Published in final edited form as:
Calcif Tissue Int. 2010 September ; 87(3): 211–217. doi:10.1007/s00223-010-9397-5.

DETERMINANTS OF PLASMA PARATHYROID HORMONE LEVELS IN YOUNG WOMEN

Julie M. Paik, M.D., M.P.H., M.Sc.[1,2], **Gary C. Curhan, M.D., Sc.D.**[1,2], **John P. Forman, M.D., M.Sc.**[1,2], and **Eric N. Taylor, M.D., M.Sc.**[2,3]

[1] Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[2] Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[3] Division of Nephrology and Transplantation, Maine Medical Center, Portland, ME

Abstract

Purpose—While the effects of calcium, phosphorus intake, and vitamin D on parathyroid hormone (PTH) have been well studied, less is known about other factors that impact PTH. Our goal was to delineate associations between demographic, dietary, and plasma factors and PTH.

Methods—We conducted a cross-sectional study of intact PTH among 1,288 non-black women in the Nurses Health Study II aged 33–53 with BMI < 30kg/m^2 and eGFR ≥60 ml/min/1.73m^2.

Results—Median PTH was 30.7pg/ml. After adjusting for 25-hydroxyvitamin D and other factors, PTH was 4.1pg/ml lower (95% CI −7.7 to −0.5) in women who smoked 1–14 cigarettes/day and 6.4pg/ml lower (95% CI −11.2 to −1.7) in women who smoked >15 cigarettes/day compared to non-smokers. After multivariate adjustment, women whose BMI was 27–29 kg/m^2 had PTH levels 2.0pg/ml higher (95% CI 0.2–3.9) compared to BMI of 21–22 kg/m^2, and women in the highest quartile of plasma phosphorus had PTH levels 4.1pg/ml lower (95% CI −5.8 to −2.4) than women in the lowest quartile. Higher vitamin A intake was independently associated with lower PTH whereas lower calcium intake, lower plasma calcium, lower plasma 25-hydroxyvitamin D, and winter blood draw were associated with higher PTH. Intakes of phosphorus, animal protein, magnesium, alcohol, and caffeine were not associated with PTH.

Conclusions—Factors not classically associated with calcium-phosphorus metabolism impact PTH. Additional research is needed to elucidate the mechanisms whereby smoking, vitamin A, and phosphorus affect PTH and to examine how body size and season may affect PTH independent of 25(OH)D.

Keywords

Parathyroid Hormone; Nutrition; Smoking; Body Mass Index; 25-Hydroxyvitamin D

Introduction

Parathyroid hormone (PTH) plays a central role in calcium and phosphorus homeostasis through direct and indirect effects on the bone, kidney, and intestine. In addition, emerging research has demonstrated that PTH may be involved in a wide variety of diseases, such as

[1]To whom correspondence should be addressed: Julie M. Paik, M.D., Channing Laboratory 5th floor, 181 Longwood Avenue, Boston, MA 02115. Telephone 617-525-2029; Fax 617-525-2008; jmpaik@partners.org.

Disclosures: None

hypertension [1] and cardiovascular disease [2]. The secretion of PTH, an 84 amino acid protein synthesized and stored in the parathyroid gland, is regulated primarily by the extracellular calcium concentration, which activates the calcium sensing receptor on the surface of parathyroid cells [3]. The effects of dietary and plasma calcium, short-term phosphorus intake, and plasma 25-hydroxyvitamin D (25(OH)D) on PTH have been well studied. Lower extracellular plasma calcium level [4] and lower calcium intake [5] elevate PTH levels. Higher plasma phosphate level directly stimulates PTH release from parathyroid tissue [6] and high phosphorus intake results in higher serum PTH [7].

Because PTH impacts bone health and may affect the development of cardiovascular disease, it is important to identify other factors that modulate PTH. Body mass index (BMI), alcohol intake, smoking, vitamin A intake, and other factors may influence PTH levels [8–17]. Individuals with a higher BMI had higher PTH levels compared to individuals with a lower BMI [8–10], possibly due to lower serum 25(OH)D levels in obese individuals compared to non-obese individuals [18]. However, past studies reporting positive associations between body size and PTH either had small sample sizes [8,9] or did not account for differences in plasma 25(OH)D [10]. The relation between PTH and ethanol intake also is unclear. Acute ethanol administration in healthy volunteers [11] resulted in lower PTH levels; on the other hand, human studies of chronic alcohol consumption have shown elevated PTH levels [12]. Previous reports that smokers have lower PTH levels were limited by small sample size or the lack of measured plasma factors such as 25(OH)D and phosphorus [13–15,19]. Although retinoic acid has been found to directly suppress PTH secretion in bovine [16] and human parathyroid cells [17], the effect of vitamin A intake on PTH is unknown.

