The Relationship Between Incidence of Fractures and Anemia in Older Multiethnic Women

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Abstract

Objectives—The purpose of this study was to prospectively examine the relationship between anemia and incident fractures of the hip, spine and all skeletal sites in women from diverse racial and ethnic backgrounds enrolled in the Women's Health Initiative (WHI) Observational Study and Clinical Trials.

Design—Prospective cohort study.

Setting—40 WHI clinical centers across the US.

Participants—Postmenopausal women (n = 160,080), mean age 63.2 (SD: 7.2) years, were recruited and followed for an average of 7.8 years.

Measurements—Anemia was defined as hemoglobin levels at baseline less than 12 g/dL. All fractures were self-reported. Hip fractures were further confirmed by trained physicians using medical records.

Results—Among the participants 8,739 women (5.5%) were anemic. The age-adjusted incidence rate of hip fractures per 10,000 person years were 21.4 in women with anemia and 15.0 in women without anemia; a higher incidence rate for spine or all fractures in anemic women was also observed. After multiple covariates were included in the Cox proportional hazards models, significant increased fracture risk associated with anemia still existed as demonstrated by the hazards ratios (95% confidence interval) of fractures associated with anemia being 1.38 (1.13–

1.68), 1.30 (1.09–1.55) and 1.07 (1.01–1.14) for hip, spine and all-types respectively. No significant racial/ethnic difference was found in these relationships.

Conclusion—A significantly increased fracture risk was observed in multi-ethnic postmenopausal women with anemia. Given the high prevalence of anemia in the elderly population, it is important to better understand the relationship and mechanisms linking anemia to fracture risk.

INTRODUCTION

Anemia is a common health problem in older populations. The World Health Organization (WHO) defines anemia as a hemoglobin level of less than 13g/dL in men, and less than 12g/dL in women.[1,2] In the Third National Health and Nutrition and Examination Survey (NHANES III) the prevalence of anemia, as defined by WHO criteria, was over 10% for adults age 65 years and older.[3] The prevalence of anemia varies by race/ethnicity and increases with age.[3]

Anemia in older adults has been shown to be associated with disability, declines in physical performance,[4] low muscle strength, reduced muscle density[5] and increased mortality independent from other co-morbidities.[6] In addition, bone density has been found to be significantly lower in older people with anemia as compared to people of the same age. This difference in bone density was persistent even after adjusting for body mass index (BMI).[7] Studies have also demonstrated low muscle mass and strength and higher risk of fall among older people with anemia.[8–11] Elevated fall rates and reduced muscle mass, muscle strength, and bone density are well known risk factors for bone fractures. Therefore, intuitively, anemia may elevate an individual's risk of fractures. To our knowledge no direct evidence are available demonstrating a greater fracture risk in older people with anemia versus those without anemia. It is well known that African Americans have an increased risk for anemia[3] but a lower risk for fractures[12,13] in comparison to people from other race/ethnic backgrounds. In contrast, both fracture[12,13] and anemia[3] risks increase with aging. However, whether the association between anemia and fracture varies by age and race/ethnicity is unknown and should be investigated in order to better identify anemic people at increased risk for fractures.

In this prospective cohort study we aimed to investigating the association of anemia with fracture risk in U.S. post-menopausal women from diverse racial and ethnic backgrounds enrolled in the Women's Health Initiative (WHI) Observational Study (OS) and Clinical Trials (CT). The following hypotheses were tested: 1) anemia is associated with an increased fracture risk in post-menopausal women and 2) in spite of the variations in anemia rates by age and/or race/ethnicity, the magnitude of the increased fracture risk associated with anemia is similar in all age and racial/ethnic groups. To evaluate potential mediating factors that link anemia with fractures we have also examined the contribution of falls and self-reported general health (fair/poor health versus good/excellent health) to the relationship between anemia and fracture risk.

