Hypertension, antihypertensive medication use, and breast cancer risk in the California Teachers Study cohort

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Abstract

Background We investigated the association between hypertension, antihypertensive (AH) medication use, and breast cancer in a large prospective study, the California Teachers Study (CTS).

Methods Information on history of hypertension and lifetime regular use of AH medications was collected from 114,549 women in 1995–1996. Among them, 4,151 invasive breast cancers were diagnosed between 1995 and 2006. Additional information on AH use was collected from 73,742 women in 2000–2001, and 1,714 of these women were subsequently diagnosed with breast cancer. Cox proportional hazards regression was used to estimate relative risks (RR) and 95% confidence intervals (CI) for breast cancer.

Results Use of AH medication for ≥5 years, when compared with no use, was associated with a modest increased risk of invasive breast cancer (RR = 1.18, 95%CI 1.02–1.36). This increased risk appeared to be confined to estrogen receptor (ER)-positive tumors (RR = 1.21, 95%CI 1.03–1.43) and pre-/peri-menopausal women (RR = 1.58, 95%CI 1.11–2.25).

Conclusions Increased risk of invasive breast cancer was observed for long-term (≥5 years) AH use, and this appeared to be confined to ER + breast cancer and younger women.

Keywords Hypertension · Breast cancer · Antihypertensive medication

Introduction

Breast cancer remains an important public health concern as it represents the most common cancer diagnosis and second leading cause of cancer-related death among women in the United States [1, 2]. Obesity and obesity-related conditions including hypertension, a highly prevalent condition among adult women, may be contributing to the burden of post-menopausal breast cancer. A report from the National Health and Nutrition Examination Survey (NHANES III) found that 22% of all U.S. females 18 years and older were hypertensive or taking AH medications in 1988–1991 [3].

Hypertension and AH medications have been consistently associated with other malignancies, including renal [4] and endometrial cancers [5], and with benign conditions including uterine fibroids [6]. However, results of studies
examining the association between breast cancer, hypertension, and AH medications have been inconsistent [7–9]. It has been suggested that the previously observed associations may be explained by uncontrolled confounding from shared risk factors, such as increased obesity, a fat-rich diet, or physical inactivity, alcohol use, and the absence of lactation [10]. However, as both conditions may share common pathophysiologic pathways involved in hormone synthesis and metabolism [11, 12] and growth factor signaling [13], it is possible that a biologic association exists.

Because hypertension is a highly prevalent condition and AH medications are among the most commonly prescribed drugs in the United States, the importance of examining occurrence of any serious side effects including influences on the risk of breast cancer has been suggested [14]. Therefore, we sought to elucidate the relationship between hypertension, AH medication use, and breast cancer risk in a large prospective cohort of women, the California Teachers Study (CTS).

### Methods

**Study population and data collection**

The CTS is a prospective cohort study of 133,479 California female teachers and school administrators who completed a baseline survey in 1995–1996. A detailed description of the study design and methods has been published previously [15]. From among 118,262 participants who were residents of California at baseline and had no prior history of breast cancer, we excluded members who were over 85 years of age at baseline (n = 1,579) or who had unknown history of hypertension or AH medication use (n = 2,134). The resulting cohort for the analysis of data items collected at baseline consisted of 114,549 women. Women in this subcohort have been followed for breast cancer incidence as well as other health outcomes from the completion of the baseline survey through December 31, 2006, their dates of death or the date of a move out of California for more than four months, whichever came first. Incidence of invasive breast cancer was ascertained through linkage with the statewide population-based California Cancer Registry (CCR). During follow-up, 4,151 women were diagnosed with invasive breast cancer. National Cancer Institute designated Surveillance, Epidemiology, and End Results (SEER) registries, including the CCR, routinely collect estrogen receptor (ER) as recorded in the medical records following diagnosis, and a summary parity variable (first full-term pregnancy (FFTP) before age 25; FFTP age 25–29; nulliparous before age 30; or unknown); breastfeeding history (never or less than 12 months; at least 12 months; or unknown); physical activity, defined as average lifetime (from high school through current age or aged 54 if 55 or older at baseline) moderate or strenuous activity per week, (<2 h; 2 to <4 h; 4 to <6 h; 6 or more hours; or unknown); smoking (never, former, current smoker; or unknown); alcohol use in the year prior to baseline, measured in average grams per day (no use; less than 20 grams per day; 20 grams per day or more; or unknown); family history of breast cancer (at least one affected first-degree relative, no affected first-degree relatives, or unknown/adopted); race/ethnicity (White; African-American; Hispanic; Asian/Pacific Islander; or other/mixed/not specified); body mass index (<20 kg/m²; 20 to <25 kg/m²; 25 to <29 kg/m²; 30 to <35 kg/m²; ≥35 kg/m²; or unknown); smoking (never smoker; former smoker; current smoker; or unknown); alcohol use in the year prior to baseline, measured in average grams per day (no use; less than 20 grams per day; 20 grams per day or more; or unknown); physical activity, defined as average lifetime (from high school through current age or aged 54 if 55 or older at baseline) moderate or strenuous activity per week, (<2 h; 2 to <4 h; 4 to <6 h; 6 or more hours; or unknown); a summary parity variable (first full-term pregnancy (FFTP) before age 25; FFTP age 25–29; nulliparous before age 30; or unknown); breastfeeding history (never or less than 12 months; at least 12 months; or unknown); hysterectomy (never; ever; or unknown); menopausal status and hormone therapy use (premenopausal; peri-menopausal; post-menopausal and never used hormone therapy; post-menopausal and ever used hormone therapy; or unknown menopausal status or HT use); diabetes history (ever; or never); and percent calories from fat, excluding alcohol (quartiles). A variable for adherence to screening guidelines was created and defined by age: for women age ≥40 at baseline having a mammogram within 1 year of baseline; for women age <40 at baseline having a breast exam by health care provider within 2 years or a mammogram within 1 year of baseline (no; yes; or unknown). This screening adherence variable was tested in the models, and