To examine the association of demographic, lifestyle, dietary, and plasma factors, and intact PTH, we conducted a cross-sectional study of 1,288 non-black younger women with normal renal function.

Methods

Source Population

The Nurses Health Study II is an ongoing, prospective cohort study which began in 1989, enrolling 116,430 female registered nurses between the ages of 25–42 who are followed with biennial questionnaires. The average follow-up has been >90% for the first 16 years. From 1997–1999, 29,616 participants contributed blood samples.

Study Population

The women for this study were selected from the nested prospective case-control study of incident hypertension conducted by Forman et al. [20] in which hypertension cases and controls (1:1 ratio) were selected from women who met the following criteria at the time of blood collection: (1) blood sample collected after fasting for at least 8 hours; (2) no diagnosis of hypertension; (3) no use of anti-hypertensive medications; (4) no diagnosis of cancer (except non-melanoma skin cancer); (5) no diagnosis of either coronary heart disease or diabetes; and (6) BMI < 30 kg/m^2.

For the current study, we excluded women if they did not complete a food-frequency questionnaire or did not have a blood sample with intact parathyroid hormone or plasma 25(OH)D available. Women with an estimated glomerular filtration rate (using the Modification of Diet in Renal Disease Study equation) less than 60 $ml/min/1.73m^2$ were excluded from the analysis. Because determinants of PTH may differ in blacks and whites [21], we also excluded the six African-American women in our study population. The

institutional review board at Brigham and Women's Hospital reviewed and approved the study.

Plasma Measurements

Intact parathyroid hormone was measured by an electrochemiluminescence immunoassay on the 2010 Elecsys autoanalyzer (Roche Diagnostics, Indianapolis, IN). The coefficient of variation (CV) for this assay using quality control samples was 13.4%. Plasma 25(OH)D was measured by an enzyme immunoassay from Immunodiagnostic Systems Inc. (Fountain Hills, AZ); the CV was 3.2%. Other plasma factors that were measured as part of this study included: calcium (colorimetric assay, CV=3.6%); phosphorus (photometric assay, CV=9.5%); and creatinine (modified Jaffe method, CV=6.5%).

Ascertainment of Dietary Intake

Self-administered semi-quantitative food frequency questionnaires (FFQ) closest to the blood draw were used to assess the nurses' average nutrient intake over the past year. In addition to questions on over 130 individual food items and 22 individual beverages, the FFQ inquired about the use of calcium supplements, vitamin D supplements, and multivitamins. The intakes of supplemental calcium and supplemental vitamin A in multivitamins or isolated form were determined by the brand, type, and frequency of reported use. Intake of specific dietary factors was computed from the reported frequency of consumption of each specified unit of food and from United States Department of Agriculture data on the content of the relevant nutrient in specified portions. Nutrient values were adjusted for total caloric intake to determine the nutrient composition of the diet independent of the total amount of food eaten. The FFQ has been extensively validated [22]. For example, the correlation coefficient between the FFQ and food diaries for food items containing high amounts of calcium were the following: skim or low-fat milk (r=0.81), whole milk (r=0.62), and yogurt (r=0.94) [23].

Ascertainment of Demographic Variables

Age and BMI (weight in kilograms divided by height in meters squared) were obtained from the questionnaire closest to the blood draw year. Smoking status (never, past, current), physical activity (in metabolic equivalent task scores; METS), current oral contraceptive use (yes, no), menopausal status, and alcohol intake (grams/day) were ascertained from the biennial questionnaire closest to time of blood draw. Race was self-reported and categorized as Caucasian and non-Caucasian (Hispanic, Asian, and other). African-American women were excluded from the analysis.

Statistical Analyses

The analysis was cross-sectional. To remove extreme values, we excluded participants in the top and bottom one percent of the distribution for intact PTH, plasma calcium, and plasma phosphorus. The final range for intact PTH was 12–76 pg/ml.

Multivariable linear regression models with PTH as the dependent variable included the following potential confounders plus factors with univariate associations: race, BMI, smoking status, alcohol intake, total calcium intake, total vitamin A intake, phosphorus intake, animal protein intake, magnesium intake, potassium intake, season of blood draw, plasma 25(OH)D, plasma phosphorus, plasma calcium, and plasma creatinine. We included age and race in all multivariate models. Variables were excluded from the final multivariate model if they were not associated with the outcome or were not confounders (change in regression coefficient <10%). Dietary and plasma variables were divided into quartiles.

