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Oral Contraceptive Use and Fracture Risk around the Menopausal Transition

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Abstract

Objective—The effect of oral contraceptive (OC) use on risk of fracture remains unclear, and use during later reproductive life may be increasing. To determine the association between oral contraceptive (OC) use during later reproductive life and risk of fracture across the menopausal transition, we conducted a population-based case-control study in a Pacific Northwest HMO, Group Health Cooperative.

Methods—For the January 2008-March 2013 interval, 1,204 case women aged 45-59 years with incident fractures and 2,275 control women were enrolled. Potential cases with fracture codes in automated data were adjudicated by EHR review. Potential control women without fracture codes were selected concurrently, sampling on age. Participants received a structured study interview.

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Using logistic regression, associations between OC use and fracture risk were calculated as odds ratios (OR) and 95% confidence intervals (CI).

Results—Participation was 69% for cases and 64% for controls. The study sample was 82% white; mean age was 54 years. The most common fracture site for cases was the wrist/forearm (32%). Adjusted fracture risk did not differ between cases vs. controls for OC use in the 10 years before menopause (OR=0.90, 95% CI 0.74,1.11); for OC use after age 38 (OR=0.94, 95% CI 0.78,1.14); for duration of use, or for other OC exposures.

Conclusions—The current study does not show an association between fractures near the menopausal transition and OC use in the decade before menopause or after age 38. For women considering oral contraceptive use at these times, fracture risk does not appear to be either reduced or—reassuringly—increased.

Keywords

contraceptives; oral; fractures; bone; menopausal transition; case-control studies; age factors

Introduction

Osteoporosis, a condition in which reduced bone density predisposes to fracture, is an important public health concern in the US and worldwide.¹⁻⁴ In the U.S., approximately 10 million individuals over the age of 50 have osteoporosis, and an estimated 1.5 million osteoporotic fractures occur annually.^{4,5} Eighty percent of osteoporosis occurs in women, and the current annual direct-care costs of osteoporosis-related fractures, over \$19 billion, are projected to soar as our population ages.² The hormonal changes around the menopause heighten fracture risk for women and offer valuable opportunities for fracture prevention. Estrogen therapy after the menopause has been found to maintain bone density and reduce the risk of fracture.⁶⁻⁹ However, the effects of premenopausal exogenous hormonal influences, such as oral contraceptives, on fracture risk remain unclear.^{10,11,12} Although estrogen is beneficial to the skeleton, oral contraceptives could potentially have negative effects, as well. These exogenous estrogens decrease ovarian estrogen production, eliminate the mid-cycle peak in estrogen, and the hepatic effects result in increased sex-hormone binding globulin, decreased available androgens, and decreased IGF-1 (insulin-like growth factor1) which is important to optimal skeletal health.^{13,14,15,16}

With nearly 12 million users, combined oral contraceptives (OCs) are the leading method of contraception in the U.S.¹⁷ and constitute the most prevalent source of exogenous hormone exposure for many women. While OC use is highest among women under age 30, use among women in their later reproductive years may be increasing.¹⁸⁻²¹ A number of factors may contribute to such an increase, including the notable decreases in the estrogen and progestin content of contemporary OC formulations with the concomitant lifting of the FDA recommendation against OC use in older women^{22,23}; and randomized trials showing that use of contemporary OCs in peri- and early menopausal women benefits bone mass.^{24,25,26}

To date, trial data on OC use and the key clinical outcome of fracture, are lacking.¹¹ Results from other studies of the OC-fracture association are inconsistent.¹⁰ However, few studies

evaluate this association with attention to age of use, which may be important,^{10,27,28} and few have focused on women using contemporary OC formulations (e.g. <50 mcg ethinyl estradiol).^{10,27,28} The World Health Organization noted the latter as an important evidence gap.¹

The goal of this study was to investigate the association between OC use during later reproductive life and fracture risk across the menopausal transition. Specifically, we undertook a population-based case-control study of 1,204 case women between the ages of 45 and 59 with incident adjudicated fractures and 2,275 comparable control women selected from the same defined population.