Risk factors included in the analyses as potential confounders were based on the data collected as part of the self-administered baseline questionnaire. These included family history of breast cancer (at least one affected first-degree relative, no affected first-degree relatives, or unknown/adopted); race/ethnicity (White; African-American; Hispanic; Asian/Pacific Islander; or other/mixed/not specified); body mass index (<20 kg/m²; 20 to <25 kg/m²; 25 to <29 kg/m²; 30 to <35 kg/m²; ≥35 kg/m²; or unknown); smoking (never smoker; former smoker; current smoker; or unknown); alcohol use in the year prior to baseline, measured in average grams per day (no use; less than 20 grams per day; 20 grams per day or more; or unknown); physical activity, defined as average lifetime (from high school through current age or aged 54 if 55 or older at baseline) moderate or strenuous activity per week, (<2 h; 2 to <4 h; 4 to <6 h; 6 or more hours; or unknown); a summary parity variable (first full-term pregnancy (FFTP) before age 25; FFTP age 25–29; nulliparous before age 30; or unknown); breastfeeding history (never or less than 12 months; at least 12 months; or unknown); hysterectomy (never; ever; or unknown); menopausal status and hormone therapy use (premenopausal; peri-menopausal; post-menopausal and never used hormone therapy; post-menopausal and ever used hormone therapy; or unknown menopausal status or HT use); diabetes history (ever; or never); and percent calories from fat, excluding alcohol (quartiles). A variable for adherence to screening guidelines was created and defined by age: for women age ≥40 at baseline having a mammogram within 1 year of baseline; for women age <40 at baseline having a breast exam by health care provider within 2 years or a mammogram within 1 year of baseline (no; yes; or unknown). This screening adherence variable was tested in the models, and
as it did not change, RR estimates by at least ten percent was subsequently dropped.

More detailed information on AH medication use was ascertained in a follow-up self-administered questionnaire mailed to cohort members in 2000–2001. This questionnaire queried daily use of the following AH medications for at least two months in the two years preceding the survey: “Thiazide diuretic (for example: Diuril, Hydrodiuril, Dyazide);” “Lasix;” “Calcium blocker (for example: Calan, Procardia, Cardizem);” “ACE inhibitors (for example: Capoten, Vasotec, Zestril);” and “Other high blood pressure medication.” This questionnaire was completed by 89,058 cohort members. Exclusions for this analysis included women who had moved out of California (n = 8,608), who were diagnosed with breast cancer prior to completion of this survey (n = 5,476), whose history of breast cancer was unknown (n = 54), or who did not complete the AH medication portion of the survey (n = 1,178). This analysis was conducted independently of hypertension or AH medication use reported at baseline. These exclusions resulted in 73,742 women eligible for analyses using the 2000–2001 questionnaire data. For these analyses, follow-up was initiated on the date the questionnaire was completed and women were followed until the first of the following: incident breast cancer, death, a move out of California, or December 31, 2006. In this period, 1,714 invasive breast cancers were diagnosed.

Multivariable Cox proportional hazards regression methods were used to estimate the relative hazard (referred to herein as the relative risk, RR) for developing breast cancer during the follow-up period; 95% confidence intervals (CI) were constructed around the point estimates for the RRs [16] associated with history of hypertension and AH medication use, using ages at start and end of follow-up (in days) to define time on study. Models included the covariates listed above and were stratified by age at baseline (in single years of age).

All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The distributions of selected baseline characteristics and the age-adjusted differences of these factors by hypertension status are described in Table 1. The mean age at baseline was 52.8, and the majority of women (86.4%) were of non-Hispanic White race/ethnicity. A history of high blood pressure was reported by 16.8% of the women. The most common category of AH medication use reported on the baseline questionnaire among all women was “other high blood pressure medication” (13.0% of all women, 68.4% of hypertensives), followed by diuretics (10.0% of all women, 45.3% of hypertensives) and reserpine (0.4% of all women, 2.2% of hypertensives). Women with a history of hypertension were significantly older and more likely to be non-White, to have a higher body mass index (BMI), to have a history of diabetes, to be nulliparous at age of 30, to be adherent to breast screening guidelines, to have had a hysterectomy, and to consume a higher percent of calories from fat than women without a history of hypertension. Furthermore, hypertensive women were less likely to have breastfed for 12 months or more or to have engaged in moderate or strenuous physical activity over their lifetimes.