We performed tests for trend for categorical variables. We also performed stratified analyses to determine whether associations with PTH varied by plasma 25(OH)D level (sufficient 25[OH]D defined as ≥ 30 ng/ml compared to insufficient and/or deficient defined as < 30 ng/ml) and whether associations varied by BMI (≥ median vs. <median). Because half the participants developed hypertension after blood draw, we also performed separate analyses of participants who did and participants who did not develop hypertension.

Results

Study Population Characteristics

The baseline characteristics of the study population (N=1,288) are shown in Table 1. The median intact parathyroid hormone level was 30.7 pg/ml and the median 25(OH)D level was 26.6 ng/ml. The median age of the participants was 44 years and the median BMI was 24 kg/m^2. Nine-hundred thirty-two women had never smoked, 296 women were past smokers, and 58 women were current smokers, with 37 women currently smoking 1–14 cigarettes per day (classified as light smokers) and 21 women currently smoking >15 cigarettes/day (classified as heavy smokers).

Predictors of Intact Parathyroid Hormone Levels

Correlations between dietary factors, plasma factors and intact PTH are shown in Table 2. Table 3 displays multivariable-adjusted differences in intact PTH levels. The final multivariable regression model included the following variables: BMI, smoking status, total calcium intake, total vitamin A intake, season of blood draw, plasma 25(OH)D level, plasma phosphorus, plasma calcium, age, race, phosphorus intake, animal protein intake, and creatinine.

After adjustment for plasma 25(OH)D and other factors, the PTH level was 2.0 pg/ml (95% CI 0.2 to 3.9) higher in women with BMI of 27–29 kg/m^2 than women with BMI of 21–22 kg/m^2. We also examined BMI categorized as normal weight (18.5–24.9 kg/m^2) or overweight (25–29.9 kg/m^2). Overweight women had a 0.83 pg/ml higher PTH level (95% CI −0.4 to 2.1) compared to women of normal weight. There were only 19 underweight (<18.5 kg/m^2) nurses in this study group. Intact PTH was 4.8 pg/ml lower (95% CI −7.7 to −1.9) in current smokers compared to non-smokers. PTH was 4.1 pg/ml lower (95% CI −7.7 to −0.5) in light smokers, and 6.4 pg/ml lower (95% CI −11.2 to −1.7) in heavy smokers compared to non-smokers. Participants with winter blood draws, spring blood draws, and fall blood draws had a 3.2 pg/ml higher PTH level (95% CI 1.3 to 5.1), 3.0 pg/ml higher PTH level (95% CI 1.1 to 4.8), and 1.7 pg/ml higher PTH level (95% CI −0.03 to 3.4), respectively, compared to participants with summer blood draws.

The highest quartile of vitamin A intake was associated with a 1.9 pg/ml lower PTH level (95% CI −3.7 to −0.07) compared to the lowest quartile of vitamin A intake. The highest quartile of plasma 25(OH)D was associated with a 4.5 pg/ml lower PTH level (95% CI −6.3 to −2.7) compared to the lowest quartile of plasma 25(OH)D. The highest quartile of plasma phosphorus was associated with a 4.1 pg/ml lower PTH level (95% CI −5.8 to −2.4) compared to the lowest quartile of plasma phosphorus. The highest quartile of plasma calcium was associated with a 5.3 pg/ml lower PTH level (95% CI −7.0 to −3.6) compared to the lowest quartile of plasma calcium.

Stratified Analysis by Plasma 25(OH)D level and Hypertension

The prevalence of 25(OH)D insufficiency/deficiency (plasma 25[OH]D <30 ng/ml) was 64.9%. In addition, by design roughly half of the study participants subsequently developed hypertension after blood draw. Thus, we performed stratified analyses to determine whether

associations with PTH varied by plasma 25(OH)D level (≥ 30 vs. < 30 ng/ml) or subsequent hypertension (yes or no). Associations with PTH were similar in participants with and without 25(OH)D insufficiency/deficiency and were similar in participants who did and who did not subsequently develop hypertension.

Other Results

The adjusted R^2 for the final regression model was 12%. There were no independent associations between intact PTH and the following factors: alcohol intake, potassium intake, vitamin D intake, caffeine intake, physical activity, oral contraceptive use, menopausal status, and bisphosphonate use. In addition, we examined characteristics related to the timing of the blood draw (time of day of blood draw, number of hours the nurses were awake prior to blood draw, number of night shifts worked during the two weeks prior to blood draw, and day of menstrual cycle on the day of blood draw) and found no significant associations between these variables and PTH level.

