Hormonal Therapy and Risk of Breast Cancer in Mexican Women

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Abstract

The use of hormonal therapies, including hormonal contraceptives (HC) and postmenopausal hormone replacement therapy (HRT) have been shown to influence breast cancer (BC) risk. However, the variations of these effects among populations and ethnic groups are not completely documented, especially among Hispanic women. We evaluated the association between HC and premenopausal BC risk, and between HRT and postmenopausal BC risk in Mexican women. Data from a Mexican multi-center population-based case–control study of women aged 35 to 69 years were analysed. A total of 1000 cases and 1074 matched controls were recruited between 2004 and 2007. Information on hormonal therapy was collected through a structured questionnaire. Results were analysed using conditional logistic regression models. Overall, HC were used by 422/891 (47.3%) premenopausal women and HRT was used by 220/1117 (19.7%) postmenopausal women. For HC, odds ratios (ORs) for BC were 1.11 (95% confidence interval (CI): 0.82, 1.49) for current users and 1.68 (95% CI: 0.67, 4.21) for ever-users. No clear effect of duration of use was observed. For HRT, the OR for BC was significantly increased in ever-users (OR: 1.45; 95% CI: 1.01, 2.08). A non-significant increased risk was observed for combined estrogen/progestogen, (OR = 1.85; 95% CI: 0.84, 4.07) whereas no effect was observed for the use of estrogen alone (OR = 1.14; 95% CI: 0.68, 1.91). Our results indicate that, HC had a non-significant effect on the risk of pre-menopausal BC, but suggested that injected contraceptives may slightly increase the risk, whereas HRT had a significant effect on post-menopausal BC in this population. This study provides new information about the effects of HC and HRT on BC risk in a Mexican population, which may be of relevance for the population of Latin America as a whole.

Introduction

Risk factors for breast cancer (BC) show variable associations with the disease according to ethnicity/race. However, these associations are still incompletely documented in many populations, including Hispanic populations [1–3]. In the United States (US), the lower incidence of BC in Hispanics compared with Caucasians is partially explained by difference in the distribution of BC risk factors such as late age at menarche, early age at first full-term pregnancy and large number of children [4,5]. Together, these reproductive factors account for less than 20% of the difference between the two ethnic groups for postmenopausal women [6]. In contrast, Hispanic women in the US have higher prevalence of obesity and physical inactivity than Caucasian, two factors associated with increased risk of BC [4].

The use of hormonal therapies including hormonal contraceptives (HC) and post-menopausal hormone replacement therapy (HRT) has been shown to be associated with increased risk of BC. HC are among the most commonly used drugs worldwide. Several large epidemiological studies that have assessed the effect of HC on the risk of BC have reported an increased risk of premenopausal BC [7–11]. For HRT, evidence from randomized controlled trials and observational studies has shown that women using HRT are at an increased risk of BC [9,12–18]. Moreover, the risk of BC associated with HRT is larger for users of combined HRT than for users of estrogen-only therapy [9,19–22]. These results, as well as data on the risk of several other cancers, have led the International Agency for Research on Cancer (IARC) to classify combined estrogen-progestogen contraceptives and combined HRT as carcinogenic for humans [23,24]. However, the majority of these studies were based on Caucasian women. Although the evidence that hormonal therapies influence BC development among Caucasian women is extensive, less is known about these relationships among Hispanic women [20,25]. There are no studies of Mexican women living in México, and given the lack of public awareness [26], the use of hormonal therapies will probably continue to increase over the next years. Therefore, there is an urgent need to know how hormonal therapies affect BC in a Hispanic population living in Latin America.

In this study, we have used data from a multi-center population-based case-control study conducted in Mexico to assess the effects of hormonal therapy on the risk of BC in a non-US Hispanic population. We have investigated the association between the use...
Classification of use of HC and HRT

Women were individually interviewed about HC and HRT using the following questions: (1) Have you ever taken HC or HRT? (2) If yes, how old were you when you started taking HC or HRT? (3) If yes, how old were you when you stopped taking such therapy? (4) If yes, how long in total did you take each therapy? (5) What type of treatment did you use? Women reported their age at starting and stopping HC and HRT in years and months. Time since last use was calculated as time since last reported use of HC in premenopausal women or of HRT in postmenopausal women and duration of use was calculated by adding together the total amount of time that HC or HRT use was reported. In premenopausal women, variables were then constructed as follows: ever use (ever versus never), time since last use (≥ 10 years, < 10 years, recent, never), total duration of use (≥ 10 years, < 10 years, never), and type of treatment (none, oral, injected or transdermal, more than one treatment). In postmenopausal women, categories were created for users of HRT as follows: ever use (ever versus never), time since last use (past, recent, never), total duration of use (≥ 5 years, < 5 years, never), and type of treatment (none, estrogen alone, estrogen/progestin).

