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Calcium plus vitamin D supplementation and lung cancer incidence among postmenopausal women in the Women's Health Initiative

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Abstract

Background—Magnesium and calcium are antagonistic in many physiologic processes. However, few studies have investigated the associations of supplemental calcium with lung cancer risk taking this antagonism into account. We evaluated the effect of calcium and vitamin D supplementation on lung cancer incidence and explored whether the ratio of baseline calcium to magnesium (Ca:Mg) intake modifies the association in the Women's Health Initiative (WHI) calcium plus vitamin D supplementation (CaD) trial.

Methods—The intervention phase of the WHI CaD was a double-blinded, randomized, placebo-controlled trial in 36,382 postmenopausal women aged 50–79 years, recruited at 40 U.S. centers. Post-intervention follow-up continued among 29,862 (86%) of the surviving participants. Risk of lung cancer in association with CaD supplementation was evaluated using proportional hazard regression models.

Results—After 11 years' cumulative follow-up, there were 207 lung cancers (incidence 0.11% per year) in the supplement arm and 241 (0.12%) in the placebo arm (hazard ratio (HR) for the

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intervention, 0.91; 95% confidence interval (CI), 0.71–1.17). Subgroup analyses suggested that the HR for lung cancer varied by baseline Ca:Mg intake ratio among women who were current smokers at enrollment ($p = 0.04$ for interaction).

Conclusions—Over the entire follow-up period, calcium and vitamin D supplementation did not reduce lung cancer incidence among postmenopausal women. In exploratory analyses, an interaction was found for the baseline Ca:Mg intake ratio on lung cancer among current smokers at the trial entry. This findings need to be further studied for the role of calcium with magnesium in lung carcinogenesis in current smokers.

Keywords

magnesium; calcium; vitamin D; lung cancer; randomized controlled trial

1. Introduction

Lung cancer is one of the most common cancers and remains the leading cause of cancer death among women in the United States [1]. Although tobacco smoking is the key risk factor, approximately 20–50% of lung cancer cases in women in the US are not attributed to smoking [2, 3]. It is still important to identify other modifiable factors in order to develop novel prevention strategies for lung cancer.

There have been several observational studies of calcium intake and lung cancer risk; results have not been consistent [4–10]. Results have included findings of lower risk [6, 7, 10], no association [8, 9], and increased risk [5]. One potential explanation for the inconsistency is that magnesium status and its interaction with calcium was not considered.

Calcium shares the same homeostatic regulatory system with magnesium [11, 12], and directly or indirectly competes with magnesium for (re)absorption in the intestine and kidneys [11, 13]. Calcium and magnesium also antagonize each other in many physiological activities including pathways related to the pathogenesis of cancer [11, 14]. Moreover, magnesium ion transient channel receptors (e.g., transient receptor potential melastatin 6 (TRPM6) and 7 (TRPM7)) have been shown to be permeable to calcium ion [15], and can be expressed in both lung and gastrointestinal tract (GI) tissues [16, 17]. Results of a clinical trial of calcium supplementation (1200 mg/day) and colorectal adenomas recurrence showed that calcium supplementation reduced recurrence risk only among those with a low baseline calcium to magnesium (Ca:Mg) intake ratio (≤2.63) (RR = 0.68, 95% CI, 0.52–0.90) (test for interaction, $p = 0.075$) [18]. There is evidence of similar modifying effect of Ca:Mg intake ratio in studies of other GI neoplasias, including colorectal adenocarcinoma, Barrett's esophagus and esophageal adenocarcinoma [19, 20].

The Women's Health Initiative (WHI), randomized controlled calcium plus vitamin D supplementation trial (CaD) was initiated to assess whether 1000 mg of calcium carbonate daily plus 400 IU vitamin D_3 reduced the risk of hip fracture and colorectal cancer among 36,282 otherwise healthy postmenopausal women [21, 22]. The CaD trial enrollment began in 1994 and intervention period ended in 2005; no significant differences were found between treatment and placebo arms during the active intervention period for a number of

outcomes [23–26], including the incidence of breast cancer [26], colorectal cancer [25] or lung cancer [24]. However, there was no investigation of potential interaction between the calcium and magnesium status in the WHI CaD trial. To address this issue, we conducted post hoc analyses to examining whether the ratio of baseline Ca:Mg intake modify the effects of supplementation of calcium and vitamin D on lung carcinogenesis in the WHI CaD trial by including post-intervention lung cancer cases through an additional 4.9 years (mean) follow-up for a mean cumulative follow-up of 11.1 years.