Discussion

We identified numerous factors that were independently associated with intact PTH levels in 1,288 non-obese younger women with normal eGFR. After adjusting for plasma 25(OH)D and other factors, we found that PTH was lower in smokers, lower in individuals with higher vitamin A intake, higher in those with higher BMI, and higher in the spring, winter, and fall (compared to summer). PTH levels were lower in women with higher plasma 25(OH)D, plasma calcium, and plasma phosphorus.

Previous reports that smokers have lower levels of PTH were limited by small sample size or the lack of measured plasma factors such as 25(OH)D and phosphorus [13–15,19,24]. In a multivariate analysis of factors influencing PTH levels in 166 Swedish women and 181 men, Landin-Wilhelmsen et al. [13] found that PTH levels were positively associated with BMI and negatively associated with smoking (−1.86 pg/ml in male smokers and −2.4 pg/ml in female smokers compared to non-smokers) and 25(OH)D. However, the study did not examine whether there was a dose-response relation between number of cigarettes and difference in PTH levels, nor did they assess diet or plasma factors such as creatinine, calcium, or phosphorus.

In the Tromso study [15], Jorde et al. also found that current smokers had lower PTH levels compared to non-smokers for both men and women (29.5±13.3 vs 34.3±18.1 pg/ml in men; 29.5±14.3 vs 34.3±17.1 pg/ml in women ($p<0.001$). The 4.8 pg/ml difference in intact PTH found by Jorde et al. is similar to the difference in intact PTH between current smokers and non-smokers found in our study. However, in the Tromso study, 25(OH)D was measured in only 205 subjects, and 100 of these individuals had secondary hyperparathyroidism. In addition, serum phosphorus was not measured. Finally, the Tromso study reported no dose-response relation between the number of cigarettes and PTH levels.

In contrast to our study, several prior studies did not find a consistent inverse relation between smoking and PTH levels [25–27]. However, Rapuri et al.'s study was performed only in elderly women aged 65–77 years, Ortego-Centeno et al's study included only 101 women, and Supervia et al.'s study had a sample size of 74 people in total (43 women and 31 men).

The mechanism underlying the association between smoking and lower PTH is unclear. Prior studies on female rats have found that nicotine either had no effect [28] on PTH levels or actually raised PTH levels [29]. Jorde et al. have suggested that in addition to serum ionized calcium, there could be several other modulators of PTH, such as chromogranin

peptides and interleukin-8 [15]. The association between smoking and PTH could also be due to an unknown toxin found in cigarettes [30]. Although smokers are at increased risk for fractures [31] and lower bone mineral density [24,32], our data suggest that the mechanism by which smoking affects bone is not PTH-mediated (since lower PTH is associated with higher bone mineral density [33,34]).

We found that higher BMI was associated with higher PTH, independent of plasma 25(OH)D. Past studies reporting positive associations between body size and PTH either had small sample sizes [9,13] or did not account for differences in plasma 25(OH)D [10,15]. Although the mechanism whereby higher BMI may lead to higher PTH remains unclear, it is possible that women with higher BMI exhibit an isolated skeletal resistance to the actions of PTH. One metabolic study including 12 obese and 14 non-obese individuals who were consuming a controlled diet showed similar levels of plasma calcium and phosphorus but higher levels of PTH, higher levels of 1,25-dihydroxyvitamin D, and lower levels of 25(OH)D and urinary calcium in obese participants [8]. Although this study did not measure sex hormones, higher BMI in women may be associated with higher levels of estrogen [35,36], a hormone which may inhibit the bone resorbing effects of PTH [37].

We found several unexpected associations. For example, PTH levels were higher in the spring, winter, and fall compared to the summer, even after controlling for simultaneously measured plasma 25(OH)D. While the reason for this finding is unclear, it may underscore the importance of cumulative 25(OH)D levels in determining levels of PTH. It is also possible that calcium intake varies by season [38,39]. Because our food frequency questionnaire measured average annual dietary intake, we could not examine this possibility.

Another unexpected finding was the inverse association between plasma phosphorus and PTH levels. Prior research has shown that acute phosphorus loading raises PTH levels [40,41], and it would be reasonable to expect, a priori, a positive association between plasma phosphorus and PTH. Dawson-Hughes et al. previously found an inverse correlation ($r=-0.16$) between serum PTH and serum phosphorus among 275 postmenopausal women [42]. However, they did not adjust for other factors such as serum calcium or 25(OH)D level. Our data suggest that other plasma factors involved in phosphorus metabolism affect PTH. Of note, higher phosphorus concentrations result in higher FGF-23 levels, and FGF-23 may suppress PTH [43]. Finally, our blood samples were collected in fasting individuals, and it is possible that relations between plasma phosphorus and PTH would be different in the post-prandial state.