Methods

Study setting

This study was conducted at Group Health Cooperative, a mixed model health care organization located in the Pacific Northwest and serving approximately 600,000 enrollees. At the midpoint of the study enrollment approximately 49,000 women enrollees were ages 45-59 years, the target age group.

Study participants

We developed a population-based sampling frame designed to select women around the menopausal transition who experienced incident osteoporotic fractures and comparable control women without such fractures. The sampling frame was limited to the Group Practice Division (GPD), approximately 70% of Group Health enrollees, as they receive the great majority of their care at Group Health facilities and their electronic health record (EHR) data are most complete. Fractures were identified for the enrollment period from January 1, 2008 through March 30, 2013. The Group Health Human Subjects committee reviewed and approved all study protocols.

Identification of potential case and control women began with the health plan electronic databases. We excluded potential participants with a hysterectomy prior to their reference date since, for these women, the exposure of interest would not apply. We also excluded women with continuous hormone therapy during the two years or more up to the reference date, as they would be unlikely to use OCs and the current long-term use of hormone therapy already has been shown to protect against fracture.⁹ Cases were defined as women 45 to 59 years of age who experienced an incident fracture during the study interval at skeletal locations that are associated with low bone density or fracture risk in women 65 and older. We defined an “incident fracture” as the first fracture occurring both within the age range of interest (45-59) and during the study enrollment period. To identify potential case women, we selected age-eligible women who received International Classification of Diseases, 9th edition, Clinical Modification (ICD9-CM) codes for the following fracture sites as part of their healthcare utilization during the study enrollment period: forearm (including wrist), humerus, rib, sternum, tibia, fibula, vertebra, clavicle, scapula, pelvis, proximal femur, and mid or distal femur (Table 1). Although ankle fractures (distal tibia and/or fibula) are not associated with low bone density^{29,30} we included this fracture site

because these fractures are common among younger women. We excluded, fractures of the cranium, neck, hand/foot, fingers/toes, and patella. We also excluded fractures due to malignancy, infection, and Paget's disease. Per findings reported by investigators from the Study of Osteoporotic Fractures (SOF), fractures were included regardless of the degree of trauma.³¹

Women with potential eligible fractures were identified at approximately quarterly intervals by searching the Group Health inpatient, enrollment, ambulatory care, and claims databases. With each subsequent sample, any additional cases that had arisen since the study start date, January 1, 2008, also were included. The study recruitment and enrollment are summarized in Figure 1.

For each sample wave, the potential cases were sent for adjudication by a trained abstractor and the study clinician. We reviewed the electronic health record (EHR) for each potential case woman, using a standard abstraction form that was data-entered directly into an Access database (Microsoft, Redmond, WA). For the first two sample waves, all records were reviewed by both adjudicators to arrive at common decisions. Subsequently, the records for each wave were initially reviewed by the study abstractor for evidence that the fracture occurred after 1/1/2008. Records that met this criterion were then reviewed by the adjudication clinician (SMO). After adjudication, remaining potential cases were assigned a "reference date", the date accompanying the fracture code in the automated data or a revised date based on the adjudication.

Potential controls were women of the same ages who were sampled from the same defined population that gave rise to the cases. Control women were identified concurrently from the health plan enrollment databases at each wave, sampling on age and using a randomized recruitment strategy.^{32,33} Randomized recruitment allowed us to achieve probability matching in the age distributions of cases and controls and provided a flexible alternative to traditional frequency matching. This strategy had the advantages of allowing for simultaneous recruitment of cases and controls and for estimation of parameters associated with the matching factor (age). For each sample wave, potential control women were selected with the aim of achieving a 2:1 control:case ratio. The same automated exclusion criteria were applied as to potential cases. In addition, potential control women could not have a study fracture code after age 45 and within the study enrollment period, except for the small group of women with fracture codes who were found not to have fractures at adjudication and who were returned to the pool of potential controls. Women selected as potential controls for each quarterly sample were assigned a randomly selected "reference date" from among the fracture dates in the adjudicated case group for that wave.