Table 2 presents associations between hypertension, AH medication use, and breast cancer for both age-adjusted and multivariable-adjusted models for the full cohort, with analyses also presented by ER status. A history of treated hypertension, when compared to either women without hypertension or without AH medication use was not significantly associated with invasive breast cancer overall or by ER subtype. Long-term use of any AH medication was associated with increased risk of invasive breast cancer overall (RR = 1.18, 95% CI 1.02–1.36; RR = 1.18, 95% CI 1.04–1.34) for 5 and 10+ years of use, respectively. This association appeared to be confined to ER-positive breast cancer (RR = 1.21, 95% CI 1.03–1.43; RR = 1.26, 95% CI 1.10–1.45, for 5 and 10+ years of use, respectively). Ten or more years of diuretic use was also associated with breast cancer overall and ER-positive subtype (RR = 1.16, 95% CI 1.01–1.33; RR = 1.21, 95% CI 1.03–1.42, respectively). Only 500 women reported regular use of reserpine, which was not associated with breast cancer risk (RR = 0.75, 95% CI 0.48–1.16).

Stratified analyses by categories of BMI (<25 kg/m²; 25 to <30 kg/m²; and ≥30 kg/m²) and menopausal status (pre-/peri-menopausal; and post-menopausal) were performed to evaluate whether risk of invasive breast cancer associated with treated hypertension, diuretic, and other AH medication use was modified by BMI or menopausal status (Table 3). A history of hypertension treated with any AH medication was not significantly associated with invasive breast cancer among any of the BMI categories women (RR = 1.12, 95% CI 0.98–1.27; RR = 0.95, 95% CI 0.81–1.11; RR = 1.09, 95% CI 0.90–1.32, for BMI <25, 25 to <30, and ≥30 kg/m², respectively). Five or more years of diuretic use was significantly associated with risk of breast cancer only among women in the highest BMI category (RR = 1.12, 95% CI 0.93–1.37; RR = 1.05, 95% CI 0.85–1.30; RR = 1.31, 95% CI 1.03–1.66, for BMI <25, 25 to <30, and ≥30 kg/m², respectively), and at least 5 years of use of “other” AH medications was associated with invasive breast cancer risk among women in the leanest and heaviest strata of BMI (RR = 1.20, 95% CI 1.01–1.42; RR = 1.00, 95% CI 0.82–1.22; RR = 1.35, 1.08–1.69, for BMI <25, 25 to <30, and ≥30 kg/m², respectively).
| Characteristic                          | All women |          |          |          |          |          |          |          |          |          |          |
|---------------------------------------|-----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|                                       | Mean (SD) | n  %    | Mean (SD) | n  %    | Mean (SD) | n  %    | Age-adjusted p-value<sup>a</sup> |
| Age [years]                           | 52.8 (13.9)| 50.9 (13.4)| 62.2 (12.1)|          |          |          | <0.0001  |
| Race/ethnicity                        |           |          |           |           |           |          | <0.0001  |
| White                                 | 98,997    | 86.4    | 82,480    | 86.6    | 16,517    | 85.6    |          |
| Non-White (includes unknown)          | 15,552    | 13.6    | 12,767    | 13.4    | 2,785     | 14.4    |          |
| Family history of breast cancer       |           |          |           |           |           |          | 0.01     |
| None                                  | 97,393    | 85.0    | 81,312    | 85.4    | 16,081    | 83.3    |          |
| At least one affected first degree    |           |          |           |           |           |          |          |
| Relative                              | 13,484    | 11.8    | 11,024    | 11.6    | 2,460     | 12.7    |          |
| Unknown                               | 3,672     | 3.2     | 2,911     | 3.0     | 761       | 3.9     |          |
| Body mass index (kg/m²)               | <0.0001   |          | <0.0001   |          |          |          |          |
| <20                                   | 12,164    | 10.6    | 11,170    | 11.7    | 994       | 5.2     |          |
| 20 to <25                             | 55,121    | 48.1    | 48,602    | 51.0    | 6,519     | 33.8    |          |
| 25 to <30                             | 27,393    | 23.9    | 21,660    | 22.7    | 5,733     | 29.7    |          |
| 30 to <35                             | 10,046    | 8.8     | 7,101     | 7.5     | 2,945     | 15.3    |          |
| ≥35                                   | 5,589     | 4.9     | 3,558     | 3.7     | 2,031     | 10.5    |          |
| Unknown                               | 4,236     | 3.7     | 3,156     | 3.3     | 1,080     | 5.6     |          |
| Hypertension                          |           |          |           |           |           |          |          |
| Never                                 | 95,247    | 83.1    | 95,247    | 100.0   | 0         | 0.0     |          |
| Ever                                  | 19,302    | 16.8    | 0         | 0.0     | 19,302    | 100.0   |          |
| Regular diuretic use                  |           |          |           |           |           |          |          |
| No                                    | 103,123   | 90.0    | 92,568    | 97.2    | 10,555    | 54.7    |          |
| Yes                                   | 11,426    | 10.0    | 2,679     | 2.8     | 8,747     | 45.3    |          |
| Regular reserpine use                 |           |          |           |           |           |          |          |
| No                                    | 114,049   | 99.6    | 95,178    | 99.9    | 18,871    | 97.8    |          |
| Yes                                   | 500       | 0.4     | 69        | 0.1     | 431       | 2.2     |          |
| Regular other antihypertensive medication use |           |          |           |           |           |          |          |
| No                                    | 99,685    | 87.0    | 93,589    | 98.3    | 6,096     | 31.6    |          |
| Yes                                   | 14,864    | 13.0    | 1,658     | 1.7     | 13,206    | 68.4    |          |
| Diabetes                              | <0.0001   |          | <0.0001   |          |          |          |          |
| Never                                 | 111,367   | 97.2    | 93,607    | 98.3    | 17,760    | 92.0    |          |
| Ever                                  | 3,182     | 2.8     | 1,640     | 1.7     | 1,542     | 8.0     |          |
| Smoking history                       | 0.10      |          |          |           |           |          |          |
| Never                                 | 75,682    | 66.1    | 63,936    | 67.1    | 11,746    | 60.8    |          |
| Former                                | 32,374    | 28.3    | 25,981    | 27.3    | 6,393     | 33.1    |          |
| Current                               | 5,828     | 5.1     | 4,778     | 5.0     | 1,050     | 5.4     |          |
| Unknown                               | 665       | 0.6     | 552       | 0.6     | 113       | 0.6     |          |
| Alcohol use, average per day in prior year (g/day) | <0.0001   |          | <0.0001   |          |          |          |          |
| No use                                | 36,463    | 31.8    | 29,541    | 31.0    | 6,922     | 35.9    |          |
| <20                                   | 63,184    | 55.2    | 53,663    | 56.3    | 9,521     | 49.3    |          |
| 20+                                   | 8,986     | 7.8     | 7,143     | 7.5     | 1,843     | 9.6     |          |
| Unknown                               | 5,916     | 5.2     | 4,900     | 5.1     | 1,016     | 5.3     |          |
Table 1 continued