We also observed that higher vitamin A intake was associated with lower PTH. Higher vitamin A intake [44] has been associated with increased risk of bone fracture, and vitamin A may interfere with the action of vitamin D by modulating the action of the vitamin D receptor-retinoid X receptor (VDR-RXR) [45]. However, our study found that higher vitamin A intake was independently associated with lower PTH, even after controlling for serum 25(OH)D levels. This could be related to direct effects of retinoic acid on PTH, since retinoic acid has been found to directly suppress PTH secretion in bovine parathyroid cells [16] and human cells [17].

There are several limitations to our study. First, since our study population was female and almost entirely Caucasian, our findings are not necessarily generalizable to men or African-Americans. Second, our analysis did not include women with a BMI≥30 kg/m^2. Third, the cross-sectional study design does not allow for inferences of causality. Fourth, we did not measure serum 1,25(OH)D or FGF-23 levels. Finally, our multivariate models accounted for only 12% of the variability in PTH levels in our study population. Thus, there likely are other factors (including genetics) that affect PTH.

In conclusion, many factors not classically associated with calcium-phosphorus metabolism impact PTH in younger women with normal eGFR. In particular, more research is needed to elucidate the mechanism whereby smoking affects PTH levels, to delineate the effects of plasma phosphorus on PTH, and to examine potential mechanisms whereby body size, vitamin A intake, and season could affect PTH independent of 25(OH)D.

Acknowledgments

This research was supported by the National Institutes of Health grants DK73381, CA50385, HL79929, DK007527, DK084707 and a grant from TAP Pharmaceuticals.

References

1. Taylor E, Curhan G, Forman J. Parathyroid hormone and the risk of incident hypertension. J Hypertens. 2008; 26:1390–1394. [PubMed: 18551015]
2. Kamycheva E, Sundsfjord J, RJ. Serum parathyroid hormone levels predict coronary heart disease: the Tromsø Study. Eur J Cardiovasc Prev Rehabil. 2004; 11:69–74. [PubMed: 15167209]
3. Murray T, Rao L, Divieti P, Bringhurst F. Parathyroid hormone secretion and action: evidence for discrete receptors for the carboxyl-terminal region and related biological actions of carboxyl-terminal ligands. Endocr Rev. 2005; 26:78–113. [PubMed: 15689574]
4. Brent G, LeBoff M, Seely E, Conlin P, Brown E. Relationship between the concentration and rate of change of calcium and serum intact parathyroid hormone levels in normal humans. J Clin Endocrinol Metab. 1988; 67:944–950. [PubMed: 3141451]
5. McKane WR, Khosla S, Egan KS, Robins SP, Burritt MF, Riggs BL. Role of calcium intake in modulating age-related increases in parathyroid function and bone resorption. J Clin Endocrinol Metab. 1996; 81:1699–1703. [PubMed: 8626819]
6. Nielsen P, Feldt-Rasmussen U, Olgaard K. A direct effect in vitro of phosphate on PTH release from bovine parathyroid tissue slices but not from dispersed parathyroid cells. Nephrol Dial Transplant. 1996; 11:1762–1768. [PubMed: 8918619]
7. Calvo M, Kumar R, Heath H. Elevated secretion and action of serum parathyroid hormone in young adults consuming high phosphorus, low calcium diets assembled from common foods. J Clin Endocrinol Metab. 1988; 66:823–829. [PubMed: 2831248]
8. Bell NH, Epstein S, Greene A, Shary J, Oexmann MJ, Shaw S. Evidence for alteration of the vitamin D-endocrine system in obese subjects. J Clin Invest. 1985; 76:370–373. [PubMed: 2991340]
9. Bolland MJ, Grey AB, Ames RW, Horne AM, Gamble GD, Reid IR. Fat mass is an important predictor of parathyroid hormone levels in postmenopausal women. Bone. 2006; 38:317–321. [PubMed: 16199216]
10. Kamycheva E, Sundsfjord J, Jorde R. Serum parathyroid hormone level is associated with body mass index. The 5th Tromsø study. Eur J Endocrinol. 2004; 151:167–172. [PubMed: 15296470]
11. Laitinen K, Lamberg-Allardt C, Tunninen R, Karonen S, Tähtelä R, Ylikahri R, Välimäki M. Transient hypoparathyroidism during acute alcohol intoxication. N Engl J Med. 1991; 324:721–727. [PubMed: 1997837]
12. Feitelberg S, Epstein S, Ismail F, D'Amanda C. Deranged bone mineral metabolism in chronic alcoholism. Metabolism. 1987; 36:322–326. [PubMed: 3494181]
13. Landin-Wilhelmsen K, Wilhelmsen L, Lappas G, Rosén T, Lindstedt G, Lundberg P, Wilske J, Bengtsson B. Serum intact parathyroid hormone in a random population sample of men and women: relationship to anthropometry, life-style factors, blood pressure, and vitamin D. Calcif Tissue Int. 1995; 56:104–108. [PubMed: 7736316]
14. Need A, Kemp A, Giles N, Morris H, Horowitz M, Nordin B. Relationships between intestinal calcium absorption, serum vitamin D metabolites and smoking in postmenopausal women. Osteoporos Int. 2002; 13:83–88. [PubMed: 11883410]

