus Progestin (EPT) Use among Women with Intact Uteri and Breast Cancer Risk by Tumor Characteristics, NIH-AARP Diet and Health Study Cohort

ET-only Use Among All Women (number of cases, n=3657)	Stage*		Histology*		Estrogen Receptor Status*		Grade*			
	In Situ (n=607)	Invasive (n=3035)	Ductal (n=1968)	Lobular (n=334)	Mixed (n=238)	ER- (n=228)	ER+ (n=1175)	Grade 1 (n=590)	Grade 2 (n=1142)	Grade 3 (n=738)
	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)
ET-only use										
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	1.22 (0.95–1.57)	1.13 (1.01–1.26)	1.04 (0.91–1.20)	1.20 (0.86–1.67)	1.89 (1.24–2.89)	1.02 (0.68–1.51)	1.14 (0.94–1.38)	1.42 (1.08–1.86)	1.16 (0.97–1.39)	0.98 (0.79–1.23)
Currency of use										
Former	1.11 (0.77–1.59)	0.96 (0.82–1.13)	0.92 (0.75–1.12)	0.93 (0.56–1.53)	1.19 (0.61–2.31)	0.92 (0.51–1.66)	1.09 (0.83–1.43)	1.21 (0.82–1.80)	0.85 (0.64–1.12)	0.95 (0.69–1.31)
Current	1.29 (0.98–1.70)	1.22 (1.08–1.39)	1.10 (0.94–1.28)	1.39 (0.96–2.00)	2.36 (1.49–3.75)	1.08 (0.70–1.68)	1.16 (0.94–1.44)	1.50 (1.10–2.03)	1.33 (1.09–1.62)	1.02 (0.79–1.31)
Duration of use (y)										
<5	1.22 (0.88–1.69)	1.15 (0.99–1.32)	1.13 (0.95–1.35)	1.01 (0.64–1.59)	1.90 (1.12–3.21)	0.96 (0.56–1.64)	1.26 (0.98–1.60)	1.58 (1.12–2.21)	1.24 (0.99–1.55)	0.93 (0.69–1.25)
5–9	1.07 (0.67–1.69)	1.08 (0.88–1.32)	0.99 (0.76–1.28)	1.15 (0.62–2.11)	1.92 (0.94–3.93)	1.09 (0.55–2.14)	1.18 (0.84–1.65)	1.34 (0.81–2.22)	0.86 (0.59–1.24)	1.19 (0.82–1.75)
≥10	1.32 (0.98–1.79)	1.12 (0.98–1.29)	0.96 (0.81–1.15)	1.46 (0.98–2.19)	1.87 (1.11–3.16)	0.96 (0.58–1.58)	1.05 (0.83–1.33)	1.32 (0.94–1.86)	1.16 (0.92–1.45)	1.00 (0.75–1.33)
EPT Use Among Women with Intact Uteri (number of cases, n=2244)										
	Stage*		Histology*		Estrogen Receptor Status*		Grade*			
	In Situ (n=349)	Invasive (n=1886)	Ductal (n=1218)	Lobular (n=213)	Mixed (n=155)	ER- (n=132)	ER+ (n=757)	Grade 1 (n=400)	Grade 2 (n=710)	Grade 3 (n=439)
	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)
EPT use										
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	1.94 (1.51–2.48)	1.81 (1.63–2.01)	1.74 (1.53–1.99)	1.60 (1.16–2.20)	3.32 (2.25–4.90)	1.11 (0.74–1.66)	2.32 (1.96–2.76)	3.51 (2.75–4.49)	1.71 (1.44–2.04)	1.48 (1.18–1.85)
Currency of use										
Former	1.39 (0.87–2.22)	0.95 (0.75–1.20)	0.93 (0.70–1.25)	0.90 (0.45–1.79)	1.07 (0.42–2.72)	1.17 (0.58–2.38)	1.07 (0.73–1.56)	1.72 (1.06–2.79)	0.66 (0.42–1.03)	1.02 (0.65–1.59)
Current	2.05 (1.59–2.65)	2.02 (1.81–2.26)	1.94 (1.69–2.22)	1.77 (1.27–2.47)	3.97 (2.67–5.91)	1.05 (0.68–1.61)	2.62 (2.20–3.13)	3.93 (3.05–5.07)	1.98 (1.66–2.37)	1.61 (1.27–2.03)
Duration of use (y)										
<5 y	1.56 (1.13–2.16)	1.34 (1.16–1.56)	1.24 (1.03–1.49)	1.45 (0.95–2.21)	2.40 (1.45–3.96)	1.02 (0.59–1.75)	1.72 (1.37–2.16)	2.52 (1.84–3.47)	1.13 (0.88–1.45)	1.29 (0.96–1.73)

E/T-only Use Among All Women (number of cases, n=3657)	Stage [*]		Histology [*]		Estrogen Receptor Status [*]		Grade [*]	
	In Situ (n=607)	Invasive (n=3035)	Ductal (n=1968)	Lobular (n=334)	ER- (n=228)	ER+ (n=1175)	Grade 1 (n=590)	Grade 2 (n=1142)
	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)	RR [†] (95% CI)
5-9 y	2.31 (1.68-3.17)	1.86 (1.60-2.16)	1.77 (1.47-2.14)	1.93 (1.26-2.96)	1.11 (0.62-1.97)	2.25 (1.79-2.84)	3.62 (2.64-4.97)	1.75 (1.37-2.23)
>10 y	2.07 (1.46-2.93)	2.48 (2.16-2.86)	2.54 (2.13-3.02)	1.37 (0.83-2.27)	1.19 (0.65-2.18)	3.28 (2.65-4.06)	4.86 (3.60-6.57)	2.60 (2.08-3.25)

^{*} Cases with missing information on stage not shown (15 for ET, 9 for EPT). Histology, estrogen receptor status and grade results are limited to invasive cases only. Not shown are cases with other or missing histologies (495 for ET, 300 for EPT), borderline or missing estrogen receptor status (1632 for ET, 997 for EPT), and missing grade (565 for ET, 337 for EPT). The threshold for a positive hormone receptor status was >10 fmol of receptor per milligram of total protein.

[†] RRs adjusted for age (continuous) and for race, age at first birth, menopausal status, number of breast biopsies, family history of breast cancer, and number of mammograms (per categorizations shown in Table 1). Models also include terms for other HT formulations.