We defined recent use as the reported use of HC or HRT during the year prior to the date of interview. The categories used for these variables were defined a priori, taking into account the sample size in the relevant categories.

Statistical analysis

We used Chi² or Fisher’s exact tests to compare frequency distributions of characteristics of HC users and non-users in the premenopausal population and of HRT users and non-users in the postmenopausal population. Conditional logistic regression models were used to examine these associations. Multivariate adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) were estimated, adjusting for age at diagnosis (continuous), SES (high/medium/low), body mass index (BMI) (kg/m², continuous), family history of BC (yes/no), parity (continuous), age at first full term pregnancy (continuous), age at menarche (continuous), total duration of breastfeeding (continuous), and diabetes (yes/no). In addition, we further adjusted for genetic admixture (genetic ancestry). We then stratified the categories (ever user or never user) by BMI and genetic ancestry (as defined based on evaluation of genetic admixture) [28] in order to evaluate potential interactions between hormonal therapy and BMI or genetic ancestry. BMI was stratified into two categories: normal weight (BMI < 25 kg/m²) and overweight (BMI ≥ 25 kg/m²). Indigenous American genetic ancestry was modeled as a categorical variable (0–50%, 51–75%, 76–100%). Log-likelihood tests were used to evaluate linear trends and interaction terms. All tests of statistical significance were two-sided and p ≤ 0.05 was considered as significant. All statistical analyses were performed using SAS software (version 9.0, SAS Institute, Inc., Cary, NC).

Results

Characteristics of the study population

The main characteristics of the study population are shown in Table 1. One thousand cases (415 premenopausal and 585 postmenopausal women) and 1074 controls (476 premenopausal and 598 postmenopausal women) were included in the study. Overall, information on the use of hormonal therapies was available for 2008 participants. A total of 422/891 (47.3%) premenopausal women used HC and 220/1117 (19.7%) postmenopausal women used HRT. In premenopausal women, compared with women who had never used HC, users were more likely to be younger at first pregnancy, to be parous, and to have a long duration of breastfeeding. In postmenopausal women, compared with women who never used HRT, users were more...
likely to have fewer children, to have a higher level of SES and to have a long duration of breastfeeding.

**HC use and breast cancer risk in pre-menopausal women**

The association between use of HC and BC risk was non-significant (OR = 1.11; 95% CI: 0.82, 1.49 for ever versus never users) (Table 2). Recent users had a non-significant increase in BC risk (OR: 1.68; 95% CI: 0.67, 4.21) compared to never users (Table 2). Time since last use did not affect the association with BC risk. ORs were 1.14 (95% CI: 0.81, 1.61) in users with time since last use of 10 years or more and 1.16 (95% CI: 0.69, 1.95) in users with time since last use under 10 years. With regard to total duration of use, multivariate adjusted ORs were 1.53 (95% CI: 0.76, 3.08) among women who used HC for ten years or more and

### Table 1. Demographic and risk factor characteristics of the study population, according to the use of hormonal contraceptive and hormone replacement therapy.