15. Jorde R, Saleh F, Figenschau Y, Kamycheva E, Haug E, Sundsfjord J. Serum parathyroid hormone (PTH) levels in smokers and non-smokers. The fifth Tromsø study. Eur J Endocrinol. 2005; 152:39–45. [PubMed: 15762185]
16. MacDonald P, Ritter C, Brown A, Slatopolsky E. Retinoic acid suppresses parathyroid hormone (PTH) secretion and PreproPTH mRNA levels in bovine parathyroid cell culture. J Clin Invest. 1994; 93:725–730. [PubMed: 8113407]
17. Liu W, Ridefelt P, Akerström G, Hellman P. Differentiation of human parathyroid cells in culture. J Endocrinol. 2001; 168:417–425. [PubMed: 11241173]
18. Liel Y, Ulmer E, Shary J, Hollis BW, Bell NH. Low circulating vitamin D in obesity. Calcif Tissue Int. 1988; 43:199–201. [PubMed: 3145124]
19. Mellström D, Johansson C, Johnell O, Lindstedt G, Lundberg P, Obrant K, Schöön I, Toss G, Ytterberg B. Osteoporosis, metabolic aberrations, and increased risk for vertebral fractures after partial gastrectomy. Calcif Tissue Int. 1993; 53:370–377. [PubMed: 8293349]
20. Forman JP, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women. Hypertension. 2008; 52:828–832. [PubMed: 18838623]
21. Aloia J, Talwar S, Pollack S, Feuerman M, Yeh J. Optimal vitamin D status and serum parathyroid hormone concentrations in African American women. Am J Clin Nutr. 2006; 84:602–609. [PubMed: 16960175]
22. Willett W, Sampson L, Stampfer M, Rosner B, Bain C, Witschi J, Hennekens C, Speizer F. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985; 122:51–65. [PubMed: 4014201]
23. Salvini S, Hunter D, Sampson L, Stampfer M, Colditz G, Rosner B, Willett W. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol. 1989; 18:858–867. [PubMed: 2621022]
24. Brot C, Jorgensen N, Sorensen O. The influence of smoking on vitamin D status and calcium metabolism. Eur J Clin Nutr. 1999; 53:920–926. [PubMed: 10602348]
25. Rapuri P, Gallagher J, Balhorn K, Ryschon K. Smoking and bone metabolism in elderly women. Bone. 2000; 27:429–436. [PubMed: 10962356]
26. Ortego-Centeno N, Muñoz-Torres M, Hernandez-Quero J, Jurado-Duce A, de la Higuera Torres-Puchol J. Bone mineral density, sex steroids, and mineral metabolism in premenopausal smokers. Calcif Tissue Int. 1994; 55:403–407. [PubMed: 7895176]
27. Supervía A, Nogués X, Enjuanes A, Vila J, Mellibovsky L, Serrano S, Aubía J, Díez-Pérez A. Effect of smoking and smoking cessation on bone mass, bone remodeling, vitamin D, PTH and sex hormones. J Musculoskelet Neuronal Interact. 2006; 6:234–241. [PubMed: 17142943]
28. Iwaniec U, Haynatzki G, Fung Y, Akhter M, Haven M, Cullen D. Effects of nicotine on bone and calciotropic hormones in aged ovariectomized rats. J Musculoskelet Neuronal Interact. 2002; 2:469–478. [PubMed: 15758416]
29. Iwaniec U, Fung Y, Akhter M, Haven M, Nespor S, Haynatzki G, Cullen D. Effects of nicotine on bone mass, turnover, and strength in adult female rats. Calcif Tissue Int. 2001; 68:358–364. [PubMed: 11685424]
30. Hoffmann D, Hoffmann I. The changing cigarette, 1950–1995. J Toxicol Environ Health. 1997; 50:307–364. [PubMed: 9120872]
31. Law M, Hackshaw A. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ. 1997; 315:841–846. [PubMed: 9353503]
32. Hollenbach K, Barrett-Connor E, Edelstein S, Holbrook T. Cigarette smoking and bone mineral density in older men and women. Am J Public Health. 1993; 83:1265–1270. [PubMed: 8363002]
33. Khaw K, Sneyd M, Compston J. Bone density parathyroid hormone and 25-hydroxyvitamin D concentrations in middle aged women. BMJ. 1992; 305:273–277. [PubMed: 1392857]
34. Pluijm S, Visser M, Smit J, Popp-Snijders C, Roos J, Lips P. Determinants of bone mineral density in older men and women: body composition as mediator. J Bone Miner Res. 2001; 16:2142–2151. [PubMed: 11697812]
35. Cauley J, Gutai J, Kuller L, LeDonne D, Powell J. The epidemiology of serum sex hormones in postmenopausal women. Am J Epidemiol. 1989; 129:1120–1131. [PubMed: 2729251]