METHODS

Participants

This study was conducted using data from the WHI, the largest U.S. health study among postmenopausal women. Between 1993 and 1998, WHI recruited 161,808 participants from 40 WHI clinical centers across the United States. To qualify for the WHI enrollment, women had to be between age of 50–79, post-menopausal and not likely to relocate or die within 3 years of study enrollment. Additional inclusion and exclusion criteria were applied to women in the WHI clinical trials. Details regarding the study design, inclusion and exclusion criteria, recruitment procedures, participants characteristics, intervention regimens, randomization, blinding, and follow-up have been previously published in a number of papers[14–17] for the WHI-OS[18] and WHI-CT[17] arms. The study protocol and consent forms were approved by the institutional review boards for all participating institutions.

Data Collection

Self-administered or interviewer-administered questionnaires were completed by WHI participants for eligibility screening and collection of baseline characteristics (such as demographic, reproductive, and health status information). Physical examinations were conducted and a blood specimen was collected at baseline. The WHI OS women visited the WHI clinical center at 3 year intervals and the WHI CT women visited the clinic every year for follow-up physical measurements and blood collections. The CT participants completed additional questionnaires every 6 months and OS participants every year. The average follow-up time was 7.8 years in this current analysis.

Anemia definition

Hemoglobin levels were measured on all WHI participants at baseline in the context of a complete blood count (CBC) test conducted by designated clinical labs in the surrounding areas of each WHI clinical center. For this analysis, a woman was considered to have anemia if her hemoglobin concentration at baseline was less than 12g/dL, using the WHO criteria. A total of 160,080 study participants had baseline hemoglobin measurements (CT= 68,080, OS=91,999).

Fracture Assessments

During follow-up, 160,934 women (CT = 67,881 and OS = 93,053) had completed at least one medical history update providing information regarding new fracture diagnosis (in the previous 12 months for OS and 6 months for CT participants). Specifically, women were asked, "Since (last reporting date), has a doctor told you that you had a broken, fractured, or crushed bone?" If "Yes" was selected, then they were asked to answer "Which bone did you break, fracture, or crush?" by marking all that apply from the following list: 1) Hip, 2) Upper leg (not hip), 3) Pelvis, 4) Knee (patella), 5) Lower leg or ankle, 6) Foot (not toe), 7) Tailbone (coccyx), 8) Spine or back (vertebra), 9) Lower arm or wrist, 10) Hand (not finger), 11) Elbow, 12) Upper arm or shoulder, 13) Other (specify). The term "all-type" includes any reported fracture from the previous list. Self-reported hip fractures were adjudicated with medical records by trained adjudicators; all non-hip fractures were self-reported without adjudication.

Assessments of Covariates

Information on age, race/ethnicity, education, cohabitation, smoking, use of hormone therapy, history of fracture, number of falls in last 12 months, medication or supplement use (corticosteroids, thiazide, estrogen, calcium regulators, calcium, vitamin D, and iron)

chronic diseases (depression, diabetes, cardiovascular disease, hypertension, arthritis, osteoporosis, cancer, asthma, and emphysema), number of hospitalization, parental fracture after age 40, parity, self-reported health status (poor/fair health versus good/excellent health), physical activity (total METS/wk) and nutrient intakes (calcium, vitamin D, iron, and total energy) were assessed from baseline questionnaires or follow-up questionnaires. Physical function and depression at baseline were measured using the 10-item Medical Outcomes Study Scale[19] and the shortened Center for Epidemiologic Studies Depression Scale (CES-D),[20] respectively. Weight was measured to the nearest 0.1kg on a balance beam scale with the participant dressed in indoor clothing without shoes. Height was measured to the nearest 0.1 centimeter using a wall-mounted stadiometer. Body mass index (BMI) was calculated as: weight (kg)/height $(m)^2$.[21,22]

Statistical Analysis

Descriptive analyses were done on baseline characteristics of the study participants and the results were presented as mean (95% confidence interval (CI), median (interquartile range) or frequencies (%) by anemia group at baseline. T-tests, Wilcoxon rank sum or chi-square tests were conducted on the baseline characteristics of the participants. Age-adjusted incidence rates of fractures (all-types and site specific), including 95% CI, were presented by anemia status for total participants and by race/ethnicity. Absolute incidence rate difference (anemia – no anemia) by 10 year age groups was calculated and presented in a bar chart. The likelihood ratio test was used to test the null hypothesis of equal incidence rate difference across age groups.