| Characteristic                                      | All women |          |          |          |          |          |          |          |
|-----------------------------------------------------|-----------|----------|----------|----------|----------|----------|----------|----------|
|                                                     | Mean (SD) | n        | %        | Mean (SD) | n        | %        | Mean (SD) | n        |
|                                                     |           |          |          |           |          |          |           |          |
| Moderate/Strenuous physical activity (average lifetime) (h/week) |           |          |          |           |          |          |           |          |
| <2                                                  | 36,148    | 31.6     |          | 28,331    | 29.7     |          | 7,817     | 40.5     |
| 2 to <4                                             | 29,075    | 25.4     |          | 24,413    | 25.6     |          | 4,662     | 24.2     |
| 4 to <6                                             | 19,168    | 16.7     |          | 16,429    | 17.2     |          | 2,739     | 14.2     |
| 6+                                                  | 29,492    | 25.8     |          | 25,577    | 26.8     |          | 3,915     | 20.3     |
| Unknown                                             | 666       | 0.6      |          | 497       | 0.5      |          | 169       | 0.9      |
| Age at first full-term pregnancy (FFTP)             |           |          |          |           |          |          |           |          |
| FFTP age <25                                        | 29,695    | 25.9     |          | 23,380    | 24.6     |          | 6,315     | 32.7     |
| FFTP age 25–29                                       | 33,465    | 29.2     |          | 27,810    | 29.2     |          | 5,655     | 29.3     |
| No full-term pregnancies prior to age 30             | 42,359    | 37.0     |          | 36,304    | 38.1     |          | 6,055     | 31.4     |
| Unknown                                             | 9,030     | 7.9      |          | 7,753     | 8.1      |          | 1,277     | 6.6      |
| Breastfeeding history                                |           |          |          |           |          |          |           |          |
| Never or less than 12 months                         | 83,774    | 73.1     |          | 68,504    | 71.9     |          | 15,270    | 79.1     |
| 12+ months                                          | 28,133    | 24.6     |          | 24,675    | 25.9     |          | 3,458     | 17.9     |
| Unknown                                             | 2,642     | 2.3      |          | 2,068     | 2.2      |          | 574       | 3.0      |
| Hysterectomy                                         |           |          |          |           |          |          |           |          |
| No                                                  | 85,953    | 75.0     |          | 74,482    | 78.2     |          | 11,471    | 59.4     |
| Yes                                                 | 26,179    | 22.8     |          | 18,770    | 19.7     |          | 7,409     | 38.4     |
| Unknown                                             | 2,417     | 2.1      |          | 1,995     | 2.1      |          | 422       | 2.2      |
| Menopausal status and hormone therapy use            |           |          |          |           |          |          |           |          |
| Premenopausal                                        | 46,927    | 41.0     |          | 44,179    | 46.4     |          | 2,748     | 14.2     |
| Peri-menopausal                                      | 2,361     | 2.1      |          | 2,012     | 2.1      |          | 349       | 1.8      |
| Post-menopausal, never HT use                        | 12,015    | 10.5     |          | 8,668     | 9.1      |          | 3,347     | 17.3     |
| Post-menopausal, any HT use                          | 39,379    | 34.4     |          | 29,034    | 30.5     |          | 10,345    | 53.6     |
| Unknown                                             | 13,867    | 12.1     |          | 11,354    | 11.9     |          | 2,513     | 13.0     |
| Adherence to screening guidelinesb                   |           |          |          |           |          |          |           |          |
| No                                                  | 41,109    | 35.9     |          | 33,347    | 35.0     |          | 7,762     | 40.2     |
| Yes                                                 | 48,911    | 42.7     |          | 38,942    | 40.9     |          | 9,969     | 51.6     |
| Unknown                                             | 24,529    | 21.4     |          | 22,958    | 24.1     |          | 1,571     | 8.1      |
| Percent calories from fat, excluding alcohol (quartiles) |           |          |          |           |          |          |           |          |
| First                                               | 26,064    | 22.8     |          | 21,718    | 22.8     |          | 4,346     | 22.5     |
| Second                                              | 26,077    | 22.8     |          | 22,088    | 23.2     |          | 3,989     | 20.7     |
| Third                                               | 26,062    | 22.8     |          | 21,885    | 23.0     |          | 4,177     | 21.6     |
| Fourth                                              | 26,106    | 22.8     |          | 21,290    | 22.4     |          | 4,816     | 25.0     |
| Unknown                                             | 10,240    | 8.9      |          | 8,266     | 8.7      |          | 1,974     | 10.2     |