36. Hankinson S, Willett W, Manson J, Hunter D, Colditz G, Stampfer M, Longcope C, Speizer F. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst. 1995; 87:1297–1302. [PubMed: 7658481]

37. Cosman F, Shen V, Xie F, Seibel M, Ratcliffe A, RL. Estrogen protection against bone resorbing effects of parathyroid hormone infusion. Assessment by use of biochemical markers. Ann Intern Med. 1993; 118:337–343. [PubMed: 8430979]

38. Watson P, McDonald B. Seasonal variation of nutrient intake in pregnancy: effects on infant measures and possible influence on diseases related to season of birth. Eur J Clin Nutr. 2007; 61:1271–1280. [PubMed: 17299488]

39. Shibata T, Murakami T, Nakagaki H, Narita N, Goshima M, Sugiyama T, Nishimuta M. Calcium, magnesium, potassium and sodium intakes in Japanese children aged 3 to 5 years. Asia Pac J Clin Nutr. 2008; 17:441–445. [PubMed: 18818164]

40. Calvo M, Kumar R, Heath H. Persistently elevated parathyroid hormone secretion and action in young women after four weeks of ingesting high phosphorus, low calcium diets. J Clin Endocrinol Metab. 1990; 70:1334–1340. [PubMed: 2335575]

41. Kärkkäinen M, Lamberg-Allardt C. An acute intake of phosphate increases parathyroid hormone secretion and inhibits bone formation in young women. J Bone Miner Res. 1996; 11:1905–1912. [PubMed: 8970892]

42. Dawson-Hughes B, Harris S, Dallal G. Serum ionized calcium, as well as phosphorus and parathyroid hormone, is associated with the plasma 1,25-dihydroxyvitamin D3 concentration in normal postmenopausal women. J Bone Miner Res. 1991; 6:461–468. [PubMed: 2068951]

43. Silver J, Naveh-Many T. Phosphate and the parathyroid. Kidney Int. 2009; 75:898–905. [PubMed: 19129794]

44. Feskanich D, Singh V, Willett W, Colditz G. Vitamin A intake and hip fractures among postmenopausal women. JAMA. 2002; 287:47–54. [PubMed: 11754708]

45. Johansson S, Melhus H. Vitamin A antagonizes calcium response to vitamin D in man. J Bone Miner Res. 2001; 16:1899–1905. [PubMed: 11585356]

Table 1

Characteristics of the Study Population (N=1288)

Characteristic		
Age (years)	44.0	(41 to 47)
Body mass index (kg/m^2)	24.0	(22.0 to 26.6)
Physical activity (METS/week)	18.9	(5 to 26)
Race (N, %)		
Caucasian	1223	95%
Non-Black (Hispanic, Asian, Other)	65	5%
Current smoker (N, %)	58	5%
1–14 cig/day	37	
15–34 cig/day	21	
Past smoker (N, %)	296	23%
Pre-menopausal (N, %)	1265	98%
Current oral contraceptive use (N, %)	22	2%
Season of blood draw		
Winter	287	22%
Spring	350	27%
Summer	255	20%
Fall	395	31%
Energy adjusted nutrient intake		
Total Calcium including supplements (mg/day)	1160	(816 to 1619)
Dietary Calcium (mg/day)	831	(658 to 1043)
Phosphorus (mg/day)	1307	(1151 to1490.5)
Vitamin D (IU/day)	323	(165 to 547)
Total Vitamin A (mcg/day)	1850	(343 to 14957)
Laboratory parameters		
25(OH)D (ng/ml)	26.6	(21.1 to 32.4)
Calcium (mg/dL)	9.3	(9.0 to 9.6)
Phosphorus (mg/dL)	4.5	(4.1 to 4.8)
Creatinine (mg/dL)	0.8	(0.7 to 0.9)
Estimated GFR (ml/min/1.73 m^2)	85.0	(76.7 to 93.9)
Intact Parathyroid Hormone (pg/ml)	30.7	(23.7 to 38.8)