2. Materials and Methods

2.1. WHI overview

Details of the WHI CaD trial have been published elsewhere [21, 22, 27]. Briefly, postmenopausal women enrolled in WHI hormone therapy (HT) or dietary modification (DM) trials were invited to join the CaD trial at their first or second annual follow-up visit. Eligible women for the WHI trials were 50 to 79 years old at baseline enrollment with anticipated survival of at least 3 years, no prior breast cancer, and no other cancer within 10 years [27]. For the CaD trial, personal supplemental calcium (up to 1000 mg/d) and vitamin D (up to 600 IU/d and subsequently raised to 1000 IU) were allowed. All participants provided informed consent, and the study protocol was approved by the Institutional Review Boards of all respective clinical centers. The WHI study is registered with ClinicalTrials.gov, number NCT00000611.

A total of 36,282 participants were randomly assigned to receive a total daily calcium (1,000 mg of elemental calcium carbonate) and vitamin D (400 IU of D_3) or matching placebo tablets (provided by GlaxoSmithKline) in two separated daily doses, to be taken with meals. When the intervention phase ended as scheduled on March 30, 2005, vital status was known for 93% of women, of whom 4.6% were deceased. At that time, 76% were still taking study medication and 59% were taking 80% or more of the study pills with little difference between groups [25]. Women were told of their treatment assignment at study closeout. The post-intervention phase began on the closeout date. The current report reflects findings through September 30, 2010. After the intervention phase ended, subsequent follow-up required re-consent which was obtained for 86% of surviving participants with no differences in participation in the follow-up by randomized groups. Baseline information in this report refers to information collected at the baseline of the initial intervention phase.

2.2 Study participants

We excluded participants who at baseline had an estimated energy intake from a baseline food-frequency questionnaire (FFQ) <600 or >5,000 kcal/day, or diagnosis of lung cancer or other cancers less than one year after enrollment in the WHI CaD trial. As a result, 34,770 WHI CaD trial participants were included in this analysis (Appendix Fig. 1).

2.3 Ascertainment of Outcomes

Self-reported health outcomes including lung cancer were ascertained semiannually during the intervention and annually in the post-intervention phase by questionnaire. Lung cancer diagnoses that were reported were confirmed and adjudicated using medical records and

pathology reports by centrally trained study physicians blinded to randomization assignments [28]. Tumor characteristics were coded according to the Surveillance, Epidemiology, and End Results (SEER) guidelines at the WHI Coordinating Center [28].

2.4 Other measurements

Dietary intake was assessed at WHI baseline before randomization using a validated, self-administered FFQ developed specifically for the WHI [29]. Dietary daily intakes of nutrients were calculated based on the FFQ using the Nutrition Data Systems for Research (version 2006) from University of Minnesota Nutrition Coordinating Center food and nutrient database. Information on the use of vitamin and mineral supplements was also obtained at the baseline clinic visit from an interview-based inventory procedure [30]. Only supplements used at least once per week were recorded and transcribed. Daily intakes of total calcium and magnesium were calculated by summing food and supplement sources.

Standardized, self-administered questionnaires were completed by participants during baseline visits, including queries regarding demographic factors, smoking history, medical history, alcohol intake, and physical activity. Never smokers were defined as participants who reported having ever smoked less than 100 cigarettes in their lifetime. Participants who had ever smoked more than 100 cigarettes in their lifetime but were not smoking at baseline were defined as former smokers. Current smokers were those who reported having smoked more than 100 cigarettes and were currently smoking. The number of cigarettes smoked per day and the number of years as a regular smoker were also queried.

2.5 Statistical analysis

The primary analyses entailed use of time-to-event methods and were based on the intention-to-treat principle. Lung cancer incidence was compared between the two randomized arms using hazard ratios (HRs) and 95% confidence intervals (95% CIs) estimated with Cox proportional hazards regression models [31] adjusted for age, smoking status, pack-years of smoking, and treatment assignment in the HT and DM trials. We further tested whether the Ca:Mg intake ratio modified the effect of treatment on lung cancer incidence in strata of baseline ratio of Ca:Mg intake. The WHI study participants reported a very high ratio of Ca:Mg. According to the physiological range of the ratios and to match the cutoff points for the ratio used in previous reports in the US population [18, 19] and other populations [32], the lowest quartile of the Ca:Mg intake ratio in our population was used as the cut-off point for stratifying Ca:Mg intake in the analyses. Additional analyses stratified on smoking status were conducted. Multiplicative interactions between continuous baseline Ca:Mg intake ratio or smoking status with randomized assignment to calcium with vitamin D supplementation or placebo were tested. Formal tests of differences between the HRs in the intervention and post-intervention phase were calculated by inclusion of a binary term for trial phase as a time dependent variable as described [33].