a P-value for association with hypertension calculated using logistic regression adjusting for age at baseline

b For women age ≥40, mammogram within 1 year of baseline; for women age <40, breast exam by health care provider within 2 years or mammogram within 1 year of baseline
respectively) and among pre-/peri-menopausal women (RR = 1.58, 95% CI 1.11–2.25), but not among post-menopausal women (RR = 1.10, 95% CI 0.98–1.24).

We were able to explore the effects of specific AH medications based on data collected during the 2000–2001 survey. Associations between reported AH medication use in the two years preceding the 2000–2001 survey and breast cancer risk are presented in Table 4. Use of AH medications including thiazide or furosemide diuretics, calcium channel blockers, ACE inhibitors, or other antihypertensive medications was not significantly associated with invasive breast cancer risk.

### Discussion

In this large prospective cohort study, long-term use of AH medication was associated with increased risk of invasive breast cancer, and this risk appeared to be confined to ER-positive tumors, and among pre-/peri-menopausal women and those who were in the lowest or highest categories of BMI.

While there is fairly consistent evidence linking hypertension and antihypertensive medications to renal cancer [7] and hypertension to endometrial cancer [5, 7, 8, 17], prior published studies of a hypertension-breast cancer

### Table 2

Relative risk estimates for association between hypertension, antihypertensive (AH) medication use, and invasive breast cancer overall and for estrogen receptor (ER) subtypes in baseline respondents in the California Teachers Study