Note: Variables are taken from the questionnaire closest to the blood draw and are expressed as median (25–75 percentile) unless otherwise specified. Vitamin A is measured in micrograms of retinol equivalents (1500 mcg RE = 5000 IU).GFR denotes glomerular filtration rate.

Table 2

Correlation Coefficients between Dietary Factors, Plasma Factors, and Intact Parathyroid Hormone

	Plasma Calcium	Plasma 25(OH)D	Plasma Phosphorus	Total Calcium Intake	Phosphorus Intake	Vitamin A Intake
Plasma PTH	−0.23 (<.001)	−0.24 (<.001)	−0.15 (<.001)	−0.09 (<.01)	−0.07 (<.01)	−0.09 (<.01)
Plasma Calcium	--	0.13 (<.001)	0.13 (<.001)	0.06 (.04)	0.03 (.26)	0.01 (.72)
Plasma 25(OH)D	--	--	.02 (0.38)	0.11 (<.001)	0.09 (<.01)	0.09 (<.01)
Plasma Phosphorus	--	--	--	−0.001 (.97)	−0.05 (.10)	0.03 (.22)
Total Calcium Intake	--	--	--	--	0.53 (<.001)	0.43 (<.001)
Phosphorus Intake	--	--	--	--	--	0.35 (<.001)

Note: Values are Spearman correlation coefficients. P-values are in parentheses.

Table 3

Multivariate-Adjusted Differences in Intact Parathyroid Hormone

Variable	Difference in PTH (pg/ml)	95% CI	P for Trend
BMI (kg/m^2)			
<21	0.4	(−1.6 to 2.3)	
BMI 21–22	Ref		
23–24	1.0	(−0.8 to 2.8)	
25–26	0.5	(−1.5 to 2.4)	
27–29	2.0	(0.2 to 3.9)	
			0.05
Smoking			
Never	Ref		
Past	−0.2	(−1.6 to 1.2)	
Current	−4.8	(−7.7 to −1.9)	
1–14 cig/day	−4.1	(−7.7 to −0.5)	
15–34 cig/day	−6.4	(−11.2 to −1.7)	
Total Calcium Intake			
Quartile 1	Ref		
Quartile 2	−0.9	(−2.7 to 0.9)	
Quartile 3	−0.5	(−2.4 to 1.4)	
Quartile 4	−1.3	(−3.4 to 0.7)	
			0.07
Total Vitamin A Intake			
Quartile 1	Ref		
Quartile 2	−1.2	(−3.0 to 0.5)	
Quartile 3	−0.5	(−2.3 to 1.2)	
Quartile 4	−1.9	(−3.7 to −0.07)	
			0.01
Season of Blood Draw			
Summer	Ref		
Winter	3.2	(1.3 to 5.1)	
Spring	3.0	(1.1 to 4.8)	
Fall	1.7	(−0.03 to 3.4)	
Plasma 25(OH)D			
Quartile 1	Ref		
Quartile 2	−2.5	(−4.2 to −0.8)	
Quartile 3	−3.1	(−4.8 to −1.3)	
Quartile 4	−4.5	(−6.3 to −2.7)	
			<.001
Plasma Phosphorus			
Quartile 1	Ref		
Quartile 2	−3.7	(−5.4 to −2.0)	

Variable	Difference in PTH (pg/ml)	95% CI	P for Trend
Quartile 3	−3.8	(−5.5 to −2.2)	
Quartile 4	−4.1	(−5.8 to −2.4)	
			<.001
Plasma Calcium			
Quartile 1	Ref		
Quartile 2	−1.7	(−3.3 to −0.1)	
Quartile 3	−3.0	(−4.9 to −1.2)	
Quartile 4	−5.3	(−7.0 to −3.6)	
			<.001

Note: The multivariate regression model was adjusted for age, race, phosphorus intake, animal protein intake, creatinine, and all other covariates listed in the table. Tests for trend were not performed for categorical or binary variables.