The Cox-proportional hazards model was used to test differences in the relative risk of fractures by anemia status. Potential confounding effects of covariates, including co-morbidity, falls, physical activity, nutrient intakes, self reported general health status, physical function and demographic characteristics were examined and controlled for when applicable. Potential confounding factors were identified in the marginal analysis if the p-value was less than 0.2, and then examined one by one and as a group in the Cox proportional hazards regression analysis to assess their independent and collective impacts on the relationship between anemia and fracture risk. If a variable significantly affected the hazards ratio (change a hazards ratio more than 10%), then it was considered as a confounding factor and included in the final model. Three sets of models were developed. The first set was adjusted for study components (OS participants versus CT controls and interventions, each separately). The second was adjusted for study assignment/intervention plus race/ethnicity, the only statistically significant confounding factor for all models. The third model set included all the above plus the following: age, height, weight, general health status (fair/poor health versus good/excellent health), baseline number of falls, total calcium intake, total vitamin D intake, total iron intake, physical function, physical activity, smoking, hormone use, fractured after the age of 55, depression, diabetes ever, osteoporosis ever, and cancer ever. The large number of covariates in model 3 was selected from previously reported risk factors for osteoporotic fractures and WHI interventions.[21,22] The third model set was developed to get a more conservative assessment on the fracture risk after adjusting for the reported factors that are related to fracture risk. Interaction terms of race/ethnicity and anemia, and age group and anemia were tested for possible racial/ethnic and age group variations in the association between anemia and fracture.

Kaplan Meier cumulative incidence probability curves were generated to show longitudinal differences in fracture risk by anemia status.

Stratified analyses were also conducted by race/ethnicity in the Cox proportional hazards regression. All analyses were performed with Stata statistical software (version 10.0, Statacorp, College Station, TX).

RESULTS

A total of 160,080 women who had a baseline hemoglobin measurement were included in this study. Among them, 8,739 women had hemoglobin levels below 12 g/dL. Descriptive analyses by baseline anemia status (Table 1) showed that women with anemia were significantly different from women without anemia in regards to most of the baseline characteristics examined. A markedly higher percent of African American women were anemic. In general, women with anemia were older, had a lower body weight and reported poorer health, lower physical function, lower level of physical activity, higher risk for depression, and a slightly higher frequency of falls. Women with anemia also reported lower intakes of calcium, vitamin D and iron. No significant difference in history of bone fractures at age 55 years or older was observed by baseline anemia status. However, women with anemia versus women without were more likely to report a previous diagnosis of osteoporosis.

Absolute Risk for Fractures---Incidence Rates

The age-adjusted incidence rates for all-types, hip, and spinal fractures by baseline anemia status are presented in Table 2. Women with anemia, among the entire cohort and the non-Hispanic white ethnic group, compared to women without anemia had a higher fracture incidence rate of the hip, spine and all-types. Since the numbers of fractures in the anemia group were small among minorities no clear patterns of associations between anemia and higher fracture incidence rates could be identified for these groups.

In Figure 1, differences in fracture incidence rates between anemic and non-anemic women are presented by 10 year age groups. The magnitude of increased fracture incidence rate by anemia appears larger in the 70 or older age group in comparison to the younger age groups, especially for the hip and all-types fracture groups.

Relative Risk for Fractures---Hazard Ratios

The results from the Cox model indicated that the risk for hip, spinal and all-types of fractures were increased among women with anemia and the largest elevated risk was for hip fractures. After adjusting for study assignment/intervention and the confounding factor, race/ethnicity, the hazards ratios (95%CI) were 1.81 (1.53–2.15), 1.41 (1.20–1.64), and 1.14 (1.08–1.20) for hip, spine and all-types of fractures, respectively (Table 3). The cumulative incidence of fracture based on model 2 is presented in Figure 2, showing greater incidence rate for hip, spine and all-types of fractures even after adjusting for the significant confounder, race/ethnicity.