| Variable                                | Observed person-years<sup>b</sup> | Invasive breast cancer | ER + breast cancer | ER − breast cancer |
|-----------------------------------------|----------------------------------|------------------------|-------------------|-------------------|
|                                         | No. of cases | Age-adjusted RR (95% CI) | Multivariable-adjusted RR (95% CI)<sup>a</sup> | No. of cases | Multivariable-adjusted RR (95% CI) |
| Treated hypertension                    |                                  |                        |                   |                   |
| Never                                   | 991,013 | 3,341 | 1.0 (ref) | 1.0 (ref) | 2,443 | 1.0 (ref) | 453 | 1.0 (ref) |
| Ever                                    | 155,427 | 810  | 1.06 (0.98–1.14) | 1.06 (0.98–1.16) | 585 | 1.09 (0.99–1.20) | 91 | 0.98 (0.78–1.25) |
| Minimum duration of any AH medication use |                                  |                        |                   |                   |
| No regular use                          | 954,624 | 31,79 | 1.0 (ref) | 1.0 (ref) | 2,312 | 1.0 (ref) | 432 | 1.0 (ref) |
| ≤ 1 year                                | 44,076 | 171   | 0.90 (0.77–1.05) | 0.90 (0.77–1.06) | 120 | 0.87 (0.72–1.05) | 23 | 0.92 (0.60–1.41) |
| 2–4 years                               | 55,797 | 256   | 1.00 (0.88–1.14) | 1.00 (0.88–1.14) | 184 | 0.99 (0.85–1.15) | 25 | 0.78 (0.51–1.16) |
| 5–9 years                               | 37,072 | 212   | 1.18 (1.02–1.36) | 1.18 (1.02–1.36) | 159 | 1.21 (1.03–1.43) | 27 | 1.19 (0.80–1.78) |
| 10+ years                               | 50,588 | 305   | 1.17 (1.04–1.32) | 1.17 (1.04–1.34) | 237 | 1.26 (1.10–1.45) | 31 | 1.00 (0.69–1.47) |
| Regular diuretic use                     |                                  |                        |                   |                   |
| No                                      | 1,038,514 | 3,598 | 1.0 (ref) | 1.0 (ref) | 2,628 | 1.0 (ref) | 477 | 1.0 (ref) |
| Yes                                     | 107,926 | 553   | 1.05 (0.96–1.16) | 1.06 (0.96–1.16) | 400 | 1.04 (0.93–1.16) | 67 | 1.06 (0.81–1.38) |
| Duration of diuretic use                |                                  |                        |                   |                   |
| No regular use                          | 1,038,514 | 3,598 | 1.0 (ref) | 1.0 (ref) | 2,628 | 1.0 (ref) | 477 | 1.0 (ref) |
| ≤ 1 year                                | 21,734 | 86    | 0.90 (0.73–1.12) | 0.91 (0.74–1.13) | 59 | 0.85 (0.66–1.01) | 13 | 1.08 (0.62–1.87) |
| 2–4 years                               | 26,642 | 120   | 0.97 (0.81–1.16) | 0.97 (0.81–1.17) | 84 | 0.92 (0.74–1.15) | 11 | 0.72 (0.40–1.32) |
| 5–9 years                               | 19,767 | 109   | 1.11 (0.92–1.35) | 1.11 (0.92–1.35) | 76 | 1.05 (0.84–1.33) | 16 | 1.34 (0.81–2.22) |
| 10+ years                               | 37,804 | 227   | 1.16 (1.01–1.32) | 1.16 (1.01–1.33) | 175 | 1.21 (1.03–1.42) | 25 | 1.11 (0.73–1.67) |
| Regular other AH medication use          |                                  |                        |                   |                   |
| No                                      | 1,005,301 | 3,424 | 1.0 (ref) | 1.0 (ref) | 2,501 | 1.0 (ref) | 456 | 1.0 (ref) |
| Yes                                     | 141,139 | 727   | 1.07 (0.99–1.17) | 1.08 (0.99–1.18) | 527 | 1.07 (0.97–1.18) | 88 | 1.06 (0.84–1.35) |
| Duration of other AH medication use      |                                  |                        |                   |                   |
| No regular use                          | 1,005,301 | 3,424 | 1.0 (ref) | 1.0 (ref) | 2,501 | 1.0 (ref) | 456 | 1.0 (ref) |
| ≤ 1 year                                | 25,032 | 96    | 0.89 (0.73–1.10) | 0.89 (0.73–1.10) | 66 | 0.84 (0.66–1.08) | 13 | 0.94 (0.54–1.63) |
| 2–4 years                               | 38,929 | 183   | 1.02 (0.87–1.18) | 1.02 (0.88–1.18) | 129 | 0.99 (0.83–1.18) | 19 | 0.84 (0.53–1.34) |
| 5–9 years                               | 30,015 | 168   | 1.16 (0.99–1.35) | 1.16 (0.99–1.36) | 127 | 1.19 (0.99–1.43) | 19 | 1.06 (0.67–1.69) |
| 10+ years                               | 42,998 | 253   | 1.14 (1.00–1.30) | 1.15 (1.01–1.31) | 188 | 1.17 (1.00–1.36) | 31 | 1.20 (0.82–1.76) |

RRs in bold have <i>p</i>-values < 0.05, and RRs underlined have <i>p</i>-values < 0.01

<sup>a</sup> Age-stratified analyses adjusted for categories of race, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies combined variable, hormone therapy and menopausal status combined variable, lifetime physical activity, diabetes, body mass index, smoking history, alcohol use, hysterectomy, breastfeeding, and quartiles of percent calories from fat

<sup>b</sup> Person-years and number of cases may not add up to total due to rounding or unknown values
association have been inconsistent [7, 8, 18–20]. Some prior studies included only women aged 50 and older [18, 19], while others included younger women as well [8, 20]. In the present study, we found the AH medication-breast cancer association was most pronounced in younger women. However, a study by Soler et al. [8] stratified by age found the risk to be confined to post-menopausal women, and two additional studies reported significant hypertension and breast cancer associations among women above age 50 at enrollment [18, 19]. Furthermore, with a fairly long list of potential or established shared risk factors, it is possible that differential or inadequate adjustment for such factors may also account for some of the inconsistencies. For example, not all prior studies accounted for alcohol use [18], lifetime physical activity [8, 18–20], breastfeeding [8, 18, 19], hormone therapy use [8, 18, 19], hysterectomy [8, 18–20], or diabetes [8, 18]. Also, because the magnitude of any true association between hypertension, AH medications, and breast cancer is likely weak, there may be issues of inadequate power for smaller studies. Studies which have stratified by BMI have tended to report stronger associations of hypertension with breast cancer among women with higher BMI [8, 19]. Stratification by BMI in the present study indicated that at least 5 years of use of other AH medication was associated with invasive breast cancer among women in the highest (≥30 kg/m²) category of BMI. Furthermore, when analyses were stratified by both menopausal status and BMI (results not shown), associations between treated hypertension, AH medication use, and invasive breast cancer risk were confined to pre-/peri-menopausal women in the highest category of BMI.