All statistical tests were based on 2-sided probability. Statistical analyses were conducting using SAS, Version 9.3 (SAS Institute, Cary, NC).

3. Results

Baseline characteristics and disease risk factors, including age, race/ethnicity, and tobacco exposure, were balanced between randomized groups (Table 1). Self-reported baseline average daily dietary intakes of calcium, magnesium and vitamin D were similar in the randomization groups. At baseline, total intakes of calcium, magnesium and vitamin D, reflecting both dietary intake and supplement use, as well as Ca:Mg intake ratio were also similar in the two randomized groups. The CaD participant movement through the study has been described previously [33]. The characteristics of women who consented to participate in the extended study are outlined in Appendix Table 1.

After 7.0 years' (mean) intervention and 11.1 years' (mean) cumulative follow-up, there were 207 (incidence 0.11% per year) lung cancers in the supplement group compared to 241 (0.12%) in the placebo group (HR = 0.91, 95% CI, 0.71–1.17; Table 2). The association between the supplementation and incidence of lung cancer by histologic subtypes also was evaluated. The distributions of small cell and non-small cell lung cancer were similar in the two randomized groups over the entire period. Additionally, the grade, stage, and size of the lung cancers were similar in the two assigned groups (data not shown).

Analyses of the effect of the CaD supplement administration on lung cancer incidence for the overall follow-up period stratified by smoking status and baseline Ca:Mg ratio were conducted (Table 3). In the overall follow-up period, the incidence of lung cancer in the two randomized groups did not differ by smoking status ($p = 0.21$ for interaction). Similarly, there was no significant effect of supplementation on lung cancer by baseline ratio of Ca:Mg ratio during the overall followup period ($p = 0.54$ for interaction). Restricting to the trial period only when the intervention might be expected to have the greatest effect, associations appeared to be similar (data not shown).

We further examined whether there was a difference in lung cancer incidence by baseline ratio of Ca:Mg intake stratified by smoking status for the entire follow-up period (data not shown). The number of lung cancers was few in never smokers over the combined trial phases and there was no evidence for differences in the effect of the intervention by baseline ratio of Ca:Mg intake in this group. Similarly, no significant interaction emerged among former smokers for baseline Ca:Mg intake ratio and supplementation. In analyses of the entire period, results for lung cancer showed a significant interaction between baseline Ca:Mg intake ratio and calcium plus vitamin D supplementation among current smokers at the enrollment ($p = 0.04$ for interaction, data not shown), suggesting potential modifying effect of baseline Ca:Mg intake ratio on the relationship between calcium plus vitamin D supplementation and lung cancer incidence. When this analysis was restricted to the intervention phase of the trial, there was no statistically significant interaction between baseline Ca:Mg intake ratio and supplementation among smokers.

4. Discussion

In the previous report of WHI clinical trial evaluating the effect of calcium and vitamin D on lung cancer risk in postmenopausal women, there was no association with lung cancer

incidence during the active trial phase (0.90% as compared to 0.10%, HR =0.86; 95% CI: 0.67–1.12) [24]. After 11 years' cumulative follow-up, we found that daily supplementation with 1000 mg of elemental calcium combined with 400 IU of vitamin D_3 was still not associated with lung cancer risk among postmenopausal women nor with risk of any specific lung cancer histologic type. In addition, the CaD supplementation with lung cancer risk by smoking stratum also did not show an effect over the entire period. We did not find that the ratio of Ca:Mg intake might be an important modifier of CaD supplementation on lung cancer risk. However, there was a qualitative interaction between the baseline Ca:Mg intake ratio and supplementation among current smokers at the enrollment ($p = 0.04$ for interaction).