In model 3 (Table 3), where baseline number of falls, self-reported general health and a large number of other covariates were adjusted for, the hazards ratios (95% CI) were changed slightly to 1.38 (1.13–1.69), 1.30 (1.09–1.55), 1.07 (1.01–1.14) for hip, spine and all-types of fractures, respectively. No significant multiplicative interactive effect of race/ethnicity with anemia on all-types of fracture risk was observed. However, stratified analysis (not shown) showed the direction is the same for these associations among the minorities. The number of fractures was too small for hip and spine regions in minorities so no interactions of race/ethnicity with anemia were examined for these site-specific fractures. The only statistically significant interaction for age group and anemia was found for all types of fractures in the 70–79 year old group.

Sensitivity analysis

We limited the above analyses to non-Hispanic white women (data not shown). Results from the stratified analyses were similar to the results from the entire cohort.

DISCUSSION

Anemia is common among older people and the prevalence increases with advancing age.[3] Both clinical and epidemiologic research has suggested that anemia is a significant risk factor for morbidity and mortality particularly among older persons. Anemia may be a clinical indicator of disease pathology or may present as a co-morbid condition which increases the severity of existing health conditions.[5,6,8,10,11,23–27]

The WHI, with its large sample size and diverse race/ethnic sample, presents a great opportunity to prospectively assess the relationship between anemia and fracture risk in post-menopausal women from different racial and ethnic backgrounds. Our analysis provides direct evidence of a significant increase in risk for hip fracture among U.S. postmenopausal women who present with anemia. The results also suggest elevated spinal and all fracture risks associated with anemia. The increased fracture risk could not be completely explained by co-morbidity, falls, or other life-style factors. The increased fracture risk associated with anemia in our study ranged from 7% to 38% across fracture sites, after including multiple covariates. Our study cannot determine whether the association between anemia and fracture is a causal relationship, but these results highlight the importance of further understanding the underlying mechanisms of this association.

No prior study has prospectively evaluated the relationship between anemia and fracture risk. However, our study results are consistent with the results from the InCHIANTI study in Italy, which showed that anemia was associated with lower bone density, an association that was most significant in older women as compared to older men. Interestingly, anemia-related bone loss was mostly associated with cortical bone loss rather than trabecular bone loss in the InCHIANTI study.[7] In contrast, our study found increased fracture risk at both high trabecular and high cortical composition bone sites, such as spine and hip. In this same Italian cohort, hemoglobin levels were also found to be related to skeletal muscle properties: lower hemoglobin concentrations were correlated with lower skeletal muscle mass and strength.[5] Reduced skeletal muscle mass and strength may have direct impacts on bone density since bone is responsive to mechanical stimulation. Low skeletal muscle mass may also increase the risk of falling. Indeed, findings have unequivocally pointed to a significant association between anemia and falls in older adults. [8,28,29] However, in our study, falls did not contribute significantly to the observed association between anemia and fracture risk.

The prevalence of anemia increases with age. In NHANES III one-fifth of women 85 or older presented with anemia. Specifically, the rates of anemia in older women doubled from 10% to 20% when comparing prevalence among 75 to 84 year olds to those over 85 years of age.[3] Our findings are in agreement with previous studies showing an increased prevalence rate of anemia with aging. In addition, we have found that the anemia-associated prevalence rate for hip fracture and all fractures was significantly higher in the 70–79 year old group in comparison to the younger age groups. A similar trend was observed for spinal fractures but the result did not reach the level of statistical significant at the p-value of 0.05. These results suggest that the absolute fracture risk and the difference of absolute risk were greatest within the oldest group of women in our study. The reason for this differential risk relationship between fractures and anemia by age group cannot be determined in this study.