An important challenge for research investigating the interrelationships between hypertension, AH medications, and breast cancer risk is that of disentangling the independent effects of the condition versus pharmacologic treatments. In a prospective study of hypertensive women which included measures of diastolic blood pressure (DBP) at baseline, increasing DBP was associated with increased risk of breast cancer among women who were not taking AH drugs but was inversely associated with risk among women taking AH drugs [21]. In the longitudinal Women’s Health Initiative Study, increasing baseline DBP also was reported to be associated with a borderline increased risk of total breast cancer (invasive and in situ), but not invasive breast cancer alone [22]. A limitation of the present study is lack of information about whether hypertension was controlled by either AH medications or lifestyle modifications as well as a lack of information about specific types of medications beyond broad classes in the baseline questionnaire. Furthermore, with the exception of the antihypertensive medications queried on the 2000–2001 survey, both hypertension and AH medication use were recorded on the baseline survey, and any changes that may have occurred during years of follow-up could have resulted in some misclassification of exposure status.

### Table 3 Relative risk estimates for association between hypertension, antihypertensive (AH) medication use, and invasive breast cancer by strata of body mass index (BMI) and menopausal status in baseline respondents in the California Teachers Study

| Strata            | Breast cancer cases, No. | History of treated hypertension, RR* (95% CI) | Diuretic use, RR* (95% CI) | Other antihypertensive medication use, RR* (95% CI) |
|-------------------|-------------------------|-----------------------------------------------|---------------------------|---------------------------------------------------|
|                   | No | Yes | <5 years of use | 5+ years of use | No | regular use | <5 years of use | 5+ years of use |
| BMI               |    |     | regular use    | regular use    |    |           | regular use    | regular use    |
| <25               | 2291 | 1.0 (ref) | 1.12 (0.98–1.27) | 1.0 (ref) | 0.77 (0.59–1.00) | 1.12 (0.93–1.37) | 1.0 (ref) | 1.01 (0.83–1.23) | **1.20 (1.01–1.42)** |
| 25–29             | 1127 | 1.0 (ref) | 0.95 (0.81–1.11) | 1.0 (ref) | 1.00 (0.78–1.28) | 1.05 (0.85–1.30) | 1.0 (ref) | 0.92 (0.73–1.16) | 1.00 (0.82–1.22) |
| 30+               | 569 | 1.0 (ref) | 1.09 (0.90–1.32) | 1.0 (ref) | 1.08 (0.80–1.45) | **1.31 (1.03–1.66)** | 1.0 (ref) | 0.89 (0.66–1.19) | **1.35 (1.08–1.69)** |
| Menopausal status |    |     |                 |                 |    |           |                 |                 |
| Pre/peri-menopausal | 1016 | 1.0 (ref) | 1.08 (0.83–1.41) | 1.0 (ref) | 0.82 (0.53–1.25) | 1.13 (0.70–1.81) | 1.0 (ref) | 0.90 (0.63–1.28) | **1.58 (1.11–2.25)** |
| Post-menopausal   | 2760 | 1.0 (ref) | 1.05 (0.96–1.15) | 1.0 (ref) | 0.94 (0.80–1.11) | 1.13 (1.00–1.28) | 1.0 (ref) | 0.96 (0.83–1.10) | 1.10 (0.98–1.24) |

* Age-stratified analyses adjusted for categories of race, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies combined variable, lifetime physical activity, diabetes, smoking history, alcohol use, breastfeeding, and quartiles of percent calories from fat: analyses stratified by BMI were further adjusted for hysterectomy, menopausal status, and hormone therapy use combined variable, and analyses stratified by menopausal status were further adjusted for BMI.

RRs in bold have p-values <0.05.
AH medications have been associated with risk of various malignancies. A pooled analysis of AH medication use and risk of malignancies revealed a significant association between rauwolfia derivatives, including reserpine, and breast cancer yielding a significant 25% increase in breast cancer risk [23]. This pooled analysis also supported an association between diuretics and increased risk of renal cell carcinoma while other AH drugs including ACE inhibitors and calcium antagonists were not found to be associated with cancer risk. In a case–control study among women aged 65–79, Li and colleagues [24] reported that thiazide diuretics (OR = 1.4, 95% CI 1.1–1.8), potassium-sparing diuretics (OR = 1.6, 95% CI 1.2–2.1), and immediate release calcium channel blockers (OR = 1.5, 95% CI 1.0–2.1) were associated with modest increased risk of invasive breast cancer, however, no trend of increasing risk with increasing duration of use was observed. It has been suggested that insulin resistance among thiazide diuretic users and increased insulin levels associated with use of potassium-sparing diuretics are potential mechanisms [24, 25] which could explain an association between diuretic use and breast cancer. One additional [19] study among women aged 50–75, but not other previous studies [25–27], investigating the risk of breast cancer associated with diuretic use, have reported a significant association. It is not clear in some of the prior studies whether in situ breast cancers were included as outcomes [26, 27]. In the present study, an association between thiazide diuretic use and invasive breast cancer risk was not observed.