| Characteristics                  | Premenopausal | Postmenopausal | P-value |
|----------------------------------|---------------|----------------|---------|
|                                  | HC non-users  | HC users       |         |
| Age (years)                      |               |                |         |
| < 40                             | 314 (66.9)    | 244 (57.8)     | 0.016   |
| 40–54                            | 150 (32)      | 173 (41)       |         |
| 55–64                            | 4 (0.9)       | 5 (1.2)        |         |
| ≥ 65                             | 1 (0.2)       | -              |         |
| BMI (kg/m2)                      |               |                |         |
| < 25                             | 96 (20.5)     | 78 (18.5)      | 0.016   |
| 25–29.9                          | 197 (42.0)    | 185 (43.9)     |         |
| ≥ 30                             | 176 (37.5)    | 159 (37.7)     |         |
| Age at menarche                  |               |                |         |
| < 13                             | 222 (47.3)    | 204 (48.3)     | 0.764   |
| ≥ 13                             | 247 (52.7)    | 218 (51.7)     |         |
| Family history of breast cancer  |               |                |         |
| No                               | 440 (93.8)    | 402 (95.3)     | 0.345   |
| yes                              | 29 (6.2)      | 20 (4.7)       |         |
| Socio economic status            |               |                |         |
| Low                              | 139 (29.6)    | 130 (30.8)     | 0.925   |
| Medium                           | 141 (30.1)    | 126 (29.8)     | 0.925   |
| High                             | 189 (40.3)    | 166 (39.3)     |         |
| Age at 1st full term pregnancy   |               |                |         |
| Nulliparous                      | 67 (14.3)     | 18 (4.3)       | < 0.001 |
| < 22                             | 188 (40.1)    | 242 (57.3)     |         |
| ≥ 22                             | 209 (44.5)    | 156 (36.9)     | < 0.001 |
| Missing                          | 5 (1.1)       | 6 (1.4)        |         |
| Number of full term pregnancies  |               |                |         |
| 0                                | 67 (14.3)     | 18 (4.3)       | 0.087   |
| ≥ 1–2                            | 203 (43.3)    | 151 (35.8)     | < 0.001 |
| ≥ 3                              | 195 (41.6)    | 253 (59.9)     |         |
| Missing                          | 4 (0.8)       | -              |         |
| Breastfeeding                    |               |                |         |
| Nulliparous                      | 67 (14.3)     | 18 (4.3)       | 0.087   |
| < 12                             | 43 (9.2)      | 49 (11.6)      | < 0.001 |
| ≥ 12                             | 124 (26.4)    | 142 (33.6)     |         |
| Missing                          | 235 (50.1)    | 213 (50.5)     |         |
| Native ancestry                  |               |                |         |
| 0–50%                            | 113 (24.1)    | 117 (27.7)     | 0.093   |
| 51–75%                           | 205 (43.7)    | 199 (47.2)     |         |
| 76–100%                          | 106 (22.6)    | 80 (18.9)      |         |
| Missing                          | 45 (9.6)      | 26 (6.2)       |         |

P-value (Ch² or Fisher’s exact tests) for the difference between HC non-users and users in premenopausal, and HRT non-users and users in postmenopausal women.

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1.15 (95% CI: 0.84, 1.58) among women who used HC for less than ten years as compared to never users. When comparing types of HC, a borderline effect on risk was observed with injectors or transdermal [Algestone/Estradiol] treatment as compared to never users (OR = 1.79; 95% CI: 0.91, 3.53). Further adjustment for admixture variables showed a slight increase of the associations (Table 2). No modification of effect was observed when data were stratified by BMI (P for interaction between HC and BMI = 0.68). There was no interaction between HC and admixture (P = 0.53) (data not shown).

### HRT use and breast cancer risk in post-menopausal women

In multivariate models, ever use of HRT was associated with a significant increase in BC (OR = 1.45; 95% CI: 1.01, 2.08) (Table 3). Both recent and past use showed a borderline significant association. The multivariate adjusted ORs were 1.86 (95% CI: 0.97, 3.55) for recent use and 1.45 (95% CI: 0.97, 2.17) for past use as compared to never use. Duration of use of less than 5 years was significantly associated with BC risk (OR = 1.48; 95% CI: 1.01, 2.17). Whereas the association was stronger for 5 or more years of use, it did not reach statistical significance, possibly because of the small sample size in this category (OR = 1.95; 95% CI: 0.90, 4.26). Types of treatment were classified as estrogen alone and combined treatment (estrogen/progestin). Although non-significant in both cases, the magnitude of the effect was higher for combined treatment (OR: 1.85; 95% CI: 0.84, 4.07) than for usage of estrogen alone (OR = 1.14; 95% CI: 0.68, 1.91) (Table 3). When taking BMI into account, a significant association was observed among overweight women (BMI > 25 kg/m²) who ever used HRT as compared to never users (OR = 1.53; 95% CI: 1.06, 2.22), but not in normal weight women (OR = 1.13; 95% CI: 0.36, 3.53) (Table 4). Results were not affected after stratifying for admixture variables (P for interaction between HRT and admixture = 0.27) (data not shown).

### Discussion

The purpose of this study was to bring a better understanding of the effect of HC and HRT on BC risk among Mexican women. Among premenopausal women, ever and recent users of HC had a non-significant increase in BC risk compared to never users. In postmenopausal women, an increase in BC risk was observed among HRT users. The effect is considerably more important for current use, for combined progestin/estrogen use, and for 5 or more years of use than for past use, estrogen only, and duration of use less than 5 years, respectively.