Following case adjudication and control selection, the sample was sent to the Group Health Research Institute Survey Research Program, which sent out an invitation to participate in the study interview. Potential participants were screened further by telephone for eligibility and excluded if they reported a fracture at one of the study anatomic sites after age 45 and before 1/1/2008; if they were regularly using at least 2 years of prescription estrogen-containing hormone therapy at the time of their reference date; or if they reported a

hysterectomy prior to the reference date and before age 53. Women who continued to be eligible and who were willing to participate were interviewed.

At the conclusion of recruitment, the study group consisted of 3,499 participants, 1,190 case women and 2,309 control women. Of 2,236 potential incident fracture case participants contacted for the survey, 1,190 (68.7%) were eligible and willing to participate (see Figure 1). Of 4,374 potential control participants, 2,309 (63.5%) were eligible and willing to participate. During the creation of the final datasets, potential control women who, at the interview, reported fractures during the study interval were adjudicated and classed as either cases (n=18), not fracture (remain controls) (n=26) or excluded for insufficient information (n=8). The final dataset consisted of 1,204 case women and 2,275 control women.

Data Collection

Study participants received a structured telephone interview. The survey was programmed for computer-assisted telephone interviewing (CATI) using software developed by Sawtooth (WinCATI).

All study interviewers were trained in standard interviewing techniques, including CATI. They received additional training in the specific aims of the project and in the use of the specific study survey instrument before fielding and were periodically monitored throughout the study. Data were collected for the time up to and prior to the reference date (that is, the presumed date of the fracture for case women and the assigned reference date for control women). The survey included demographic characteristics, reproductive history, morbidities and medication/supplement use, dietary calcium and vitamin D intake, and information on other factors associated with fracture risk (height and weight, family and personal fracture history, smoking and alcohol consumption, physical activity, health conditions, medication use, and others). We specifically asked participants about the risk factors identified as predictors of future fractures in the World Health Organization FRAX analysis.³⁴ We then sent a de-identified dataset to the FRAX analysis group (Sheffield, UK) who provided the predicted 10-year fracture risks (using body mass index, and without the bone mineral density; the index fracture for case women was excluded).

Data collected on OC use included ever use (for 3 months or more), age at first use and episodes of use through to the reference date, and reasons for use and discontinuation at last use. From the episodes of use, we derived date and age of last use; use of OCs at the reference date; recency of use; durations of use overall and during later reproductive years (age ≥ 38 years, and OC use in the 10 years before menopause); reasons for use and discontinuation; types or brands of OCs at last use.

At the conclusion of the survey, we asked participants for permission to review their records and collect EHR or other computerized data that were potentially related to bone health, including bone density test results, medication prescriptions, health conditions and other health information. Ninety-eight percent of both case and control women agreed to record review.

Statistical methods

We used descriptive statistical methods (number and proportion for categorical variables, mean and standard deviation for continuous variables) to characterize patterns of OC use in cases and controls, principally OC use in the 10 years prior to menopause and use in later reproductive years (after age 38). We used the Kaplan-Meier estimator to calculate median age at menopause, with pre-menopausal women censored at their reference dates. We also examined all other study variables by case-control status. We compared the age distribution between cases and controls to assess the efficiency of the randomized-recruitment scheme to see if possible participation bias may have led to differing age distributions between cases and controls.

We used logistic regression to analyze the association between incident adjudicated fracture and OC exposure. The outcome in the models was case/control status. For the main analysis, OC exposure was quantified using the total cumulative duration of OC use in the 10 years prior to menopause or, in pre-menopausal participants, the 10 years prior to the estimated age of future menopause. (For pre-menopausal participants, future age at menopause was estimated by sampling from a normal distribution based on age at menopause observed among post-menopausal women [mean=age 51, standard deviation=3] truncated at the participant's age at her reference date.) To account for the randomized recruitment scheme, we used the approach of Weinberg and Sandler.³³ Under this approach, sampling probabilities for each age stratum were included as an offset term in the logistic regression model. We created categories of cumulative OC exposure to allow for possible non-linear associations between exposure and fracture risk. Inference was based on the odds ratio comparing cumulative OC exposure to unexposed participants. Our regression models adjusted for those variables that were judged *a priori* to be associated with both the outcome and exposure: age, past hormone therapy use, body mass index (BMI) at reference date, current smoking and drinking, menopausal status at reference date and age at menopause, parity, and race. Additional variables believed to be associated only with the outcome were considered for inclusion in the model as precision variables depending on their prevalence in the population. The final multivariable model included age at reference date, hormone therapy use, menopausal age, post-menopausal status, parity, BMI (<20, 20-<25, 25-<30, 30), smoking status (current, former, never), alcohol consumption (0, <1, 1-14, >14 drinks per week), and race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, more than one race). The same modeling strategies were used to evaluate the additional primary exposure of interest, OC use during later reproductive years (age 38 years), as well as other OC exposures (ever use, and age at first use). With the target sample size of 3,400 participants, the study was estimated to have 84% to 90% power to detect an odds ratio of 0.70, similar to the Michaelsson 1999 study²⁷ for OC use at age 40 years. Our study recruitment exceeded this target (study n=3,479).