Calcium plays an important role in carcinogenesis through its function in cellular activities including cell signaling and cell cycle regulation [34]. Furthermore, the calcium regulation of reactive oxygen species metabolism may influence the initiation and progression of cancer [35]. Magnesium is essential in numerous biological activities including cell proliferation, inflammation, energy production, and nucleic acid metabolism [14, 36, 37]. Calcium and magnesium share the same homeostatic regulation system involving their (re)absorption to maintain a normal balance [12]. Both ionized calcium and magnesium are monitored by the same receptor, the calcium sensing receptor (CaSR) [11]. Ionized magnesium (Mg^{2+}) is a powerful ionized calcium (Ca^{2+}) antagonist in many physiological activities important in cancer pathogenesis [11, 14, 38], including inflammation [39], oxidative stress, cell differentiation and proliferation, apoptosis and angiogenesis [40], which are involved in the pathogenesis of cancers. Previous i*n vivo* and i*n vitro* studies also showed the importance of the balance between calcium and magnesium in relation to the physiological functions of these micronutrients [12–14, 41]. Magnesium specific ion transporters, TRPM6 and TRPM7, form an ionized calcium and magnesium permeable cation channel [15], and are largely expressed in lung [16, 17, 42]. A recent study reported that depressing TRPM7 induced a reduction in EGF-enhanced and basal migration of a human non-small cell lung cancer cell line [43]. It is possible that an increase in Ca:Mg ratio, which may increase Ca^{2+} influx by interfering with the TRPM6/7 channel, could lead to proliferation of lung cancer cells and a final lung cancer phenotype. No study has examined a modification effect of Ca:Mg ratio on the association between CaD supplementation and lung cancer risk including differences by smoking status. It is possible, through the homeostasis regulation by (re)absorption, that the Ca:Mg ratio in the lung of current smokers may be different from former smokers or never smokers. Future studies are needed to clarify this possibility.

Both calcium and magnesium intakes from food and supplements have increased in the US population over the past several decades; however, calcium intake has increased at a greater rate than that for magnesium [12, 44]. As a result, an increased Ca:Mg ratio intake is common in American adults, especially in women [12, 45–47]. Recent human studies have shown that the imbalance between calcium and magnesium intake may affect total mortality and cardiovascular disease mortality [32].

The possible modifying role of the Ca:Mg ratio on the effect of calcium may provide an explanation for the inconsistent findings observed in previous observational studies of the

association of calcium intakes with lung cancer risk [4–10]. Consistent with previous reports on lung cancer mortality [32], risks of GI neoplasia [19, 20] and the recurrence of colorectal adenoma [18], we found some suggestion that CaD supplementation reduces the risk of lung cancer among current smokers with lower Ca:Mg ratio (≤2.53) (HR=0.65, 95% CI, 0.32–1.30) but not for those with higher ratio (>2.53) (HR=1.36, 95% CI, 0.78–2.36, *p* for interaction = 0.04). On the other hand, recent results from a cohort study conducted in a Chinese population with lower Ca:Mg intake ratio showed that the inverse associations of intakes of calcium and magnesium with risk of lung cancer mortality were limited to those women with a Ca:Mg intake ratio >1.7 [32]. Collectively, the finding from our current study as well as previous studies conducted in populations with low Ca:Mg ratio suggest that a Ca:Mg intake ratio ranging between 1.7 and 2.53 could be required for calcium to be protective against lung cancer. These ratio ranges are consistent with those for GI neoplasia [19, 32]. However, the number of lung cancer cases in these subgroup analyses was still limited, and it is still possible that we did not have enough power to detect weak associations in some strata in our study. Future studies are needed to confirm this suggestion, as well as to better understand the molecular mechanisms of the modifying effect of Ca:Mg on associations between calcium and lung carcinogenesis.