The potential association between HC and BC risk has been investigated in a number of epidemiological studies [7,8,10,11,30–32]. They often reported that recent use of HC, as well as long duration, was associated with an increased risk of BC. In premenopausal Hispanic women, Sweeney et al. [25] reported a non-significant increased risk of BC among recent users of HC compared to never users (OR = 1.22; 95% CI: 0.80, 1.84 for oral contraceptives). In our study, the highest increased risk was observed in the class of injected contraceptive (OR was 1.79; 95% CI: 0.91, 3.53) despite the small size of the subgroup (cases/controls = 27/23). In the largest meta-analysis including 54 epidemiologic studies, women currently using HC had a modestly

### Table 2. OR (95% CI) of breast cancer in pre-menopausal women according to the use of hormonal contraceptive treatment.

| Time since last use | Age adjusted | Multivariate Adjusted* | Multivariate Adjusted** |
|---------------------|--------------|------------------------|-------------------------|
| Never               | 216/253      | 1.00 (reference)       | 1.00 (reference)        |
| > 10 years          | 120/134      | 0.98 (0.71–1.36)       | 1.14 (0.81–1.61)        |
| < 10 years          | 37/39        | 1.04 (0.63–2.72)       | 1.16 (0.69–1.95)        |
| recent (***)        | 12/9         | 1.58 (0.65–3.86)       | 1.68 (0.67–4.21)        |
| P trend             |              | 0.59                   | 0.22                    |
| Total duration of use |             |                        |                         |
| Never               | 216/253      | 1.00 (reference)       | 1.00 (reference)        |
| < 10 years          | 149/164      | 1.00 (0.74–1.34)       | 1.15 (0.84–1.58)        |
| > 10 years          | 22/19        | 1.39 (0.72–2.71)       | 1.53 (0.76–3.08)        |
| P trend             |              | 0.36                   | 0.12                    |
| Type of treatment   |              |                        |                         |
| Never               | 216/253      | 1.00 (reference)       | 1.00 (reference)        |
| Oral                | 47/61        | 0.90 (0.58–1.39)       | 0.94 (0.59–1.49)        |
| Injected or transdermal | 27/23      | 1.54 (0.83–2.88)       | 1.79 (0.91–3.53)        |
| Others              | 9/15         | 0.86 (0.35–2.07)       | 0.99 (0.39–2.54)        |
| More than one treatment | 40/51       | 0.85 (0.53–1.36)       | 0.94 (0.57–1.57)        |

(*) Adjusted for: age, socioeconomic status (high/medium/low), BMI (kg/m²), familial history of breast cancer in first degree relatives (yes/no), diabetes (yes/no), number of full term pregnancy, age at first full term pregnancy (years), total duration of breast feeding (months) and age at menarche (years).

(**) Additional adjusted for European ancestry.

(***) We defined the recent use as the reported use of contraceptive treatment during the year prior to the date of interview.

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elevated risk for BC. This risk continuously decreased with years of treatment cessation and became null after ten years (RRs: in current users = 1.24 (95% CI: 1.15, 1.33); 1–4 years after stopping = 1.16 (95% CI: 1.08, 1.23), 5–9 years after stopping = 1.07 (95% CI: 1.02, 1.13) and 10 or more years after stopping = 1.01 (95% CI: 0.96, 1.05)) [7]. In our study, the time since last use and the total duration of use did not affect the association with BC risk; however the size of many of the subgroups was too small to provide an accurate estimate of the effect.

Our findings reported for HRT in relation to BC risk among postmenopausal women are essentially compatible with published epidemiological studies [17,19,21,33–37]. In a nested case-control study, current HRT users have been found to have a higher risk of BC than never-users, adjusted OR = 2.1 (95% CI: 1.5, 3.0). In the Million Women Study [38], current use of HRT was associated with an increase in BC risk and was significantly different from the risk associated with past use. The use of combination HRT (estrogen and progestin) for more than 5 years resulted in the highest risk of BC, OR = 3.0 (95% CI: 1.9–4.7) [21]. The WHI (Women’s Health Initiative) reported that the magnitude of the effects for combined estrogen/progestin treatment was higher than for the usage of estrogen treatment alone [19,22]. Similarly, Lee et al reported that current estrogen-progestin therapy use was associated with a 29% increased risk of BC per 5 years of use (95% CI: 23, 35%), and current estrogen therapy use with a 10% increase in risk per 5 years of use (95% CI = 5–16%) [20]. Additionally, one recent cohort study reported that estrogen plus progestin was associated with more invasive BC

Table 3. OR (95% CI) of breast cancer in post-menopause women according to the use of hormone replacement therapy.