We conducted a sensitivity analysis in which we examined ankle fractures separately from other osteoporotic fracture sites.

All analyses were conducted using SAS version 9 and Stata version 10. Statistical significance was evaluated at the two-sided 0.05-level.

Results

The types of index fracture that the 1,204 case women experienced are summarized in Table 1. The most common site for fractures in this age group of women was the wrist and forearm (32% of fractures). Ankle fractures were the next most common (25%).

In comparing participant characteristics at the reference date, case and control women were similar in age (mean age 54 years) (Table 2). Case women were more likely to be white, unmarried, less parous, to be current smokers, to have had an adult fracture prior to age 45, and to have had a parent with a hip fracture, a younger age at menopause, and previous hormone therapy use. Case women also reported other health conditions (cancer, diabetes, hypertension, for example) more frequently, but did not differ from control women on their self-reported health status. Control women were more likely to consume 1-14 alcoholic drinks per week. The FRAX mean 10-year risk for both osteoporotic fractures and hip fractures was higher for case women than for control women (9.0% vs. 7.7% for future osteoporotic fracture, and 1.0% vs. 0.91% for future hip fracture, for cases vs. controls, respectively).

We evaluated OC exposure in a number of ways (summarized in Table 3). For the main exposure variable—OC use during the 10 years prior to menopause—identical proportions (15%) of case and control women reported OC use. Mean durations of use during that time were similar (mean 0.70 vs. 0.72 years). Proportions of use in duration categories also were similar (7.2% of cases and 7.5% of controls reported between 5 and 10 years of use, for example). Similar proportions of case and control women also reported OC use after age 38 (16.6% and 17.5%, respectively). Other patterns of OC use did not differ markedly between cases and controls. Seventy-seven percent of case women and 75% of control women reported ever use of OCs, with 15% and 13% reporting ten or more years of use, respectively. Among case and control women who had prior OC use, the great majority of study participants last used OCs twenty or more years prior to the reference date. More than 50% of previous users reported first OC use at age 19 or younger.

After adjustment for relevant covariates, case and control women did not differ in their fracture risk by their OC use in the 10 years prior to menopause (adjusted odds ratio [OR]=0.90, 95% CI 0.74,1.11)(Table 4). Results for duration categories within the 10 years prior to menopause also did not differ significantly: OR=0.78 (95% CI 0.53,1.15)for use <1 year to <2 years before menopause, OR=1.04 (95% CI 0.73,1.49) for 2 to <5 years, OR=0.90 (95% CI 0.68,1.19) for 5 years (Table 4). The relative risk for OC use after age 38 was 0.94 (95% CI 0.78,1.14), and risks for the any OC use and for age at first OC use also were close to 1.0 (Table 4). In sum, there were no significant differences in fracture risk for any of the OC exposure measures we investigated.

In our sensitivity analysis, we evaluated ankle fractures separately from other fracture sites. Women with ankle fractures were slightly younger than either control women or other case women, were more likely to be African American, and to have BMIs classed as 'overweight' or 'obese' (data not shown). They were less likely than control or other case women to have used OCs in the 10 years prior to menopause or to have OC use after age 38.

Although not significant, OC use in the 10 years prior to menopause was more strongly associated with lower risk of ankle fractures, relative to control women (OR 0.71, 95% CI 0.48,1.04; p-value=0.075) than with risk at the other fracture locations (OR= 0.97, 95% CI 0.78,1.21).