We demonstrated significant race/ethnic differences in the prevalence of anemia in this population supporting the findings from other reports. In NHANES III, the lowest overall prevalence in persons over age 65 was seen in Non-Hispanic whites (9.0%). Mexican Americans (10.4%) had a slightly higher rate, but African Americans (27.8%) had a rate 3 times higher than non-Hispanic whites when the same WHO criteria for anemia was applied. [3] In spite of the strikingly high prevalence of anemia in African Americans, one study has

suggested that older African Americans, classified as anemic by WHO criteria, were not at risk for higher mortality and disability; however, an increased risk of death and disability was found in whites with anemia from the same cohort study.[30] Their results suggest racial differences in the association between WHO defined anemia and adverse health events, thus lending support for different anemia cutoff points by race/ethnicity. We did not find race/ethnic differences in the association between anemia and risk for all fractures. However, smaller numbers of fractures in some minority groups have limited our ability to make a conclusive statement.

The underlying mechanisms of the relationship between anemia and fractures are most likely to be complicated and heterogeneous. The association we observed here may be the reflection of direct, indirect or a combination of direct and indirect effects of anemia on fracture risk. Many known risk factors of anemia in older adults, such as androgen insufficiency, chronic inflammation, age-associated renal insufficiency, stem cell aging,[31] and nutrient deficiency including iron, cobalamin (B12) and folate deficiencies, [32,33] are also known risk factors for osteoporosis and fractures. Thalassemia patients are at higher risk for bone diseases, including severe osteoporosis and fractures,[34] but we do not have information on thalassemia in this current study. Sickle cell disease predisposes an individual to low bone density[35] and hence increases the person's risk for future fractures. It is unlikely that the increased risk of fracture in our study was mainly due to sickle cell disease since only two participants reported having the disease in the baseline questionnaire. In addition to these possible indirect links for the association between anemia and fracture risk, low hemoglobin levels may directly affect precursors of bone cells.[36–38] In future investigations, bone density, geometric structures and bone metabolic markers may be used to help understand the underlying mechanisms related to this increased fracture risk among older anemic women.

Anemia has been considered a modifiable risk factor for adverse health consequence.[39,40] Although anemia is associated with an increased risk of fractures in our study, whether improving hemoglobin concentration in anemic women can reduce risk for fractures remains to be studied. One prior study[41] showed that after hip fractures women who had hemoglobin levels less than 12 g/dL stayed longer in the hospital and more likely died from the fracture than those with normal hemoglobin levels at the time of hospital admission. Our analysis indicates anemia is associated with higher risk for fractures, but does not provide evidence as to whether a pre-existing anemic condition contributes to longer-term health outcomes of fractures.

In this study only hip fractures were adjudicated. Non-hip fractures were self-reported so they are subject to reporting error. Although the agreement between self-report of fractures and medical record confirmed diagnosis of fractures is estimated to be 70% in this cohort, there was a range of variation in the accuracy of the self-reported fractures by fracture anatomical site,[42] which may have prevented us from accurately assessing the associations between non-hip fractures and anemia. In the current study, spine fractures referred to clinical spinal fractures only, so under-reporting for undiagnosed spinal fractures might have also occurred. It is unknown if these information biases differ by anemia status; hence, their impact on the study findings is difficult to assess. It has been suggested that only anemia linked with renal disease or chronic inflammation are associated with a higher mortality rate. [43] A case-control study in the WHI has suggested that poor renal function, as measured by cystatin, is associated with increased hip fracture risk.[44] Lack of renal function measurements is a limitation of this current study and needs to be addressed in future investigations. Anemia was defined using a single baseline measurement of hemoglobin and may not reflect persistent anemia. No information on inflammation status was collected during the study. Previous studies have shown that one third of the anemia cases in older

populations are due to nutrient deficiency; one third to renal insufficiency and chronic inflammation; and one third related to factors that are less understood and difficult to detect in clinical settings.[33] The contributing causes for anemia could not be determined in our study. Whether different subtypes of anemia are associated with fracture risk differently is impossible to be addressed in this study, but remains an interesting research topic for future investigation.