The strengths of the study include the large, diverse study population, the randomized, double-blinded, placebo-controlled design, prospective, detailed measurement of calcium and magnesium intakes from both food and supplements, the standardized central adjudication of lung cancers, and a relatively large number of incident lung cancer cases allowing stratified analyses by smoking status, histological subtypes, and the Ca:Mg intake ratio. Nevertheless, several issues regarding the design and study population should be noted. Lung cancer was not a predefined study outcome in the WHI. Since the protocol did not require participants to undergo chest radiology imaging tests, some cancers may have been missed and misclassification of the outcome is possible. However, the misclassification would be nondifferential. The average intervention and post-invention follow-up of 11 years may have been insufficient to demonstrate a weak effect of CaD supplementation on overall lung cancer incidence, if the benefit of calcium with vitamin D supplement is to prevent or slow lung cancer progression in its early stages. Although self-reported baseline smoking status and pack-years of smoking were similar in the randomization groups, we were unable to eliminate possible residual confounding. Moreover, this trial cannot separate calcium from vitamin D influence on lung cancer because these agents were used together in the study. In addition, we obtained dietary information at the baseline but have no information on dietary calcium, magnesium and vitamin D for the post-intervention period. Thus we could not evaluate the effects of changes in dietary intakes of these nutrients over time. At the end of extended follow-up, 44% of women in the intervention group and 42% of women in the placebo group reported taking calcium and vitamin D supplements. However, it is unknown whether changes in supplement use during the post-intervention phase could attenuate weak associations between CaD supplementation and overall lung cancer incidence. We had 80% power to detect HRs of 0.57 in a univariate comparison for lung cancer risk among women with low Ca:Mg intake ratio. We cannot rule out that we did not have enough power to detect weak associations in some strata in our study. Replication our findings in studies with large sample size of lung cancer cases will be important. Finally, the

generalizability of the WHI CaD trial might be limited because the study was limited to postmenopausal women, all volunteers rather than women randomly selected from the population.

In summary, after an average of 11 years, there was no difference in the effect of the calcium carbonate plus vitamin D_3 intervention on lung cancer risk in groups defined by smoking status or baseline Ca:Mg intake ratio. Exploratory analyses found an indication that baseline Ca:Mg intake ratio may modify the effect of calcium and vitamin D supplement on lung cancer incidence among current smokers. Further studies are necessary to explore the modifying effects of the Ca:Mg intake ratio on the association between calcium supplement and lung cancer in different populations, including potential mechanism studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The effect of calcium and vitamin D supplementation on lung cancer was evaluated.
- There was no difference in lung cancer incidence between randomization groups.
- An interaction between baseline Ca:Mg ratio and supplementation in current smokers.

Table 1

Selected baseline characteristics of participants by randomization assignment in the WHI CaD Trial

	CaD (n = 18,176)	Placebo (n = 18,106)	*p* value
Age at screening (y) (%)			
<50–59	6726 (37.5)	6696 (37.0)	>0.99
60–69	8276 (45.5)	8243 (45.5)	
70–79	3174 (17.5)	3167 (17.5)	
Race-ethnicity (%)			
Non-Hispanic white	15051 (83.0)	15104 (83.6)	0.41
Black/African American	1680 (9.3)	1635 (9.0)	
Hispanic/Latino	785 (4.3)	717 (4.0)	
American Indian	77 (0.4)	72 (0.4)	
Asian/Pacific islander	370 (2.0)	351 (1.9)	
Unknown	213 (1.0)	227 (1.1)	
Education (%)			
High school or less	4286 (23.6)	4290 (23.7)	0.98
School after high school	7217 (39.7)	7156 (39.5)	
College degree or higher	6557 (36.1)	6545 (36.2)	
Unknown	116 (0.6)	115 (0.6)	
Smoking status (%)			
Never	9325 (51.9)	9428 (52.6)	0.31
Former smoker	7255 (40.3)	7133 (39.8)	
Current smoker	1405 (7.8)	1356 (7.6)	
Pack years of smoking (%)			
Never	9325 (52.0)	9428 (53.9)	0.10
<5	2498 (14.2)	2436 (13.9)	
5–20	2463 (14.0)	2475 (14.2)	
≥ 20	3323 (18.8)	3138 (18.0)	
Frequency of walking outside >10 min (%)			
Rarely/never	2975 (18.6)	3043 (19.0)	0.47
1–3 times/month	2771 (17.3)	2676 (16.7)	
1 time/week	1846 (11.5)	1860 (11.6)	
2–3 times/week	4250 (26.5)	4144 (25.9)	
4–6 time/week	3069 (19.1)	3120 (19.5)	
≥ 7 times/week	1130 (7.0)	1160 (7.3)	
Physical activity (MET/week) (%)			
0–3.00	5517 (33.3)	5478 (33.3)	0.84
>3.00–<11.75	5463 (33.0)	5477 (33.3)	
≥ 11.75	5566 (33.6)	5493 (33.4)	
Alcohol intake (%)			
Never	1863 (10.3)	1891 (10.5)	0.89
Past drinker	3192 (17.7)	3209 (17.8)	