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### Table 4

| Variable                      | n          | Observed person-years | Invasive breast cancer cases, no. (1,714 total) | Multivariable adjusted RR (95% CI) |
|-------------------------------|------------|-----------------------|-----------------------------------------------|----------------------------------|
| Any antihypertensive medication |            |                       |                                               |                                  |
| No regular use                | 56,710     | 361,865               | 1,206                                         | 1.0 (ref)                        |
| Regular use within 2 years    | 17,032     | 103,558               | 508                                           | 1.09 (0.98–1.22)                 |
| Thiazide diuretic             |            |                       |                                               |                                  |
| No regular use                | 68,409     | 432,781               | 1,540                                         | 1.0 (ref)                        |
| Regular use within 2 years    | 5,324      | 32,583                | 172                                           | 1.16 (0.99–1.37)                 |
| Unknown                       | 9          | 59                    | 2                                             |                                  |
| Furosemide diuretic (Lasix)   |            |                       |                                               |                                  |
| No regular use                | 72,175     | 457,054               | 1,664                                         | 1.0 (ref)                        |
| Regular use within 2 years    | 1,562      | 8,350                 | 50                                            | 1.22 (0.91–1.65)                 |
| (Unknown)                     | 5          | 19                    | 0                                             |                                  |
| Calcium channel blocker       |            |                       |                                               |                                  |
| No regular use                | 70,862     | 448,175               | 1,630                                         | 1.0 (ref)                        |
| Regular use within 2 years    | 2,873      | 17,208                | 84                                            | 1.05 (0.84–1.31)                 |
| Unknown                       | 7          | 40                    | 0                                             |                                  |
| ACE inhibitor                 |            |                       |                                               |                                  |
| No regular use                | 69,698     | 440,762               | 1,592                                         | 1.0 (ref)                        |
| Regular use within 2 years    | 4,034      | 24,593                | 122                                           | 1.05 (0.86–1.27)                 |
| Unknown                       | 10         | 68                    | 0                                             |                                  |
| Other antihypertensive medication |        |                       |                                               |                                  |
| No regular use                | 63,242     | 401,638               | 1,410                                         | 1.0 (ref)                        |
| Regular use within 2 years    | 10,441     | 63,428                | 303                                           | 1.04 (0.91–1.18)                 |
| Unknown                       | 59         | 357                   | 1                                             |                                  |

a Age-stratified analyses adjusted for categories of race, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies combined variable, hormone therapy and menopausal status combined variable, lifetime physical activity, diabetes, body mass index, smoking history, alcohol use, hysterectomy, breastfeeding, and quartiles of percent calories from fat

b Totals may not add up due to rounding

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The observation in the present study of increased breast cancer risk with long-term use of AH medication raises a question as to whether it is the condition of hypertension itself or exposure to medications which may influence breast cancer risk. It is likely that long-term use of AH medication is a surrogate marker for longer duration of a hypertensive condition. However, certain AH medications may have been taken for other conditions, including cardiac arrhythmia (beta blockers, calcium channel blockers), coronary artery disease with or without history of myocardial infarction (beta blockers), congestive heart failure.
(ACE inhibitors, furosemide diuretics), diabetic nephropathy (ACE inhibitors), or off-label usage such as diuretics for weight loss. One hypothesis for why duration of exposure to the condition of hypertension may be an important factor in a hypertension-cancer association has been reviewed by Hamet [13] who postulates that with short-term exposure to hypertension, during the period in which hypertension is developing, apoptosis is increased which may be associated with reduced risk of cancer [28]. Long-term exposure, on the other hand, could be associated with increased cancer risk as it is associated with cellular senescence, telomere shortening [29], and inhibition of apoptosis. Other potential biologic mechanisms contributing to an association between hypertension and cancer include pathways shared in steroid hormone synthesis and metabolism [12], angiogenesis [30], growth factor signaling [31], and inflammation [22, 32].

Strengths of the current study include the prospective design where hypertension and AH medication use were assessed prior to follow-up for breast cancer incidence thus largely eliminating the potential for recall bias. However, because the primary exposures of interest, history of hypertension, and AH medication use were primarily assessed by self-report, the potential for misclassification exists. A recent NHANES report revealed that 87% of hypertensive women in the United States are aware of their condition; further, less than 5% of women were hypertensive, but had never been diagnosed by a health care provider [33]. The sensitivity of self-reported antihypertensive medication use among older women has been reported to be 79–92% [34]. Any such misclassification of AH medication is, however, expected to be non-differential with respect to breast cancer status, and thus our findings should if anything be an underestimate of the true effects.

The ascertainment of incident breast cancer diagnoses through linkage with the comprehensive population-based CCR, rather than relying on self-reports, is another strength of our study as case ascertainment is 99% complete in the state of California [35].

The CTS cohort is also well characterized with respect to covariates of interest which allowed for adjustment for several potential confounding factors. While breast cancer and hypertension appear to share many common risk factors, the age-adjusted and multivariate-adjusted risk estimates were quite similar in this study, suggesting that the covariates did not have a major influence on the association between AH medications and breast cancer. However, these effects were rather moderate, and so we cannot exclude the possibility that residual confounding may account for the observed associations.

In summary, it is difficult to separate the independent effects of the condition of hypertension itself (and varying levels of severity and control) and treatment in the form of AH medications on the risk of breast cancer. However, given the high prevalence of both hypertension and AH medication use, even small effects on breast cancer risk could potentially have population-wide implications. Future research into the biologic mechanisms may help disentangle the etiologic roles of hypertension itself versus the use of specific antihypertensive medications in breast cancer risk.

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