WHI is the largest health study ever undertaken among postmenopausal women in the United States. The racially and ethnically diverse cohort makes this study unique in understanding possible differential associations between anemia and fracture risk across racial and ethnic sub-groups. Over the course of the study, 20,006 fractures were diagnosed between January 1999 and September, 2006, making WHI the largest number of reported fractures in post-menopausal women. Hence the study results have provided first hand evidence on the association between anemia and fracture risk in postmenopausal women.

CONCLUSION

In conclusion, in this prospective cohort study we have found that anemia is significantly associated with increased fracture risk in postmenopausal women from the Women's Health Initiative. Given the high prevalence of anemia in older women it is of great public health interest for future research to investigate the mechanisms contributing to this observed association between fracture risk and anemia and to further understand whether age and race/ethnicity modify the relationship between anemia and fracture risk.

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Appendix
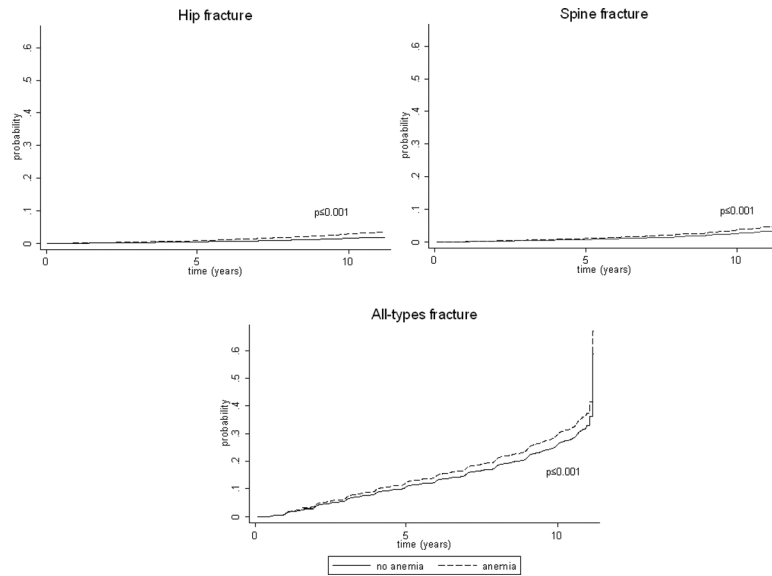
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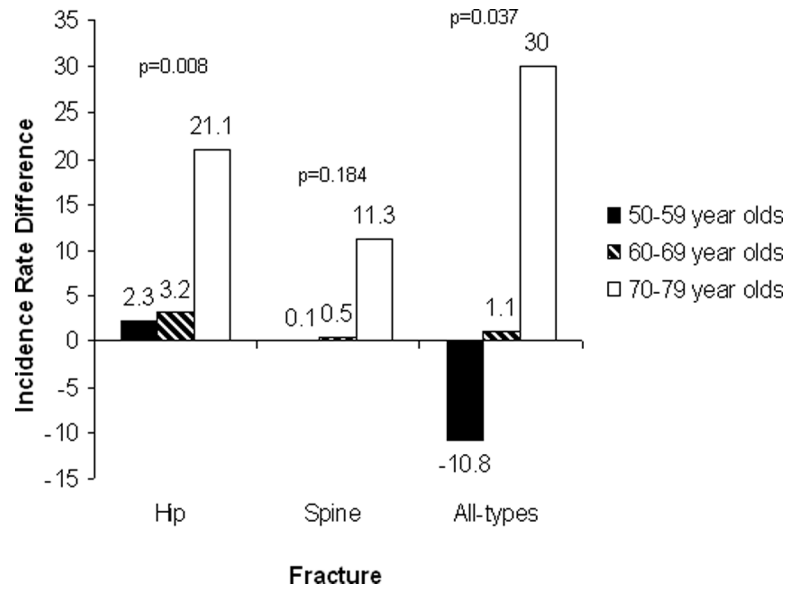
Figure 1.
Differences in incidence rates of fracture per 10,000 person-years between anemic and non-anemic women (absolute incidence rate difference= anemia group incidence – no anemia group incidence)
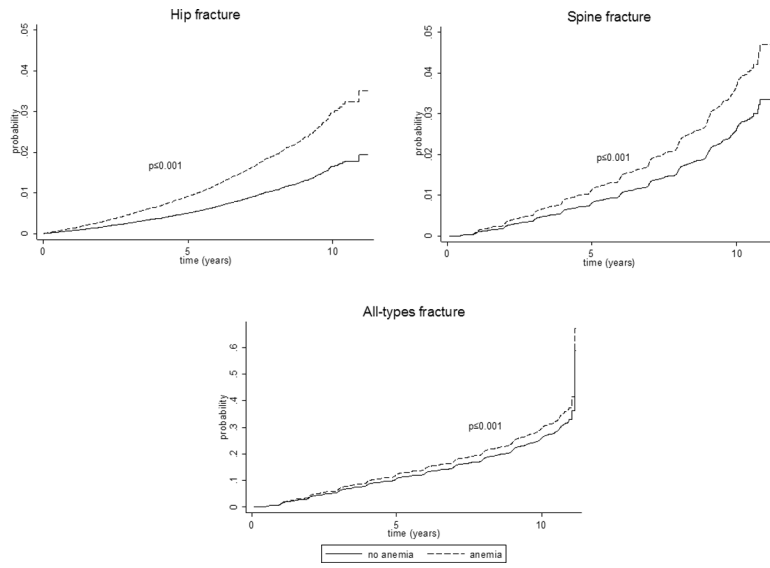
Figure 2.
Cumulative incidence of fracture, adjusted for study arm assignment and race/ethnicity