Discussion

The disproportionate fracture burden borne by women is heightened with the hormonal changes that occur during the menopausal transition. Oral contraceptives are the main exogenous hormonal exposure across the lifespan for many women, and exposure is often lengthy. However, while the benefits of postmenopausal estrogen therapy on fracture risk are well-established, the role of pre-menopausal hormonal exposure through OC use is still unclear. The current evaluation of a large, well-characterized population-based study group of over 3,400 participants provides evidence that use of contemporary OCs is not associated with risk for osteoporotic fractures occurring across the menopausal transition. We examined OC exposure in several ways, including use during later reproductive life (OC in 10 years prior to menopause and after age 38), ever use, and age at first use. In all instances, the risk estimates showed no association with fracture risk, either beneficial or unfavorable.

At present, trial evidence of the effects of hormonal contraception on fracture risk is lacking,³⁵ and assessment of the OC-fracture relationship from the available observational studies has been complicated by numerous changes in the hormonal content of OC formulations over the years and by evidence that impacts may vary by age of use. Studies to date of the association of previous OC use with postmenopausal fractures report mixed results. A cross-sectional study of 939 perimenopausal women with past OC use and 2283 nonusers found no difference in fracture rates.³⁶ A population-based cross-sectional study of 491 postmenopausal women from Australia found a decreased risk of vertebral fractures in those who had OC use with duration greater than 5 years.³⁷ The European Vertebral Osteoporosis Study, including 7,530 women aged 50-79, found a past history of OC use was associated with a 25% reduction in the risk of vertebral fracture.³⁸ A prospective study using data from the Women's Health Initiative (women aged 50-75 years) reported a relative risk of 1.07 (95% CI 1.1-1.5) for postmenopausal self-reported fractures among women with past OC use.³⁹

A few studies have focused specifically on the possible impacts on fracture risk of OC use during later reproductive years. A 1999 case-control study by Michaelsson et al. reported a substantially lower risk of hip fracture among women aged 55-81 who reported prior OC use (OR 0.75, 95% CI 0.59-0.96).²⁷ Women who used OCs at ages 40 and over had the lowest risk (OR 0.69, 95% CI 0.51-0.94), particularly those with low BMI or >5 years of use. However, very few of these generally older study participants had used OC agents with contemporary estrogen doses (<50 mcg ethinyl estradiol [EE]), making the generalizability of these results to users of contemporary OC agents inconclusive. A more recent population-based case-control study by Vestergaard et al⁴⁰, using large administrative databases, reported no overall association between any fracture and OC use during the previous 5 years. After adjusting for available variables, the authors reported a non-significant trend of decreasing OR's by increasing age group (<25 years, 25-49, and 50).

Studies of the association between OC use and bone density report different results depending on the menopausal status. In our study of mature pre-menopausal women up to age 39, bone density was stable among OC users and did not differ from non-users.⁴¹ In women aged 40 to 46 who were still cycling regularly, a 2-year longitudinal study of OCs (20 mcg EE) also showed no change in the bone density.⁴² Bone density is typically stable until the year or so prior to the last menstrual period⁴³, and thus improvements in bone density with OC use may not occur until ovarian function is disrupted. A number of studies have been conducted among women nearing or just past the menopausal transition. Of particular relevance are several randomized trials conducted among peri- or early postmenopausal women that used contemporary dose OCs (20-30 mcg EE). Trials conducted by Gambacciani and colleagues, which randomized irregularly cycling peri-menopausal women (aged 40-49 years) to 20 mcg EE OCs vs. calcium/placebo, have consistently shown that this low-dose OC use significantly increases bone density at the femoral neck, spine, and other sites relative to control women after 24 months.²⁴⁻²⁶ Other trials of peri-menopausal women aged 40-60 years that used 20 or 30 mcg EE OCs vs. placebo or hormone therapy comparison groups also reported significantly increased BMD with OC use during 1- to 3-year follow-ups.^{44,45} Investigation of hormone and BMD trajectories following OC discontinuation at these peri-menopausal ages would be informative.