	CaD (n = 18,176)	Placebo (n = 18,106)	*p* value
<1 drink per month	2528 (14.0)	2520 (14.0)	
<1 drink per week	3859 (21.4)	3755 (20.9)	
1–<7 drinks per week	4678 (26.0)	4702 (26.2)	
≥7 drinks per week	1908 (10.6)	1900 (10.6)	
BMI, kg/m^2 (%)			
<25	4745 (26.3)	4834 (26.8)	0.23
25–30	6476 (35.8)	6487 (36.0)	
≥30	6870 (38.0)	6692 (37.2)	
Hormone-therapy use (%)			
Never used	8787 (48.4)	8627 (47.7)	0.07
Former user	3239 (17.8)	3150 (17.4)	
Current user	6135 (33.8)	6317 (34.9)	
Users of multivitamin supplement (%)	6419 (35.3)	6508 (35.9)	0.21
Total energy intake (kcal/day) [§]	1738.6 ± 682.9	1744.6 ± 686.0	0.40
Dietary calcium intake (mg/day) [§]	823.8 ± 436.1	826.8 ± 439.9	0.52
Total calcium intake (mg/day) [2§]	1118.4 ± 670.1	1120.8 ± 656.9	0.73
Dietary magnesium intake (mg/day) [§]	254.5 ± 95.0	255.7 ± 95.7	0.23
Total magnesium intake (mg/day) [2§]	311.2 ± 159.4	314.0 ± 167.6	0.11
Ca:Mg intake ratio [§]	3.73 ± 1.97	3.70 ± 2.03	0.31
Dietary vitamin D intake (IU/day) [§]	175.1 ± 116.7	176.0 ± 117.2	0.47
Total vitamin D intake (IU/day) [2§]	345.3 ± 259.3	350.5 ± 259.1	0.06

[*] Includes American Indian, Alaska Native, Asian, Pacific Islander, other races and unknown.

[§] Excludes participants who had an estimated energy intake from a baseline food-frequency questionnaire (FFQ) <600 or >5,000 kcal/day

[1] Mean ± SD

[2] Supplements + diet

Table 2

Lung cancer incidence by randomization group in the WHI CaD Trial over the cumulative follow-up period*

	CaD Placebo No. cases (% per year)	CaD intervention No. cases (% per year)	HR (95%CI)[a]
Lung cancer incidence	241 (0.12)	207 (0.11)	0.91 (0.71–1.17)
SCLC	21 (0.01)	25 (0.01)	1.44 (0.64–3.25)
NSCLC	220 (0.09)	182 (0.10)	0.87 (0.67–1.27)
Squamous cell	31 (0.02)	38 (0.02)	1.65 (0.91–2.97)
Adenocarcinoma	118 (0.06)	85 (0.04)	0.71 (0.49–1.04)

*HR: hazard ratios; CI: confidence interval; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer.

[a]The HRs and 95% CIs for the overall combined periods events adjusted by age, HT and DM randomization arm, smoking status, pack-years of smoking, and trial phase (time dependent).

Table 3

Effect of Calcium/Vitamin D supplementation on lung cancer incidence for the cumulative follow-up period according to baseline smoking status and ratio of Ca:Mg intake

Characteristic	CAD Placebo No. cases (% per year)	CAD intervention No. cases (% per year)	HR (95%CI)[a]	Test for interaction
Smoking status				
Never smokers	26 (0.02)	32 (0.03)	1.26 (0.63–2.55)	$p = 0.21$ [c]
Ever smokers	212 (0.23)	172 (0.18)	0.85 (0.65–1.11) [b]	
Former smokers	130 (0.16)	99 (0.12)	0.81 (0.57–1.15) [b]	
Current smokers	82 (0.58)	73 (0.50)	1.02 (0.67–1.57) [b]	
Ca:Mg intake ratio				$p = 0.54$ [d]
Ratio ≤ 2.53	73 (0.14)	62 (0.13)	0.74 (0.47–1.17)	
Ratio >2.53	168 (0.11)	145 (0.09)	1.00 (0.75–1.35)	

[*] HR: hazard ratios; CI: confidence interval.

[a] The HRs and 95% CIs for overall combined periods events adjusted by age, HT and DM randomization arm, and trial phase (time dependent).

[b] Among ever smokers, additionally adjusted for smoking status, and pack-year.

[c] Interaction was assessed between smoking status and calcium plus vitamin D treatment versus placebo.

[d] Interaction was assessed between continuous Ca:Mg intake ratio and calcium plus vitamin D treatment versus placebo.