Table 1

Baseline characteristics by anemia (N= 160,080)

	No Anemia N= 151,341		Anemia N= 8,739	
	N	**%**	**N**	**%**
Age at Baseline				***
50–59	50,204	33.2	2,729	31.2
60–69	67,998	44.9	3,853	44.1
70–79	33,139	21.9	2,157	24.7
Ethnicity				***
American Indian or Alaskan Native	652	0.4	52	0.6
Asian or Pacific Islander	3,970	2.6	170	1.9
African-American	12,101	8.0	2,316	26.6
Hispanic/Latino	6,118	4.1	318	3.7
White (not of Hispanic origin)	126,450	83.8	5,726	65.8
Other	1,673	1.1	121	1.4
Study arm				***
OS	86,459	57.1	5,540	63.4
CT	64,881	42.9	3,199	36.6
Smoking Status				***
never smoked	75,952	50.8	4,600	53.5
past smoker	62,760	42.0	3,639	42.4
current smoker	10,685	7.2	352	4.1
Hormone therapy use				***
Never	66,402	43.9	3,790	43.4
past user	24,412	16.1	1,248	14.3
current user	60,402	39.9	3,694	42.3
fracture at age 55+				
No	96,403	83.6	5,618	82.9
yes	18,850	16.4	1,156	17.1
Depression				***
No	131,118	89.0	7,354	87.5
Yes	16,119	11.0	1,052	12.5
Diabetes ever				***
No	142,525	94.2	7,942	91.0
Yes	8,721	5.8	785	9.0
Osteoporosis ever				***
No	137,937	92.4	7,762	90.5
yes	11,276	7.6	820	9.5
Cancer ever				***
no	136,402	90.9	7,691	88.8
yes	13,623	9.1	974	11.2
General self-reported health status				***

	No Anemia N= 151,341		Anemia N= 8,739	
	N	%	N	%
excellent	25,890	17.2	1,172	13.5
very good	61,867	41.1	3,067	35.4
good	49,417	32.9	3,126	36.1
fair	12,122	8.1	1,173	13.5
poor	1,087	0.7	128	1.5
Physical Functioning Score [†]			***	
<80	44,885	30.2	3,410	40.1
80–90	48,307	32.5	2,440	28.7
91–100	55,317	37.3	2,655	31.2
Number of falls in past year			***	
none	97,948	67.6	5,662	66.5
1 time	29,087	20.1	1,678	19.7
2 times	11,977	8.3	748	8.8
3 or more times	5,993	4.0	423	5.0