In the current study, the use of OCs in the decade prior to menopause or after age 38 did not reduce fracture risk in the years around the time of menopause. Nor was fracture risk associated with other OC use patterns that we examined. As there are some ways in which the impacts of OCs could be negative^{13,14,15,16}, it is reassuring that their use was not associated with any increased fracture risk.

A potential limitation of this study, given the null results and the results from trials of OC use and BMD change, is that BMD data prior to the reference date were not available for the majority of participants and, given the retrospective design, could not be obtained. The data on OC dose also had high percentages missing. However, given the recency of this study and the peri-/early postmenopausal age group, the OC exposure for this study group, particularly at later ages, is almost entirely lower estrogen dose formulations (35mcg EE). Random misclassification has the potential to bias the results toward the null. This would occur, for example, in the instance of random misclassification of OC use. As part of this study, we were able to validate the recall of OC use in a subset of participants by comparing participants' reported use of OCs to their dispensing records in the Group Health pharmacy database. This assessment found good agreement between the interview and pharmacy records, particularly for OC use close to the reference date (adjusted kappa=0.88 and 0.74 for <5 and 5-10 years before reference date, respectively), which was our main exposure.⁴⁶ Cases and controls did not differ in their recall. As fractures are the result of decreased bone strength and mechanical impact to the bone, we included in our case group all women with fractures at the selected anatomic sites, across the range of trauma.³¹ If OC use had a role only with lower-energy fractures, severe trauma may have obscured this association. The study clinician assessed the role of trauma as part of case adjudication, finding that severe trauma occurred in 8.2% of cases in the pool of potential participants. Exclusion of this group would not markedly alter the OC results. In addition, the FRAX data for this study

group demonstrate significant differences in future fracture risk by case-control status; and our assessment of, and adjustment for, other risk factors for fractures in older women were in the expected directions (although not all were significant).

The current study has a number of strengths, in addition to size. We have focused on a serious, potentially preventable adverse health event in an understudied age group of women. Relative to older women, fracture rates are lower for this age group. However, we have a substantial body of research regarding fracture rates and risks in older women. And, although fracture rates are lower during the early menopausal years, they begin to climb during this time. We found that about 5% of our study population--a substantial number of women--had a fracture at one of the selected osteoporotic locations. Affected women may enter their older years at considerably increased risk of a more serious fracture experience. This study assessed the role of a widespread, modifiable hormonal exposure (OC use) for which current data on fracture risk are sparse, particularly with regard to use of current OC formulations during later reproductive life. We examined numerous OC exposures, and used health plan pharmacy data to assist in validating self-reported OC use, noting very good agreement.⁴⁶ Fracture case status was confirmed via adjudication using the health plan EHR. We employed a population-based sampling strategy, which selected case and control women from the same defined population, thereby minimizing bias and comparability concerns. Participation rates were excellent and were very similar for case and control women. The OC exposures in this community-dwelling sample also may typify the use patterns of many US women.

Conclusion

Our results provide additional clarity and guidance to women and their providers at a time of increasing public health concern about fractures. In considering the clinical importance of these results, our findings show that, for women who may choose to use OCs during late pre-menopause (around ages 38-48), fracture risk around the menopausal transition will not differ from women not choosing this option. Further research is needed to assess the potential impacts of OC use during later reproductive life on osteoporotic fractures at older ages.

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Figure 1. Study Flow Diagram

^a Not mutually exclusive ^b Reasons for not osteoporotic fracture: radiologist said no fracture or was uncertain (186), fractures of hand, feet or skull (111), miscoding (86), or no images were taken (37). These women were included as potential controls. ^c Exclusions by survey were hierarchical. Hormone use was within previous 2 years, hysterectomy was prior to age 53. ^d At the survey, N=52 potential control women self-reported a possible qualifying fracture. Upon review, N=18 were adjudicated to be fracture and included as case women; N=26 remained controls; N=8 were excluded for insufficient information. Abbreviations: fx= fracture, info= information. Size of shaded boxes is proportional to the number of subjects.