| Age adjusted | Multivariate Adjusted* | Multivariate Adjusted** |
|--------------|------------------------|-------------------------|
| OR (95% CI)  | OR (95% CI)            | OR (95% CI)             |
| Never user   | 1.00 (reference)       | 1.00 (reference)        | 1.00 (reference)        |
| Ever user    | 1.78 (1.32–2.41)       | 1.45 (1.01–2.08)        | 1.41 (1.01–1.99)        |
| Time since last use |                |                        |                        |
| Never        | 1.00 (reference)       | 1.00 (reference)        | 1.00 (reference)        |
| Past         | 1.60 (1.10–2.32)       | 1.45 (0.97–2.17)        | 1.40 (0.93–2.13)        |
| Recent (*** )| 2.19 (1.19–4.03)       | 1.86 (0.97–3.55)        | 1.82 (0.94–3.54)        |
| P trend      | 0.0009                 | 0.02                    | 0.03                    |

Total duration of use

| Never        | 1.00 (reference)       | 1.00 (reference)        | 1.00 (reference)        |
| < 5 years    | 1.54 (1.08–2.20)       | 1.48 (1.01–2.17)        | 1.42 (0.96–2.11)        |
| > 5 years    | 2.79 (1.36–5.73)       | 1.95 (0.90–4.26)        | 1.96 (0.87–4.39)        |
| P trend      | 0.006                  | 0.07                    | 0.10                    |

Type of treatment

| Never        | 1.00 (reference)       | 1.00 (reference)        | 1.00 (reference)        |
| Estrogen alone | 1.36 (0.84–2.20)     | 1.14 (0.68–1.91)        | 1.17 (0.69–2.00)        |
| Estrogen/Progestin | 2.26 (1.07–4.80) | 1.85 (0.84–4.07)        | 1.89 (0.84–4.29)        |

(*) Adjusted for: age, socioeconomic status (high/medium/low), BMI (kg/m2), familial history of breast cancer in first degree relatives (yes/no), diabetes(yes/no), number of full term pregnancy, age at first full term pregnancy (years), total duration of breast feeding (months) and age at menarche (years).

(**) additional adjusted for European ancestry.

(***) We defined the recent use as the reported use of menopausal hormone therapy during the year prior to the date of interview.

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Table 4. OR (95% CI) of breast cancer in premenopausal women according to ever use of hormone contraceptive, and in postmenopausal women according to ever use of hormone replacement therapy, stratified by BMI.

|                  | Premenopausal | Postmenopausal |
|------------------|---------------|---------------|
|                  | BMI < 25 *    | BMI ≥ 25 *    | BMI < 25 *    | BMI ≥ 25 *    |
|                  | Case/control  | OR (95% CI)   | Case/control  | OR (95% CI)   |
| Never use        | 51/45         | 1.00 (reference) | 165/208      | 1.00 (reference) |
| Ever use         | 49/29         | 1.50 (0.63–3.56) | 150/194      | 1.03 (0.74–1.43) |
|                  | 1.00 (reference) | 165/208      | 1.00 (reference)  | 165/208      |
| Recent           | 2/1           | 1.15 (0.08–16.26) | 10/8         | 1.78 (0.67–4.77) |
| Past             | 40/23         | 1.60 (0.64–4.02) | 117/150      | 1.08 (0.75–1.53) |

Adjusted for: age, socioeconomic status (high/medium/low), BMI (kg/m2), familial history of breast cancer in first degree relatives (yes/no), diabetes(yes/no), number of full term pregnancy, age at first full term pregnancy (years), total duration of breast feeding (months) and age at menarche (years).

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Estrogens are known to increase the rate of cell division within the ductal epithelium of the breast, and hence increase the probability of mutation occurring or of promotion of an existing mutation. In addition, progesterone and progestin may augment this effect [40,41]. Another hypothesis is that HRT use increases the radiological breast density (mammography density), a marker of change in composition of breast tissues, which is known to be a main risk factor for BC occurrence [42].

In conclusion, our results indicate that, among Mexican women, the use of HC had a non-significant effect on the risk of premenopausal BC, but suggested that injected contraceptives may slightly increase the risk. HRT had a significant effect on postmenopausal BC, in particular for combined hormones and long duration users. This study provides new information about the effects of HC and HRT on BC risk in this population, which may be of relevance for the population of Latin America as a whole. Further research on the impact of injected contraceptives is warranted.

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Conceived and designed the experiments: A.Amadou AF GT CO A.Angel-Llerenas IR PH. Performed the experiments: A.Amadou CB AF. Analyzed the data: A.Amadou AF GT CO A.Angel-Llerenas CB IR PH. Contributed reagents/materials/analysis tools: A.Amadou AF GT CO A.Angel-Llerenas IR PH. Performed the experiments: A.Amadou CB AF GT CO A.Angel-Llerenas IR PH. Wrote the paper: A.Amadou AF FM PH IR. Critical review of manuscript: A.Amadou AF GT CO A.Angel-Llerenas FM IR PH.

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