	Mean	SD	Mean	SD
Physical Activity (mets)	12.4	13.7	11.7	13.6***
Height (cm)	161.8	6.6	161.2	6.7***
Weight (kg)	73.6	16.8	73.0	18.3***
BMI (kg/m^2)	28.0	5.9	27.9	6.5

	Median	IQR	Median	IQR
Total intake of Iron (mg)	16.2	10.4–27.9	15.4	9.6–27.7***
Total intake of Calcium (mg)	1035.0	654.6–1,542.9	925.4	554.5–1,444.2***
Total intake of Vitamin D (IU)	306.2	135.3–552.6	257.5	113.6–525.6***

***
p≤0.001; calculated using chi-square T-tests, or Wilcoxon rank sum tests IRQ: interquartile range

[†]better physical function with higher score

Table 2

Incidence rates * of fractures per 10,000 person-years (95% CI) by race/ethnicity

	Hip				Spine				All-types			
	Anemia		No Anemia		Anemia		No Anemia		Anemia		No Anemia	
	#Fx	IR (95% CI)	#Fx	IR (95% CI)	#Fx	IR (95% CI)	#Fx	IR (95% CI)	#Fx	IR (95% CI)	#Fx	IR (95% CI)
Total WHI	150	21.4 (17.9, 24.8)	1,756	15.0 (14.3, 15.7)	174	25.5 (21.7, 29.3)	2,692	23.0 (22.1, 23.9)	1,449	234.3 (222.2, 246.4)	25,245	232.5 (229.6, 235.4)
White	128	26.6 (21.9, 31.2)	1,657	16.8 (16.0, 17.7)	159	34.4 (29.0, 39.8)	2,502	25.4 (24.4, 26.4)	1,129	275.9 (259.7, 292.1)	22,549	248.1 (244.9, 251.4)
Hispanic	1	4.8 (0, 14.1)	23	5.2 (3.1, 7.3)	3	13.0 (0, 27.9)	47	10.6 (7.5, 13.6)	33	161.0 (105.6, 216.5)	639	150.9 (139.2, 162.6)
African American	14	7.4 (3.5, 11.4)	37	4.1 (2.8, 5.4)	4	2.3 (0.04, 4.6)	51	5.6 (4.1, 7.1)	235	142.0 (123.7, 160.2)	1,215	139.4 (131.6, 147.2)
Asian	3	16.6 (0, 35.3)	15	5.1 (2.5, 7.6)	4	25.4 (0, 50.9)	45	15.2 (10.8, 19.7)	21	158.5 (86.0, 230.9)	428	151.3 (137.0, 165.6)
American Indian	0	NA	8	16.6 (5.1, 28.1)	0	NA	10	20.6 (7.8, 33.4)	6	153.8 (28.2, 279.3)	120	272.3 (223.6, 321.1)

*
age-adjusted; #Fx: number of fractures; IR: incidence rate; CI: confidence interval

Table 3

Risk of fracture by anemia status

	Model 1 (N= 159,218)[*]		Model 2 (N=158,809)[†]		Model 3 (N=112,269)[†‡]	
	HR	95% CI	HR	95% CI	HR	95% CI
Hip	1.55	1.32, 1.84	1.81	1.53, 2.15	1.38	1.13, 1.69
Spine	1.17	1.01, 1.37	1.41	1.20, 1.64	1.30	1.09, 1.55
All-types	1.04	0.98, 1.09	1.14	1.08, 1.20	1.07	1.01, 1.14

[*]
adjusted for study arm assignment and interventions (observation study participants versus clinical trial controls or interventions)

[†]
adjusted for all in model 1 plus race/ethnicity

[‡]
adjusted for all in model 2 plus age, height, weight, self reported general health (fair/poor health versus good/excellent health), baseline number of falls (none versus one, two, or three or more falls), diabetes ever, osteoporosis ever, cancer ever, total calcium intake, total iron intake, total vitamin D intake, physical function(< 80 score versus 80–90 score or 91–100 score), physical activity (total METS/ wk), smoking (never versus past or current smoker), hormone therapy (never versus past or current user), fractured after age 55, and depression