Table 1
Distribution of Incident Osteoporotic Fractures in Case Women, by Skeletal Site

Fracture type ^a (ICD-9-CM code)	Number of fractures	Percent of study fractures
Forearm (813, 814, 733.12)	384	32%
Ankle (824)	300	25%
Humerus (812, 733.11)	106	9%
Rib/sternum (807)	103	9%
Tibia/fibula (823, 733.93)	88	7%
Vertebra (clinical) (805, 806, 733.13)	72	7%
Clavicle/scapula (810, 811,)	30	3%
Pelvis (808, 733.98)	25	2%
Hip (820, 733.14, 733.96)	20	2%
Femur (821, 733.15, 733.97)	12	1%
Multiple	65	5%
Total	1,204	100%

^aExcluded fractures were: cranium, hand/foot, fingers/toes; fractures due to malignancy, infection, Paget's disease

Table 2
Characteristics of the Study Population by Case/Control Status

Variable ^a	Fracture case women ^b		Control women	
	(N=1204)		(N=2275)	
	mean or %	SD or n	mean or %	SD or n
Age at refdate	54.1	3.5	54.0	3.4
Age at refdate				
44 – 59 years	13.9%	168	11.8%	269
50 – 54 years	35.3%	425	37.6%	855
55 – 59 years	50.7%	611	50.6%	1,151
Age at menarche	12.7	1.6	12.7	1.6
Age at menopause, median	51.0		52.0	
Weight (n=1199, 2260)	169.3	43.2	168.2	44.2
Height (n=1204, 2271)	65.0	2.9	64.7	2.7
Race				
American Indian or Alaska Native	0.7%	9	0.8%	19
Asian	3.7%	44	5.9%	134
Black/African American	2.1%	25	3.0%	69
Native Hawaiian or Other Pacific Islander	0.6%	7	0.6%	13
White	85.2%	1,026	81.0%	1,842
More Than One Race	5.6%	67	6.5%	147
Other or Unknown	2.2%	26	2.2%	51
Ethnicity: Hispanic	3.1%	37	3.9%	88
Education, <= high school	14.1%	170	15.9%	362
Marital status				
Married	62.8%	756	66.2%	1,505
Living with Partner	7.3%	88	6.5%	148
Widowed	3.2%	39	2.7%	62
Divorced/Separated	17.0%	204	15.0%	342
Never Married/Single	9.6%	116	9.5%	216
Parity	73.4%	884	76.6%	1,742
BMI				
Underweight, <20	5.8%	70	4.9%	110
Normal, 20–<25	34.2%	410	35.2%	795
Overweight, 25–<30	28.0%	336	27.4%	619
Obese, >=30	31.9%	383	32.5%	733
Smoking, current	12.4%	149	10.5%	238
Alcohol consumption				
None/past	25.4%	304	22.8%	517

Variable ^a	Fracture case women ^b		Control women	
	(N=1204)		(N=2275)	
	mean or %	SD or n	mean or %	SD or n
<1 drink/week	31.4%	377	40.3%	914
1-14 drinks/week	40.3%	483	36.1%	819
>14 drinks/week	2.9%	35	0.8%	19
Prior fracture (at ages 25 to <45 yr)	21.0%	253	16.6%	378
Parental history of (hip) fracture, excludes those adopted	13.8%	162	11.0%	245
Post-menopausal	77.4%	932	73.3%	1,667
Any HT use	26.5%	318	20.4%	463
Calcium supplements	45.6%	546	42.7%	965
Vitamin D supplements	59.7%	712	60.7%	1,372
Regular physical activity at refdate (% yes)	70.6%	848	71.5%	1,624
Diabetes	9.7%	117	7.6%	172
Overactive thyroid	5.2%	62	3.9%	89
Prior BMD scan	36.1%	427	29.7%	661
Falls (prior year), mean/median	2.0	1.0	1.5	0.0
FRAX score, mean/median ^c				
10-year risk of osteoporotic fracture	9.03	7.73	8.24	7.22
10-year risk of hip fracture	1.04	0.71	0.91	0.63
Self-reported health, mean/median ^d	2.3	2.0	2.2	2.0

^a At or before 'reference date': date of incident fracture for case women, randomly assigned date for control women.

^b Fracture case women experienced an adjudication-confirmed incident fracture between the ages of 45-59 years.

^c Excluding the Index fracture for case women.

^d Likert scale, 1 "Excellent" 2 "Very Good" 3 "Good" 4 "Fair" 5 "Poor."

Table 3
OC Exposures by Case and Control Status

	Cases		Controls	
	N=1204		N=2275	
	N	%	N	%
Cumulative OC Use, 10 years prior to menopause ^a				
No use	1,012	84.9%	1,915	84.7%
<1year	18	1.5%	39	1.7%
1 to <2years	22	1.8%	48	2.1%
2 to <5years	54	4.5%	88	3.9%
5 to 10years	86	7.2%	170	7.5%
Mean/median duration	0.70	0	0.72	0
OC Use, Age 38 years ^b				
No use	1,002	83.4%	1,875	82.5%
<1year	21	1.7%	54	2.4%
1 to <2years	18	1.5%	43	1.9%
2 to <5years	62	5.2%	104	4.6%
5+ years	98	8.2%	196	8.6%
Mean/median duration	0.90	0	1.02	0
OC Use, ever ^c				
No use	278	23.3%	556	24.6%
<2 years	119	10.0%	230	10.2%
2 to <5 years	308	25.9%	618	27.4%
5 to <10 years	303	25.4%	557	24.7%
10+ years	183	15.4%	295	13.1%
Time since last OC use (prior to refdate) ^{d,f}				
0 years	18	2.0%	42	2.5%
<2 years	11	1.2%	24	1.4%
2 to <5 years	30	3.3%	77	4.5%
5 to <10 years	64	7.0%	123	7.2%
10 to <20 years	177	19.3%	296	17.4%
20 to <30 years	316	34.4%	601	35.2%
30+ years	302	32.9%	543	31.8%
Age at first OC use ^{e, g}				
<=19 years	481	52.4%	919	53.6%
20 to 29 years	391	42.6%	696	40.6%
30+ years	46	5.0%	98	5.7%

^{a-e} Missing, out of n=1204 cases and n=2275 controls:

^a cases – 12, controls – 15;

^b cases – 3, controls – 3;

^c cases – 13, controls – 19;

^d cases – 286, controls – 569;

^e cases – 286, controls – 562

^{f-g} Missing, out of n=913 OC user cases and n=1700 OC user controls:

^f cases – 5, controls – 6;

^g cases – 5, controls – 13

Table 4
Associations between OC use and Fracture

	Cases n=1204	Controls (n=2275)	Age adjusted Odds Ratio (95% CI)	Multivariable adjusted Odds ^a Ratio (95% CI)
Cumulative OC Use, 10 years prior to menopause ^{b, c}				
None	1012	1915	1.00 (ref)	1.00 (ref)
Any	180	345	0.98 (0.80,1.19)	0.90 (0.74,1.11)
<1 to <2 years	40	87	0.84 (0.57, 1.23)	0.78 (0.53, 1.15)
2 to <5 years	54	88	1.13 (0.80, 1.60)	1.04 (0.73, 1.49)
>=5 years	86	170	0.97 (0.74, 1.27)	0.90 (0.68, 1.19)
OC Use, Age 38 years ^{b, c}				
None	1002	1875	1.00 (ref)	1.00 (ref)
Any	199	397	0.94 (0.78,1.13)	0.94 (0.78,1.14)
OC Use, ever				
None	278	556	1.00 (ref)	1.00 (ref)
Any	913	1700	1.08 (0.92,1.28)	1.01 (0.85,1.21)
Age at first OC use				
<= 19 years	481	919	1.00 (ref)	1.00 (ref)
20 to 29 years	394	696	1.06 (0.89,1.25)	1.10 (0.92,1.31)
>= 30 years	46	98	0.89 (0.62,1.29)	0.94 (0.64,1.38)

^a Adjusted for reference age, other hormone usage (yes,no[ref]), menopausal age, post-menopausal status (yes,no[ref]), parity (yes,no[ref]), bmi (<20, 20-<25[ref], 25-<30, >=30), smoking status (never[ref], current, ever or not current), alcohol consumption (0 drinks per wk, <1, 1-14[ref], >14) and race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White[ref], Other or unknown, More than one race)

^b Defined as at least 3 months' use

^c Does not exclude OC exposure at younger ages